NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

Annual Scientific and Technical Report

October 1, 2001 – September 30, 2002

Cooperative Agreement NCC 9-58

with the

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

September 30, 2002

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

ANNUAL SCIENTIFIC AND TECHNICAL REPORT
OCTOBER 1, 2001 – SEPTEMBER 30, 2002
(Cooperative Agreement NCC 9-58)

TABLE OF CONTENTS

Tables

Appendices

A. NSBRI Strategic Plan Volume I

B. NSBRI Strategic Plan Volume II

C. Review of the National Space Biomedical Research Institute Strategic Research Plan

D. NSBRI Strategic Plan Correspondence

E. NSBRI Core Research Program – Year 5

F. NSBRI Research Team Program Reports – FY 2002

G. NSBRI Retreat Agenda

H. Exercise Simulation Workshop for Digital Human Modeling Core

I. NSBRI Progress Report

J. Director's Report for the September Board of Directors Meeting

K. Publications and Presentations: October 1, 2001 – September 30, 2002

L. Medical Operational Support Team Proposal

M. NIDCD-NSBRI Joint Program for the Support of Vestibular Research

N. NASA/NSBRI Solicitation NRA 01-OBPR-07

O. NSBRI Education and Public Outreach Project Summaries – FY 2002

P. NSBRI Education and Public Outreach Program Report – FY 2002

Q. NSBRI Summer Interns at the Johnson Space Center

TABLE OF CONTENTS

VOLUME I

52 **VOLUME II**

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

ANNUAL SCIENTIFIC AND TECHNICAL REPORT

OCTOBER 1, 2001 – SEPTEMBER 30, 2002
(Cooperative Agreement NCC 9-58)

1.0 INTRODUCTION

This report outlines the activities of the National Space Biomedical Research Institute (NSBRI) during FY 2002, the fifth year of the NSBRI's programs. It is prepared in accordance with Cooperative Agreement NCC 9-58 between NASA's Lyndon B. Johnson Space Center (JSC) and the Institute's lead institution, Baylor College of Medicine.

2.0 BACKGROUND

In June 1996, NASA released a Cooperative Agreement Notice (CAN) inviting proposals to establish a National Space Biomedical Research Institute (9-CAN-96-01). This CAN stated that:

> **The Mission of the Institute will be to lead a National effort for accomplishing the integrated, critical path, biomedical research necessary to support the long term human presence, development, and exploration of space and to enhance life on Earth by applying the resultant advances in human knowledge and technology acquired through living and working in space.** The Institute will be <u>**the**</u> focal point of NASA sponsored space biomedical research.

This statement has not been amended by NASA and remains the mission of the NSBRI.

The Institute was selected by NASA in March 1997 following a two-phase, competitive review of proposals received in response to the CAN. In April 1997, the NSBRI was chartered in the State of Texas as a non-profit corporation. After a 60-day definition period, NASA and the NSBRI signed a Cooperative Agreement (NCC 9-58) and Cooperative Agreement Management Plan with JSC. The Cooperative Agreement is for a five and one-half year base period and three, five-year optional extensions. The first optional extension, lasting until September 30, 2007, will be exercised.

The NSBRI partners with NASA to develop countermeasures against the deleterious effects of long-duration space flight, and performs fundamental and applied space biomedical research directed toward this goal. This is accomplished by:

- designing, testing and validating effective countermeasures to address the biological and environmental impediments to long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that ultimately determine these impediments, where such activity fosters the development of novel countermeasures;
- establishing biomedical support technologies to maximize human performance in space, reduce biomedical hazards to an acceptable level and deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the general benefit of humankind;

- including the treatment of patients suffering from gravity- and radiation-related conditions on Earth; and
- ensuring open involvement of the scientific community, industry and the public in the Institute's activities and fostering a robust collaboration with NASA, particularly through the JSC.

The NSBRI is governed by a consortium of twelve institutions – Baylor College of Medicine, Brookhaven National Laboratory, Harvard Medical School, The Johns Hopkins University School of Medicine and Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School of Medicine, Mount Sinai School of Medicine, Rice University, Texas A&M University, the University of Arkansas for Medical Sciences, the University of Pennsylvania Health System and the University of Washington. The Institute's headquarters are located in Houston at Baylor College of Medicine.

The initial Institute research program consisted of eight research teams carrying out 37, three-year projects and four, one-year "synergy" projects designed to bridge between discipline research team activities and create an appropriate atmosphere for future interdisciplinary research. Because of the competitive process used by NASA to select the NSBRI, most of the initial program was carried out at the seven original consortium institutions. There are, however, no restrictions concerning institutional participation in Institute activity. As a result of two research announcements in FY 2000, the institute expanded to 12 research teams and 85 research projects during its fourth year. In the fifth year, the number of research teams was consolidated to 11 teams, with a total of 88 research projects. In addition to its research program, the NSBRI has developed vital education and outreach and communications programs that take advantage of the Institute's core research activities. Currently there is funding of research and education projects at 75 institutions across 22 states.

The management plan for the Institute is based on the model used by the National Institutes of Health. An independent Board of Scientific Counselors is responsible for assuring excellence in the Institute's intramural program through independent external peer review, and an External Advisory Council is responsible for advising Institute management concerning programmatic effectiveness. The NSBRI also has a User Panel of former and current astronauts and flight surgeons responsible for assuring that the research program is focused on astronaut health and safety. An Industry Forum of representatives of aerospace, biomedical and technology industries assists in developing industry participation in NSBRI and in timely technology transfer.

Primary support for the NSBRI's activities is furnished by NASA through NCC 9-58 although funds to support Institute activities also come from several sources, including the institutions involved in carrying out the NSBRI's programs. Initial annual base funding for the Institute's first two years of operation (FY 1998 and FY 1999) was approximately $10 million. In FY 2000, base annual funding was increased to approximately $14 million to develop the infrastructure needed to support planned program growth in FY 2001. In support of the expanded research and education program, the FY 2001 base annual funding was increased to approximately $25 million. In FY 2002, the base annual funding was approximately $22 million. Detailed information on the budget and allocation of resources appears as part of the Strategic Plan (Appendix A).

On August 29, 2002, the NSBRI received a letter from the JSC Contracting Officer informing the Institute that, for planning purposes, the NSBRI should presume a $30 million total budget ($29 million plus $1 million for Advanced Medical Care Systems) for FY 2003 through FY 2007.

3.0 SUMMARY OF FY 2002 ACTIVITIES

A summary of major NSBRI activities taking place in FY 2002 appears at Table 1. The activities ranged from the appointment of a full-time director and the development and NASA external review of a strategic plan to the scientific and management meetings of the External Advisory Council and Board of Directors designed to highlight scientific and technological achievements and to provide guidance and oversight to the Institute's programs.

Table 1. MAJOR NSBRI ACTIVITIES
October 1, 2001 – September 30, 2002

DATE	ACTIVITY	LOCATION
October 17-18	External Advisory Council Meeting	Houston
October 31	Release of Research Announcement NRA 01-OBPR-07	N/A
November 8	Board of Directors Meeting	Houston
November 8	Appointment of Full-Time Director	N/A
January 13-17	NSBRI Retreat	Montgomery, TX
January 31	Proposal Due Date for Research Announcement NRA 01-OBPR-07	N/A
March-April	Peer Review of NSBRI's NRA 01-OBPR-07 Proposals	Washington, DC
March 12-13	External Advisory Council Meeting	San Jose, CA
April 4	Board of Directors Meeting	Houston
April 17	Department of Health and Human Services Audit Exit Conference	Houston (Teleconference)
May 24	Submission of NSBRI Strategic Plan to NASA	N/A
June 10-11	Strategic Plan Review Panel Presentation	Washington, DC
August 12-14	Exercise Simulation Workshop for NSBRI Digital Human Modeling Core	Seattle, WA
September 4-5	External Advisory Council Meeting	Philadelphia, PA
September 26-27	Board of Directors Meeting	Washington, DC

4.0 STRATEGIC PLAN

In response to specific requests from NASA, the NSBRI produced an updated Strategic Plan covering the next five years of the Institute's growth and development. The plan consists of two volumes. The first volume (Appendix A) lays out an Institute-wide strategy, performs a gap analysis between current strategies and resource requirements to meet the Institute's goals and objectives as set forth by NASA, and provides a breakdown of the Institute's budget and allocation of resources. The second volume (Appendix B) contains individual strategic plans for the 11 research teams and the education and public outreach team. The individual Team Strategic Plans also review projects within the teams for their impact, synergistic value with other team projects, contribution to inter-team interactions and collaborations with NASA towards developing countermeasures that address critical questions in risk areas on the Critical Path Roadmap.

The NSBRI Strategic Plan development was a collaborative effort, reflective of the cooperative partnership between NSBRI and JSC. The plan was completed on May 24, 2002, and distributed by NASA for external peer review. The review committee, chaired by Dr. Judith Vaitukaitis, met in Washington on June 10-11, 2002. Their report, "Review of the National Space Biomedical Research Institute Strategic Research Plan," is included in Appendix C.

The report contains critiques and recommendations on 11 topics. Matters pertaining to these topics were addressed in a joint JSC/NSBRI response to NASA HQ. Shortly thereafter, the Acting Director of the Division of Bioastronautics at NASA HQ, along with Dr. Vaitukaitis, wrote a letter to the Associate Administrator of NASA's Office of Biological and Physical Research (OBPR) stating that the peer review of the NSBRI Strategic Plan had been successfully completed. Post-review correspondences are contained in Appendix D.

Since the review, the Institute continues to refine the Strategic Plan and provide augmentation and clarification where needed. For example, Institute Senior Management in consultation with Team Leaders has prepared a draft document concerning policy on team leadership. The document addresses one of the topics raised in the Strategic Plan Review. The policy guidelines on team leadership will be evaluated by the Institute's External Advisory Council and Board of Directors before being forwarded to NASA.

The Institute also is working to address the areas of productivity metrics and bioinformatics. All efforts are being made to coordinate with NASA's efforts in these areas. This is important as NASA develops and implements its strategic plan in Bioastronautics. The ability to monitor progress and integrate data across the NASA/NSBRI interface is critical to the success of the NSBRI mission and its contribution to NASA's Bioastronautics program.

5.0 RESEARCH PROGRAM

Each research team consists of investigator groups working on complementary projects focused on a common theme. Team management and coordination is the responsibility of a program director called a Team Leader while overall scientific direction is the responsibility of the Institute Director and Associate Director. A summary of each NSBRI research project is provided in Appendix E.

The 11 research teams focus on:

- *Bone Loss* – Addressing the loss and weakening of bone during space flight with the inherent fracture risks;
- *Cardiovascular Alterations* – Addressing inflight increase of cardiac dysrhythmias and postflight impairment of the cardiovascular response to orthostatic and exercise stress;
- *Human Performance* – Investigating maintenance of high cognitive performance and vigilance despite environmental stress and sleep disturbances;
- *Immunology, Infection and Hematology* – Addressing immune system impairment and altered susceptibility to infection, increased allergic response, decreased blood volume and postflight anemia;
- *Muscle Alterations and Atrophy* – Focusing on the loss of skeletal muscle mass, strength and endurance that accompanies space flight;
- *Neurobehavioral and Psychosocial Factors* – Investigating methods and tools crews can utilize to cope with stress, isolation and compatibility;

- *Neurovestibular Adaptation* – Addressing the problems of space motion sickness and disorientation during flight and the postflight problems of balance and gaze disorders;
- *Nutrition, Physical Fitness and Rehabilitation* – Developing methods to maintain health and fitness before, during and after space flights;
- *Radiation Effects* – Addressing the problem of increased cancer risk caused by the natural space radiation environment;
- *Smart Medical Systems* – Developing new methods of remote medical diagnosis and treatment; and
- *Technology Development* – Developing instrumentation that will enhance the research of the other teams and transferring the technology to industry for the benefit of society.

During FY 2002, projects from the former Integrated Human Function Team were reassigned to other appropriate research teams. This action was in response to a recommendation from the 2000 NASA Site Visit Report of the National Space Biomedical Research Institute and the External Advisory Council.

5.1 Core Program Scientific and Technical Achievements

Team Program Reports that detail the scientific and technical accomplishments of the Institute's research teams for FY 2002 are provided in Appendix F. *(Note that the pre-publication results presented in this Appendix are intended for NASA internal use only as these results are privileged.)* These reports outline research program accomplishments and research program structure and design.

In January, the investigators met with members of the JSC Space and Life Sciences community, as well as other NASA personnel, at the Institute's retreat in Montgomery, Texas, to present new research findings. Appendix G contains the retreat agenda. Throughout the year, research teams also held retreats to coordinate efforts within their teams and with NASA. At the October meeting of the External Advisory Council, the Smart Medical Systems Team did a "hands on," proof-of-principle demonstration of inter-project synergy. Specifically, ultrasound was used across three team projects to assess physiological adaptation to simulated microgravity, diagnose medical conditions remotely (and with limited bandwidth communications), and apply high-intensity focused acoustic energy for non-invasive surgical treatment. The demonstration of these and other projects brought together NSBRI investigators, former astronauts and NASA flight surgeons. In addition to this meeting, an Exercise Simulation Workshop for Digital Human Modeling was also successful. A detailed report from the workshop is included in Appendix H.

Highlights of the Institute's accomplishments were delivered as part of a Progress Report to NASA in May 2002 (Appendix I). Principal findings in FY 2002 were also summarized in the Director's report to the Board of Directors in September 2002 (Appendix J). Publications and presentations resulting from full or partial NSBRI support are listed in Appendix K.

Despite a reduced expenditure rate of approximately 25% on research awards in FY 2002 because of budget constraints, NSBRI investigators made significant achievements towards countermeasure development as delineated in the Team Strategic Plans (Appendix B). Selected achievements directly relevant to the Institute's mission include the following:

- Advancement of biomedical microsensor technologies for multiple applications in space and on Earth. One project, led by Dr. Babs Soller of the University of Massachusetts Medical School, uses lightweight, low power, portable and non-invasive near infrared sensors and algorithms to determine blood and tissue chemistry. Applications include assessing muscle pH in real time, which could be used in space to optimize exercise countermeasures. The technology has been shown to be accurate, reliable and useful despite skin color differences. Earth-based applications include the ability to non-invasively detect reduced peripheral perfusion in diabetes, a condition affecting 17 million Americans. The investigators are currently working with JSC space medicine personnel to make a flight prototype device.

- Discovery by Dr. Alfred Goldberg and colleagues at Harvard Medical School of Atrogin-1, a muscle-specific protein highly expressed during muscle atrophy that is not only relevant for microgravity adaptation but also for molecular therapeutic approaches to combat muscle atrophy associated with diverse diseases. Their findings were reported in *Proceedings of the National Academy of Science* and in *Nature Medicine*.

- Demonstration by Dr. Mark Bolander of the Mayo Clinic, Rochester, that fracture healing in the hind-limb suspension rat model occurs, but that the quality, quantity and rate of healing are different from normal weight-bearing fractures. This aligns with the Bone Loss Team Strategic Plan to develop ways to prevent fractures and promote strong fracture healing.

- Clinical observations by Dr. Jay Shapiro and collaborators at the National Rehabilitation Hospital that the spinal cord injury model for bone loss induces changes that differ from those of age-related bone loss. The group has also found that the response to bisphosphonates as a countermeasure is more complex than initially thought; the class of drugs attenuates bone loss but does not stop it.

- Development by Dr. Yi-Xian Qin of State University of New York–Stony Brook of a novel portable confocal acoustic imaging device to assess bone mineral density *and* strength in real-time in the space environment. Earth applications include the use of the device to monitor treatment for osteoporosis, which is estimated to affect 10 million individuals.

- Advancement by Dr. Richard Cohen of Massachusetts Institute of Technology, Dr. Janice Meck of JSC and their co-workers on the Cardiovascular Alterations Team, of the midrodrine countermeasure to flight evaluation phase. The project, if selected, will test midodrine as a means to combat postflight orthostatic hypotension. Mechanisms are being investigated that underlie the observation that nearly all females, while only 50% of males, are tilt intolerant following simulated microgravity.

- Progress by Dr. George Brainard and colleagues from Jefferson Medical College at optimizing the light spectrum, especially at 420 nm, to enhance human performance. In addition to light as a countermeasure, members of the Human Performance Factors, Sleep and Chronobiology Team have shown entrainment with food. Their findings are in press for *Genes, Brain and Behavior*.

- Demonstration by Dr. Janet Butel and colleagues at Baylor College of Medicine that in a microgravity model of animals exposed to proton and gamma radiation, there is less ability to clear infection, with increased mortality. Dr. Gerald Sonnenfeld's team at Morehouse School of Medicine has also shown increased morbidity and mortality in gravity-challenged animals. The effects of radiation on immunity speak to possible replacement of gamma globulin as a protective countermeasure. Drs. Butel and Sonnenfeld have published findings this year in *The Lancet* and the *Journal of Allergy and Clinical Immunology*, respectively.

- Identification by Dr. JoAnna Wood of Baylor College of Medicine and colleagues at the University of Texas at Austin, the NIH, and the Australian Antarctic Division of factors that reduce interactions among crew. The team found in their Antarctic study that female leaders consistently feel more isolated than male leaders. Countermeasure development is providing details on the roles various relationships play, how groups react in relation to gender and what factors in crew selection are important for long-duration missions.

- Progress reported in the *Journal of American Medical Association* by Drs. James Carter and Jay Buckey, Jr., of Dartmouth Medical School on using interview data from astronauts and cosmonauts who participated in long-duration missions to develop a computer-based system for self-diagnosis and treatment of psychosocial problems. Dr. Al Holland of JSC is a co-investigator on this project.

- Delivery by Drs. Conrad Wall and Lars Oddsson of a compact, portable balance disturber countermeasure to JSC, where Drs. Jacob Bloomberg and Ajitkumar Mulavara have established normative locomotion data and visual acuity for use as a clinical measure of fitness for return-to-duty and of efficacy of rehabilitative countermeasures. This achievement on the Neurovestibular Adaptation Team is one of several team accomplishments, including a successful Portland Space Vestibular Symposium and an upcoming special issue of the *Journal of Vestibular Research.*

- Completion of a bed-rest study conducted by Dr. Robert Wolfe at the University of Texas Medical Branch. The study finished ahead of schedule and with findings that indicate use of amino-acid supplements maintains protein synthesis and muscle mass but not muscle strength. The role of nutrition in space will be highlighted in the October 2002 special issue of *Nutrition*, which is co-edited by the Team Leader and a co-investigator on the Nutrition, Physical Fitness and Rehabilitation Team. Work on the issue involved 23 members throughout the NSBRI/NASA community and occurred in FY 2002.

- Investigation by Dr. Marcelo Vazquez and Radiation Effects Team collaborators at Brookhaven National Laboratory of 180 of the 498 C57B1/6 male mice exposed to acute doses of 0.15 to 4.8 Gy Fe ions and gamma radiation during the last NASA run (BNL-8, April 2002). The animals are being monitored to detect memory function alterations and changes in hippocampal biochemistry. These investigators have recently shown that doses as low as 0.25 Gy of heavy ions are able to up-regulate p53 within hours in human neural precursor cells and rodent glial progenitor cells (CG4). As a countermeasure, bFGF is able to protect apoptosis induction in CG4.

- Use of a new software program, SpaceDOCK, to evaluate performance in awake and sleep-deprived subjects undergoing simultaneous brain fMRI and diffuse optical tomography imaging. Dr. Jeffrey Sutton, colleagues at Massachusetts General Hospital, and a NASA flight surgeon, developed this software program. The results reveal objective measures of brain function obtained by a portable, non-invasive means suitable for neuroimaging in the space environment. The technology is being used to monitor neurological disorders in children and adults, including the assessment of stroke, a condition that is experienced by 750,000 Americans per year.

- Testing of a miniature time-of-flight mass spectrometer developed at The Johns Hopkins University Applied Physics Laboratory by Dr. Richard Potember and colleagues. The portable configuration has great potential for onboard analysis of chemical and biological substances, yielding state-of-the-art technology for autonomous scientific studies, and countermeasure assessment. The device also has relevance to homeland security.

5.2 NASA/NSBRI Space Medicine Achievements

NASA's budget to the NSBRI specifies funding for Advanced Medical Care Systems, where the NSBRI is to collaborate with JSC personnel on joint projects having direct operational need. In FY 2002, the first project proposal in this area was completed, outlining the creation of a Medical Operational Support Team (MOST). The MOST project brings together the NSBRI's clinical expertise and resources to refine an onsite space-adapted human patient simulator for training flight medical personnel. Dr. Harold Doerr from Baylor College of Medicine is the principal investigator. The project will be funded in October 2002. Project details are in Appendix L.

The Institute participated in the NASA Risk Mitigation Collaborative Group, headed by Dr. Jeffrey Davis, the new Director of the Space and Life Sciences Directorate at JSC, and by Dr. Guy Fogleman, the Acting Director of the Division of Bioastronautics at NASA HQ. The group examines, in part, biomedical risk-reduction strategies for different mission scenarios, which include multiple factors, such as risk type, consequences, likelihood, current countermeasure readiness, and crew health, safety and performance requirements. NASA participants include Chief Scientist Dr. Shannon Lucid, Chief Health and Medical Officer Dr. Richard Williams, and leaders from OBPR, the Office of Space Flight, and JSC. The activities of this group help determine the research priorities on the Critical Path Roadmap, and hence of the NSBRI, whose research activities must be coordinated with NASA priorities and needs.

At the External Advisory Council meeting in March, Dr. Jonathan Clarke, a JSC flight surgeon, addressed the Team Leaders and Council regarding space- and evidence-based medicine. At the September Council meeting, Ms. Mary Kicza, NASA Associate Administrator for OBPR, gave an address discussing the OBPR Enterprise and the role of the NSBRI within NASA and the Bioastronautics Program.

To help "fast track" meritorious projects towards space medicine, as well as commercial applications, a Committee on Research and Technology Transfer was established. Reporting to the Director, the committee consists of representatives from the Team Leaders, Industry Forum, User Panel, External Advisory Council, Board of Scientific Counselors, Board of Directors, NASA medical operations and venture capital programs.

5.3 Flight Projects

Five NSBRI flight proposals began the NASA evaluation process in FY 2002. A principal achievement of the Cardiovascular Alterations Team this year was the advancement to flight evaluation and definition phase of the first NSBRI proposal in this area. The proposed countermeasure is midodrine as a means to reduce postflight orthostatic hypotension. This accomplishment was a team effort that included (a) animal studies that demonstrated that hind-limb suspension leads to venous and arteriolar hyporesponsiveness, and in particular, to alpha-sympathetic stimulation, (b) computer simulations that demonstrated that increasing venous and arterial tone would be an effective countermeasure, and (c) human studies that demonstrated that a single, small dose of midodrine was highly effective in increasing tolerance to tilt after 16 days of bed rest. The human studies also demonstrated that cardiovascular system identification measures obtained prior to bed rest can identify those individuals at greatest risk for orthostatic hypotension following bed rest.

Midodrine has been used under a supplemental medical objective to date on one astronaut with a history of severe postflight orthostatic hypotension. This individual took a single dose of midodrine post flight and did not have any symptoms of orthostatic hypotension.

5.4 Research Program Partnerships

In addition to the core intramural research program, the NSBRI has developed a joint program with the National Institute on Deafness and Other Communication Disorders that jointly funds six competitively-awarded extramural grants related to the dynamic adaptation of central vestibular function, an area of common interest. Appendix M gives project information for this five-year joint program initiated in FY 1999.

The Institute also has international research affiliations with the Institute of Aerospace Medicine of the German Aerospace Center (agreement signed in Cologne on January 21, 1998); the Politecnico di Milano (framework agreement signed in Milan on April 29, 1999); the Institute for Space Physiology and Medicine (MEDES) (agreement signed in Paris on June 16, 1999); and the Institute for Biomedical Problems, Moscow (joint projects by contract in 1999 and 2000).

In FY 2002, there were valuable international exchanges. A partial list includes a visit by principal investigators from three NSBRI teams to Germany to discuss ground-based research efforts and a joint NASA/NSBRI trip to Scotland to discuss collaborative opportunities in the space life sciences with members of the Scottish Enterprises Forum.

5.5 Research Announcement

On October 31, 2001, NASA released solicitation NRA 01-OBPR-07 on behalf of three programs, including the NSBRI (Appendix N). Fifty-one proposals were received by the NSBRI and subsequently underwent peer review along with the other NASA proposals. Twenty-five proposals were in the competitive range (a score of 70 or greater out of 100). Four proposals were transferred to NSBRI from the NASA portion of the solicitation. Representatives of NSBRI Senior Management attended the NASA selection meeting. All 29 proposals were reviewed for programmatic relevance by appropriate NSBRI Team Leaders. A combination of peer-review score and relevancy categorized the proposals, which were then prioritized by the External Advisory Council for funding. Selection of new proposals will depend upon the FY 2003 budget.

In addition to research proposals submitted in response to the joint NASA/NSBRI solicitation, Morehouse School of Medicine submitted a proposal for a fellowship program. The establishment of an Institute fellowship program is a priority. The FY 2003 budget will determine if this program can be launched. The Morehouse proposal is being forwarded to the Institute's Board of Scientific Counselors for review.

6.0 EDUCATION AND PUBLIC OUTREACH PROGRAM

The Education and Public Outreach Team supports the NSBRI's mission by ensuring open involvement in the Institute's activities by the scientific community, industry and the public, and by ensuring a robust exchange with NASA. Activities target multiple and diverse populations and aim to:

- inform a large community about NSBRI activities;
- attract young people to careers in science, engineering and medicine;
- promote excellence and innovation in America's science education system;
- increase scientific literacy among teachers, students, their families and the public; and
- create public awareness and appreciation of the opportunities and benefits of NSBRI's space biomedical research.

Through a variety of innovative programs, space research activities and discoveries are transferred to teachers at levels K-undergraduate, students and the public.

The National Research Council's Committee on Undergraduate Education has challenged the scientific community and institutions of higher learning to provide opportunities for professional collaborations that create innovative inquiry-based, multidisciplinary courses and instructional materials, to use the most sophisticated multimedia capabilities to disseminate new materials, and to develop a seamless pipeline of minority-group science students. The NSBRI has embedded this challenge in its education and public outreach mission.

Initially, education and public outreach activities were led by teams at three consortium institutions: Morehouse School of Medicine, Texas A&M University and Baylor College of Medicine. In response to a NSBRI Special Program Announcement issued in FY 2000, seven projects were selected for funding to form the current Education and Public Outreach Team. In FY 2002, the team has emerged as a national force by making presentations at national meetings and collaborating with NASA's OBPR Education and Outreach group. The combined team activities have reached 1,000 teachers and 100,000 students. Beyond the specific goals of each project, the educators have a follow-on goal to produce at least one paper and presentation per year. The NSBRI's emphasis on education and public outreach is consistent with the NASA Administrator's priorities in education.

Appendix O gives the current NSBRI Education and Public Outreach project summaries. The Team Progress Report appears in Appendix P. The progress correlates well with the strategic plan for the team (Appendix B). A brief outline of each project follows.

Baylor College of Medicine
Baylor College of Medicine is producing and disseminating a series of teacher activity guides, *From Outerspace to Innerspace*, that make NSBRI research areas relevant to young students and allow students to investigate these topics. The guides are designed for grades 4-6.

Massachusetts Institute of Technology
The Massachusetts Institute of Technology is developing and evaluating two graduate-level curricula and adapting these materials for undergraduate-level courses, to educate a generation of scholars in space life sciences.

Morehouse School of Medicine
Morehouse School of Medicine is providing teacher professional development and student educational opportunities by writing secondary-level problem-based cases, conducting a summer research program and maintaining an NSBRI film archive.

Mount Sinai School of Medicine
Mount Sinai School of Medicine investigators are working with teachers and students in the New York City area to develop a stand-alone curriculum that will use space biomedical research as a theme to teach math and science.

Rice University (in collaboration with The University of Texas Medical Branch)
Led by researchers and educators at Rice University and The University of Texas Medical Branch, high-school students spend a summer working in research laboratories and exploring the life of a research scientist. The project also features a professional development opportunity for secondary-school teachers that enhances their knowledge of space biomedicine.

Texas A&M University
Through the Teacher Academy, Texas A&M University is establishing a group of highly-trained teachers recruited from across the nation. These Master Teachers will take what they learn about

implementing space-based science curriculum and pass their skills and knowledge on to peers in their own schools and regions.

University of Washington
Students in the University of Washington's Technical Communications program will have the opportunity to interview NSBRI researchers as part of a science-writing course. Articles appear in the magazine, *Northwest Science & Technology*.

7.0 MANAGEMENT

The NSBRI management structure was strengthened in FY 2002. Information on the management structure is included in the Strategic Plan (Appendix A). In addition, the Institute underwent a successful audit by the Department of Health and Human Services, Office of Inspector General. The auditors complimented the NSBRI on its excellent records, business practices and compliance with rules and policies.

7.1 Key Personnel

In November 2001, Dr. Jeffrey Sutton was appointed Institute Director. Dr. Laurence R. Young became Senior Advisor to the Director. The roles of Dr. Bobby R. Alford, Chairman of the Board and Chief Executive Officer, and Dr. Ronald J. White, Associate Director, did not change.

During FY 2002, the Team Leaders continued to function as the research or education and outreach "program directors." Dr. Harry Charles assumed the leadership of the Technology Development Team, with Dr. Jay Buckey, Jr., filling the position of Associate Team Leader. Dr. Lawrence Crum became the Acting Team Leader for the Smart Medical Systems Team, replacing Dr. Sutton, who became the Director.

One Principal Investigator changed in FY 2002. On the Technology Development Team, Dr. Isaac Bankman of The Johns Hopkins Applied Physics Laboratory replaced Dr. Paul Bottomley as the Principal Investigator for "Development of a Space Qualifiable MRI System."

7.2 Board of Directors

The current membership of the NSBRI Board of Directors appears in Table 2. Due to the postponement of the second FY 2001 Board meeting slated for September 2001, the Board convened three times in FY 2002. Two meetings were held in Houston and one in Washington, D.C. Five new members were added, either filling a vacancy or replacing a member who stepped down. New members included Dr. James B. Bassingthwaighte, University of Washington; Dr. Susanne E. Churchill, Harvard Medical School; Dr. Theresa W. Fossum, Texas A&M University; Dr. Alice P. Gast, Massachusetts Institute of Technology; and Dr. Kenneth I. Shine, Rand Corporation. Board members stepping down included Aaron Cohen, Texas A&M University, and Dr. Dennis Kasper, Harvard Medical School. Two members moved to Emeritus status – Dr. J. David Litster, Massachusetts Institute of Technology and Dr. Torsten N. Wiesel, Rockefeller University. Emeritus Member, Dr. Francis D. Moore passed away.

7.3 External Advisory Council

The current membership of the NSBRI External Advisory Council appears in Table 3. Due to the postponement of its second FY 2001 meeting scheduled for September 13-14, 2001, the Council met three times in FY 2002. The meetings occurred in Houston, San Jose and Philadelphia. Dr. Robert Moore, University of Pittsburgh, and Dr. Warren Sinclair, National

Council on Radiation Protection and Management, stepped down from the Council. Two new members joined – Dr. Theodore Berger, University of Southern California, and Dr. Eileen Hasser, University of Missouri-Columbia. Team Leaders submitted nominations to Senior Management for new members in disciplines not represented or underrepresented on the current Council. These positions will be filled in FY 2003.

Table 2. **NSBRI BOARD OF DIRECTORS**

Bobby R. Alford, M.D. (Chairman) Baylor College of Medicine	**William L. Allen** National Geographic Magazine	**Carl W. Anderson, Ph.D.** Brookhaven National Laboratory
Thomas E. Andreoli, M.D. University of Arkansas College of Medicine	**James B. Bassingthwaighte, M.D., Ph.D.** University of Washington	**Joseph V. Bonventre, M.D., Ph.D.** Harvard-MIT Division of Health Sciences and Technology Harvard Medical School
James F. Buchli United Space Alliance	**Susanne E. Churchill, Ph.D.** Harvard Medical School	**Michael E. DeBakey, M.D.** Baylor College of Medicine
Richard E. Ewing, Ph.D. Texas A&M University	**Martin J. Fettman, D.V.M., Ph.D.** *(ex officio)* Colorado State University	**Alfred P. Fishman, M.D.** University of Pennsylvania Health System
Theresa W. Fossum, D.V.M., Ph.D. Texas A&M University	**Alice P. Gast, Ph.D.** Massachusetts Institute of Technology	**Glen N. Gaulton, Ph.D.** University of Pennsylvania School of Medicine
Martha L. Gray, Ph.D. MIT-Harvard Division of Health Sciences and Technology Massachusetts Institute of Technology	**E. Nigel Harris, M.D.** Morehouse School of Medicine	**Richard J. Johns, M.D.** The Johns Hopkins University School of Medicine
Joseph P. Kerwin, M.D. Wyle Laboratories	**Steven Knapp, Ph.D.** The Johns Hopkins University	**Jordan Konisky, Ph.D.** Rice University
Alvin L. Kwiram, Ph.D. University of Washington	**J. David Litster, Ph.D.** (Emeritus) Massachusetts Institute of Technology	**Larry McIntire, Ph.D.** Rice University
James W. Patrick, Ph.D. Baylor College of Medicine	**Peter Paul, Ph.D.** Brookhaven National Laboratory	**Mary R. Rifkin, Ph.D.** Mount Sinai School of Medicine
Alan L. Schiller, M.D. Mount Sinai School of Medicine	**Kenneth I. Shine, M.D.** Rand Corporation	**Walter W. Sullivan, Ph.D.** Morehouse School of Medicine
Jeffrey P. Sutton, M.D., Ph.D. *(ex officio)* Institute Director	**W. Dalton Tomlin** (Secretary/Treasurer) Baylor College of Medicine	**Arnold N. Weinberg, M.D.** (Emeritus) Massachusetts Institute of Technology
Torsten N. Wiesel, M.D. (Emeritus) Rockefeller University	**I. Dodd Wilson, M.D.** University of Arkansas for Medical Sciences	

Table 3. **NSBRI EXTERNAL ADVISORY COUNCIL**

Martin J. Fettman, D.V.M., Ph.D. (Chairman) Associate Dean for the Professional Veterinary Medical Program Colorado State University	**Leon Alkalai, Ph.D.** Director Center for Integrated Space Microsystems Jet Propulsion Laboratory	**J. A. Anderson, Ph.D.** Professor of Cognitive and Linguistic Sciences Brown University
Ruth Benca, M.D., Ph.D. Professor and Associate Chair Department of Psychiatry University of Wisconsin Medical School	**Theodore W. Berger, Ph.D.** Professor, Biomedical Engineering University of Southern California	**Hal E. Broxmeyer, Ph.D.** Scientific Director Walther Oncology Center Indiana University School of Medicine
Thomas F. Budinger, M.D., Ph.D. Professor and Chair Department of Bioengineering Lawrence Berkeley National Laboratory	**Dennis S. Charney, M.D.** Chief of Mood and Anxiety Disorders Research Program National Institute of Mental Health	**Victor A. Convertino, Ph.D.** Research Physiologist U.S. Army Institute of Surgical Research
Thomas A. Fleisher, M.D. Chief, Department of Laboratory Medicine National Institutes of Health	**Michael N. Gould, Ph.D.** Professor of Human Oncology University of Wisconsin Medical School	**Eileen M. Hasser, Ph.D.** Professor, Veterinary Biomedical Sciences University of Missouri-Columbia
Amy Kronenberg, Sc.D. Group Leader Radiation Biology and Environmental Toxicology Lawrence Berkeley National Laboratory	**Charles B. Nemeroff, M.D., Ph.D.** Professor and Chairman Department of Psychiatry Emory University	**Lawrence A. Palinkas, Ph.D.** Professor Family and Preventive Medicine University of California, San Diego
Danny A. Riley, Ph.D. Professor of Cell Biology, Neurobiology and Anatomy Medical College of Wisconsin	**Irwin H. Rosenberg, M.D.** Professor of Medicine and Nutrition Tufts University	**M. Rhea Seddon, M.D.** Assistant Chief Medical Officer Vanderbilt University Medical Center
Jeffrey P. Sutton, M.D., Ph.D. (*ex officio*) Institute Director	**Ronald J. White, Ph.D.** (*ex officio*) Institute Associate Director	**Thomas J. Wronski, Ph.D.** Professor of Physiological Sciences University of Florida
Bill J. Yates, Ph.D. Associate Professor of Otolaryngology and Neuroscience University of Pittsburgh	**F. Eugene Yates, M.D.** Professor of Medicine University of California, Los Angeles	

7.4 Board of Scientific Counselors

The Board of Scientific Counselors did not change. Dr. Hal Broxmeyer is serving on the Institute's Committee on Research and Technology Transfer.

7.5 User Panel

The User Panel membership was stable. Dr. Owen Garriott agreed to represent the User Panel on the Institute's Committee on Research and Technology Transfer.

8.0 SUPPORTING PROGRAMS

Three programs, Industry Forum, Data Archive, and Communications and Outreach, support the research and educational activities of the Institute. A summary of each program's activities in FY 2002 follows.

8.1 Industry Forum

During FY 2002, the Industry Forum membership (Table 4) remained stable. The Forum continues to be interested and involved in educating the Institute's investigators in the management and protection of intellectual property. The group is seeking additional representation from the biotechnology and pharmaceutical industries. InDyne, Inc., continued to support the nsbri.com Web site containing the Industry Forum Web pages, and The Boeing Company supported the Institute by providing graphic design for NSBRI public service ads and for the NSBRI exhibit. Dr. Joseph Kerwin of Wyle Laboratories and Mark Wilson of The Boeing Company will represent the Forum on the Institute's Committee on Research and Technology Transfer.

Table 4. NSBRI INDUSTRY FORUM MEMBERSHIP

The Boeing Company
The Charles Stark Draper Laboratory
InDyne, Inc.
Lockheed Martin Astronautics
MBI International
Payload Systems, Inc.
Raytheon Technical Services Company
Roche Laboratories, Inc.
SGI
Southwestern Bell
United Space Alliance
Veridian
Wyle Laboratories

8.2 NSBRI Data Archive

Established in FY 1998, the goal of the Web-based Data Archive system is to maintain an appropriate, accessible archive of the data collected through NSBRI research projects. During FY 2002, the Data Archive group assisted NSBRI HQ in deployment of the Institute's Electronic Proposal Submission System. The system was utilized for the first time for proposals in response to the NSBRI portion of NASA's NRA 01-OBPR-07 and will be used for all future NSBRI research opportunities. The group brought on a Ph.D. to assist investigators in uploading data products. Additional projects include work with NSBRI HQ to develop information systems for NSBRI administrative data and the development of the Annual Project Report System to be launched in FY 2003.

8.3 Communications and Outreach

The NSBRI Communications and Outreach Office develops and implements diverse communications and outreach initiatives contributing to the successful accomplishment of the NSBRI mission. The program identifies and targets messages to the NSBRI's key publics – the public, the scientific community, industry, consortium members and NASA. Key activities in FY 2002 included the continuation of a research-based news release program, the collaboration with public affairs offices at numerous funded institutions to maximize news outreach related to the FY 2002 NSBRI research program, meetings with JSC public affairs to increase awareness of NSBRI activities, and an increase in media inquiries and news clippings related to NSBRI's space-related research. In FY 2002, the Institute received 114 media inquiries compared to 94 inquiries received in FY 2001. Similarly, 204 newspaper, magazine or on-line articles mentioned NSBRI, up from 121 the previous year. Since the NSBRI does not utilize a news clipping service, the clipping figure is based on material received from reporters and other sources. Key NSBRI research feature articles appeared in the New York Times, Los Angeles Times, Highlights for Children, Dallas Morning News, Science, Nature, Miami Herald, Space.com, Florida Today, Houston Chronicle, Fort Worth Star-Telegram and Seattle Times.

9.0 INSTITUTE DIVERSITY AND SCIENTIFIC COMMUNITY OUTREACH

The NSBRI continued its efforts to provide research announcements to a wide and diverse group of potential investigators. Interested researchers can register on-line at www.nsbri.org for NSBRI E-News announcements. The service had 386 subscribers at the end of FY 2002. In addition, a postcard mailing announcing NSBRI's participation in NRA 01-OBPR-07 utilized NASA's mailing list for announcements related to the life sciences. This list is the backbone of all postcard mailings used to inform the community of NSBRI research announcements.

This year, as part of its outreach program, four minority undergraduate students participated in the NSBRI Summer Research Program held at Morehouse School of Medicine. Participants came from three different institutions, Morehouse College, Spelman College and University of South Florida, and were selected from a national pool of 63 applicants.

Education and Public Outreach projects at Baylor College of Medicine, Mount Sinai School of Medicine, Rice University and The University of Texas Medical Branch include underrepresented minority students and teachers of those student groups. Summer programs for high school students provided research experiences for underrepresented minority students. While these programs do not exclude non-minority applicants, the programs draw applicants from school districts that have large African-American, Hispanic and Puerto Rican populations. Field testing of new NSBRI curriculum materials for elementary and secondary teachers occurred in areas with high numbers of African-American, Hispanic and Puerto Rican students.

The Institute continued its summer internship program in cooperation with JSC. The program provides the opportunity for undergraduate, graduate or medical students to join ongoing project activities at the JSC. Appendix Q contains a list of the FY 2002 participants.

Institute investigators, Team Leaders and management continued to reach out to the scientific community through presentations made at symposia and meetings. A partial list of these presentations is provided in Appendix K. A sampling of meetings involving NSBRI participants include: the Space Technology and Applications International Forum – STAIF 2002, the International Space Life Sciences Working Group Meeting, the International Workshop on Behavior and Performance, the Medicine and Mobility Congress, and the 18th National Space Symposium. Preliminary discussions between NASA, NSBRI and the British National Space Centre/Rutherford Appleton Laboratory, University College London, and the British Vice Consul for Science and Technology were held in Houston in May 2002. Participants discussed opportunities for possible future research collaboration.

10.0 SPECIAL PROJECTS

The Cooperative Agreement Management Plan between NASA and the NSBRI enables the partners to undertake special projects outside of the core-funding envelope of the NSBRI. During FY 2002, four new projects were initiated and 12 projects were continued. Detailed information on the four new projects and two projects that experienced change is provided.

Project 97-3, *National Space Biomedical Research Institute Visiting Scientist/Research Associate Program*, continues to enable young and established university-based researchers an opportunity to work side-by-side with government employees in JSC laboratories. Table 5 provides a list of the participants in this program and other projects relating to Bioastronautics positions at JSC.

Project 01-3, *Manager, ISS Internal Volume Configuration Working Group*, continues to provide an academically qualified and experienced Internal Volume Configuration Working Group project lead to the Bioastronautics Office at JSC. The person in this position is responsible for researching and analyzing systems engineering, human/machine interaction, configuration management, and SHF/habitability control requirements and techniques and their effects on habitability. To carry out this project, the NSBRI, in cooperation with JSC SHFHO management, hired Todd Hellner to replace Laura Duvall in FY 2002.

Project 02-2, *Space Human Factors (SHFE) Human Factors Data Base Development Project*, provides an academically qualified and experienced human factors practitioner and science facilities leader to the Habitability and Human Factors Office. The person in this position is responsible for coordinating across the scientific community and for performing human factors research and analysis to structure the human factors database, to determine relationships between knowledge captured and the Bioastronautics Critical Path Roadmap and existing human-systems design standards, and to develop an updated set of human factors standards that will be useful to the world-wide community, in particular for the development of space missions. NSBRI, in cooperation with the JSC Habitability and Human Factors Office, hired Dr. Frances E. Mount as an independent contractor for this project in FY 2002.

Table 5. VISITING SCIENTIST/RESEARCH ASSOCIATE PROGRAM – FY 2002

Name	Current Position	JSC Sponsor	Period
Jennifer Blume, Ph.D.	Assistant Professor	Thomas Rathjen	1/4/00 -
Tatiana Christian	Senior Engineer	Thomas Rathjen	5/22/00 -
Johnny Conkin, Ph.D.	Assistant Professor	Michael Gernhardt, Ph.D.	6/1/98 -
Dominick D'Aunno, M.D.	Assistant Professor	Janice Meck, Ph.D.	11/1/97 -
Laura E. Duvall	Lead Engineer	Thomas Rathjen *(see Project 01-03)*	9/25/00 – 10/13/01
John N. Evanoff, Ph.D.	Assistant Professor	William Paloski, Ph.D.	7/23/01-
Philip Foster, M.D., Ph.D.	Assistant Professor	Michael Gernhardt, Ph.D.	10/19/98 -
Wendy Garner, Ph.D.	Assistant Professor	Janice Meck, Ph.D.	11/24/97 -
Todd Hellner	Lead Engineer	Thomas Rathjen *(see Project 01-3)*	9/24/01
Meena Husein	Manager, Data Administration	James Logan, Ph.D.	6/1/01 -
Ralph Krog	Manager, Data Administration	James Logan, Ph.D.	9/17/01 -
Lawrence H. Kuznetz, Ph.D.	Assistant Professor	William Paloski, Ph.D.	8/20/01 -
Giles Maule, Ph.D.	Research Associate	Clarence Sams, Ph.D. *(see Project 97-3)*	1/24/00 – 3/1/02
Ajitkumar Mulavara, Ph.D.	Assistant Professor	Jacob Bloomberg, Ph.D.	8/20/01 -
John B. Peacock, Ph.D.	Associate Professor	Thomas Rathjen	10/30/00 -
Michele Perchonok, Ph.D.	Assistant Professor	Thomas Rathjen	9/5/00 -
Lanny Rudner	Student Intern	Donald Hagan, Ph.D. *(see Project 02-4)*	6/17/02 -
Sudhakar Rajulu, Ph.D.	Assistant Professor	Thomas Rathjen	4/17/00 -
Lawrence Spector	Lead Engineer	Thomas Rathjen	9/25/00 -
Cary J. Zeitlin, Ph.D.	Co-Investigator	Francis Cucinotta, Ph.D. *(see Project 02-3)*	5/13/02 -

Project 02-3, *Experimental Charged Particle Detector Radiation Project*, provides an internationally known expert in the area of experimental charged-particle detection to work with the JSC Office of Radiation Health. Duties include providing leadership in designing, trouble-shooting, calibrating and analyzing radiation detectors that measure the charge and energy of heavy ions and protons in Mars orbit, in Earth-Mars transit, and on the International Space Station. NSBRI, in cooperation with JSC management, hired Dr. Cary J. Zeitlin in FY 2002 and also appointed him as Co-Principal Investigator of the Experimental Charged Particle Detector Radiation (MARIE) Project.

Project 02-4, *Evaluation of In-Flight Daily Exercise of ISS Crewmembers*, provides a student intern to evaluate ISS crewmember in-flight exercise data for exercise mode, frequency, duration and intensity to determine the total amount of power expended per week. The power data will be correlated with the preflight and postflight changes in bone mineral density, muscle size and strength, orthostatic tolerance, and changes in aerobic capacity to determine the efficacy of the exercise prescription. The second specific task is to perform data analysis on the development of the Artificial Gravity Project. To carry out this project, the NSBRI hired Lanny Rudner, a first-year medical student at Baylor College of Medicine, in FY 2002.

Project 02-5, *Experimental Radiation Biologist*, provides an experimental radiation biologist to work with the JSC Radiation Biophysics Laboratory and the Space Radiation Health Project (SRHP). The person in this position will provide leadership in developing new methods in cytogenetics, biomarkers and studies of genomic instability. Duties include developing protocols for understanding the origin and outcome of clonal aberrations found in blood samples, supporting the biodosimetry activities ongoing in the Radiation Biophysics Laboratory and coordinating the research integration efforts of the SRHP. Recruiting efforts were initiated for this position at the end of FY 2002.

11.0 FUTURE DIRECTIONS

As the Institute moves forward in partnership with NASA to develop countermeasures to mitigate biomedical risks and ensure the health and safety of astronauts on long-duration missions, it will be necessary to increase collaborative efforts between the NSBRI and NASA. The research teams will require increased presence of medical operations personnel, NASA engineers and flight surgeons. Productivity metrics need to be introduced, based in part on outcomes models to meet requirements for various length missions. To this end, a driving force for NSBRI countermeasure development should be NASA's increasing emphasis on the Clinical Status Examination and its associated requirements for astronaut health and safety.

NASA is currently writing its Strategic Plan for Bioastronautics, and it will be important that the Institute's Strategic Plan be consistent and complementary to the NASA plan. Moreover, both volumes of the NSBRI Strategic Plan will be presented to the External Advisory Council for critiques. The Council will require added members, and the Board of Scientific Counselors will be reconstituted. The User Panel will be engaged as the Institute moves forward with developments at higher countermeasure readiness levels. The Committee on Research and Technology Transfer, along with the Industry Forum, will also be more active in supporting the applications of new discoveries and technologies for space and Earth.

The tactical implementation plan will depend on the actual FY 2003 budget. It is a priority to support the ongoing research program, as well as to fund several new proposals and launch the fellowship program. Approximately one-half of the research projects will turn over in FY 2004.

It is critical that the solicitation for FY 2004, which will likely be released in coordination with NASA in early 2003, be targeted to ensure the success of the Team Strategic Plans.

The terms of the Team Leaders will expire in FY 2004, and it is important that the Team Leader Guidelines be completed, reviewed through the External Advisory Council and Board of Directors and then forwarded to NASA, to bring closure to one of the topics raised in the Review of the National Space Biomedical Research Institute Strategic Research Plan. A special call for Team Leader applications will likely accompany the 2003 research proposal solicitation.

In addition to Team Leader Guidelines, several other documents and policies will be developed and/or clarified. For example, it will be helpful for investigators to know the various pathways to flight for their scientific and technical projects.

The Institute will continue to emphasize education and public outreach, communications, bioinformatics, data archiving, integration of its activities and diversity. With a commitment from NASA of a stable budget and the possession of a bold forward-looking vision with the people and resources to meet the Institute's goals and objectives, FY 2003 holds great promise for the NSBRI and its NASA partner in space life sciences and countermeasure development.

Appendix A

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

STRATEGIC PLAN

Volume I

May 24, 2002

TABLE OF CONTENTS

VOLUME II

1. EXECUTIVE SUMMARY

The National Space Biomedical Research Institute (NSBRI) is a unique, non-profit scientific partnership established in 1997 following competitive selection by the National Aeronautics and Space Administration (NASA). Within its first five years, and in collaboration with the Johnson Space Center (JSC), the NSBRI has made enormous progress in initiating and implementing strategies to meet its mission, goals and objectives as set forth in its Cooperative Agreement Notice.

The NSBRI has engaged and coordinated outstanding academic, industrial and government researchers and educators in a team-based effort to develop countermeasures to reduce the significant health risks associated with human space travel. It has leveraged and added value to the resources of the nation's leading biomedical research institutions, NASA facilities and industry. Looking forward, the NSBRI is well positioned to efficiently and effectively conduct ground and critical in-flight studies of high relevance and impact for NASA, with tangible benefits for the American people.

Over the next five years, the NSBRI plans to build on its strengths and fill gaps in three interconnected Strategic Programs that allow its mission to be achieved. These Programs are the:

- Countermeasure Research Program
- Education, Training and Outreach Program
- Cooperative Research and Development Program

In this Strategic Plan, current strategies, identified gaps and proposed modifications, and the resource requirements to maintain momentum in a changing program environment at NASA are described for each of the Programs. Program integration, combined with an efficient administrative infrastructure, yields a bold plan that is science driven and in accord with the President's Management Agenda.

This Plan lays out the requirements for a baseline program, as well as an augmentation plan to fully implement the Institute's strategies for the next five years.

2. INTRODUCTION

2.1. PURPOSE

The purpose of this document is to present the strategic plan and associated organizational structure that the NSBRI will utilize to achieve the defined mission and objectives provided by NASA. Much of the information regarding the background and establishment of the NSBRI by NASA has been provided in other documentation and will not be repeated in this Strategic Plan.

This Strategic Plan is presented in two volumes. Volume I (this volume) begins with an Introduction (Section 2) that provides the Institute's NASA-defined mission and objectives, and the organizational structure adopted to implement these through three Strategic Programs: Countermeasure Research; Education, Training and Outreach; and Cooperative Research and Development. These programs are described in Sections 3 to 5. Each program is presented in a similar way, using four subsections: Goals and Objectives; Current Strategies; Gaps and Modifications; and Resource Requirements. Section 6 provides the administrative infrastructure and total budget required to implement the Strategic Programs and assures that they form a single cohesive plan. This plan is science driven and is in accord with the President's Management Agenda. Following this plan will ensure continued success of the Institute for the next five years.

Volume II of the Strategic Plan provides an in-depth analysis of the current and future strategic programs of the 12 current NSBRI teams, including their goals, objectives, mutual interactions and schedules.[1]

2.2. MISSION

In June 1996, NASA released a Cooperative Agreement Notice (CAN) inviting proposals to establish a National Space Biomedical Research Institute (9-CAN-96-01). This CAN stated that:

> **The Mission of the Institute will be to lead a National effort for accomplishing the integrated, critical path, biomedical research necessary to support the long term human presence, development, and exploration of space and to enhance life on Earth by applying the resultant advances in human knowledge and technology acquired through living and working in space.** The Institute will be <u>the</u> focal point of NASA sponsored space biomedical research.

This statement has never been amended by NASA and remains the mission of the National Space Biomedical Research Institute.

2.3. COMPETITIVE SELECTION

The institute, now called the NSBRI (or "Institute"), was selected by NASA in March 1997 following a two-phase, competitive review of proposals received in response to the CAN. Seven academic institutions (Baylor College of Medicine, Harvard Medical School, The Johns Hopkins University School of Medicine and Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School

[1] A separate Progress Report provides additional information related to the Institute's activities, including current membership in NSBRI's boards and advisory panels. It also summarizes progress of the NSBRI since the Site Visit Review Report of the National Space Biomedical Research Institute in 2000.

of Medicine, Rice University and Texas A&M University) made up the initial consortium governing the NSBRI.[2] Baylor College of Medicine is the lead institution and houses the NSBRI Headquarters.

On April 14, 1997, the NSBRI became chartered in the State of Texas as a not-for-profit 501(c)3 corporation. After a 60-day definition period, on May 29, 1997, NASA and the NSBRI signed a Cooperative Agreement (NCC-9-58) and Cooperative Agreement Management Plan with NASA JSC.

2.4. OBJECTIVES

The CAN specified eight objectives that the NSBRI should fulfill in order to accomplish its mission. These are listed below. For ease of reference in this document, these objectives are numbered and given a brief description.

Objective 1. **Knowledge Integration and Risk Evaluation**
Integrate the knowledge base relevant to the biomedical response of humans in space, including understanding the risk levels associated with this knowledge base, and to recommend acceptable risk levels for long-duration missions. Risk levels in this context relate to the medical risk to the human participants as a result of deleterious effects of space flight, as well as to the subsequent risk to overall mission success.

Objective 2. **Countermeasure Development**
Develop and manage the implementation of a research plan that will lead to the required knowledge and technologies (across all biomedical and associated technological disciplines) for long-duration human space flight, including specific countermeasures where required.

Objective 3. **Science Management Plan**
Develop and provide a science management process that will support the overall human in space biomedical research program.

Objective 4. **Scientific Knowledge Dissemination**
Ensure the dissemination of advances in knowledge resulting from this program to the scientific community.

Objective 5. **Science Community Access**
Facilitate science community access to the NASA space infrastructure associated with biomedical research.

Objective 6. **Industry Partnerships**
Promote and provide active collaboration with for-profit entities to ensure that developed technologies are transferred to the private sector.

Objective 7. **Research Optimization**
Implement a "best value" research program for the available resources.

Objective 8. **Education and Public Outreach**
Conduct educational and outreach programs consistent with the Institute's mission.

---

[2] In 2000, the consortium membership expanded from seven to twelve institutions following a competitive review process. The additional members are Brookhaven National Laboratory, Mount Sinai School of Medicine, University of Arkansas for Medical Sciences, University of Pennsylvania Health System and University of Washington. See ***Guideline 8*** (Section 2.5).

2.5. AUGMENTATION GUIDELINES

In March 1999, as NASA and the NSBRI prepared an augmentation plan that NASA would submit to Congress as part of the President's budget plan for FY 2001, NASA provided guidelines to the NSBRI concerning expected growth and strategic modifications if the augmentation were approved. These guidelines included:

Guideline 1. **Original Team Growth**
Strengthening the original research teams by increasing the number of tasks/team and opening participation to the entire academic community.

Guideline 2. **New Team Formation**
Identification and initiation of new discipline research teams (i.e., neurobehavioral and psychosocial health); Initiation of new integrated research teams (i.e., nutrition, physical fitness and rehabilitation; integrated human function); and Increased focus on crew health (i.e., smart medical systems).

Guideline 3. **Space Flight**
Initiation of space flight studies.

Guideline 4. **Critical Path Roadmap**
Increased emphasis on and potential management of the Critical Path Roadmap.

Guideline 5. **Education and Public Outreach Expansion**
Expansion of original education and outreach program, consistent with Institute growth.

Guideline 6. **Training Program**
Development of graduate and postdoctoral training programs.

Guideline 7. **Data Consolidation**
Increased emphasis on space biomedical data collection, evaluation, and consolidation.

Guideline 8. **Consortium Growth**
Growth in consortium membership through open competition.

The augmentation for FY 2001 was approved.

2.6. STRATEGIC PROGRAMS

A gap analysis was carried out by comparing the status of current NSBRI activities with both the original Institute objectives, as specified in the CAN (Section 2.4), and the augmentation guidelines, defined in 1999 (Section 2.5). The result of this analysis led to the present Strategic Plan, which is designed to continue activities, and to fill existing gaps, in order to achieve the CAN objectives and augmentation guidelines through measured growth and development over the next five years. This approach involves three interconnected Strategic Programs:

- **Countermeasure Research Program** (Section 3)
  Designed to accomplish all or part of ***Objectives 1, 2, 3, 4, 5, 6 and** 7* and follow ***Guidelines 1, 2, 3, 4 and** 7.*
- **Education, Training and Outreach Program** (Section 4)
  Designed to accomplish ***Objectives 4, 5 and 8*** and follow ***Guidelines 5 and 6.***
- **Cooperative Research and Development Program** (Section 5)
  Designed to accomplish all or part of ***Objectives 1, 2, 3, 4, 5, 6 and** 7* and follow ***Guidelines 3, 6, 7 and 8.***

The Countermeasure Research Program is a core program that enables the Institute to achieve its primary goal. The Education, Training and Outreach Program is also a core program that allows the Institute to accomplish its secondary goals. The Cooperative Research and Development Program is a non-core program that enhances the other two programs and allows the Institute to accomplish additional goals. The goals of the Institute, listed by Program, are to:

- **Primary Goal - Countermeasure Research Program**
  Lead an integrated research effort focused on development of countermeasures that eliminate, ameliorate, or mitigate the biomedical risks of long-duration space flight, that enable safe and productive exploration and development of space and that improve healthcare on Earth.
- **Secondary Goals - Education, Training and Outreach Program**
  - Develop coordinated, multi-institutional graduate and postgraduate training programs designed to produce the next generation of space biomedical researchers.
  - Transfer the medical and biomedical findings of space research to the scientific community, the home and the classroom, particularly by stimulating interest in the space life sciences in students of all ages across the entire spectrum of diversity.
- **Additional Goals - Cooperative Research and Development Program**
  Create mechanisms for integrating knowledge and technologies, addressing operational requirements early in research development and translating discoveries for possible commercialization.

These programs, and their associated goals, build on the strategies that have been utilized during the first five-year period of the Institute's operation; yet they allow the Institute to maintain momentum in a changing program environment at NASA. For example, while the focus of the human space program has shifted recently from exploration-class missions beyond low-Earth orbit to extended-duration missions in low-Earth orbit, the Institute's Countermeasure Research Program remains relevant, and provides for effective and efficient structure and flexibility. Priorities and risk understanding and mitigation concerning human space flight will undoubtedly continue to change, and this has been factored into the strategic planning for this and the other Programs over the upcoming five-year period.

The three Strategic Programs are described in detail in separate sections (Sections 3 to 5). There is coordination and added value among the Programs, enabling the Institute as a whole to carry out its mission with high impact for NASA. Figure 1 shows how the programs are interconnected through the Institute's organizational structure. In describing each Program, Sections 3 to 5 each contain four parts:

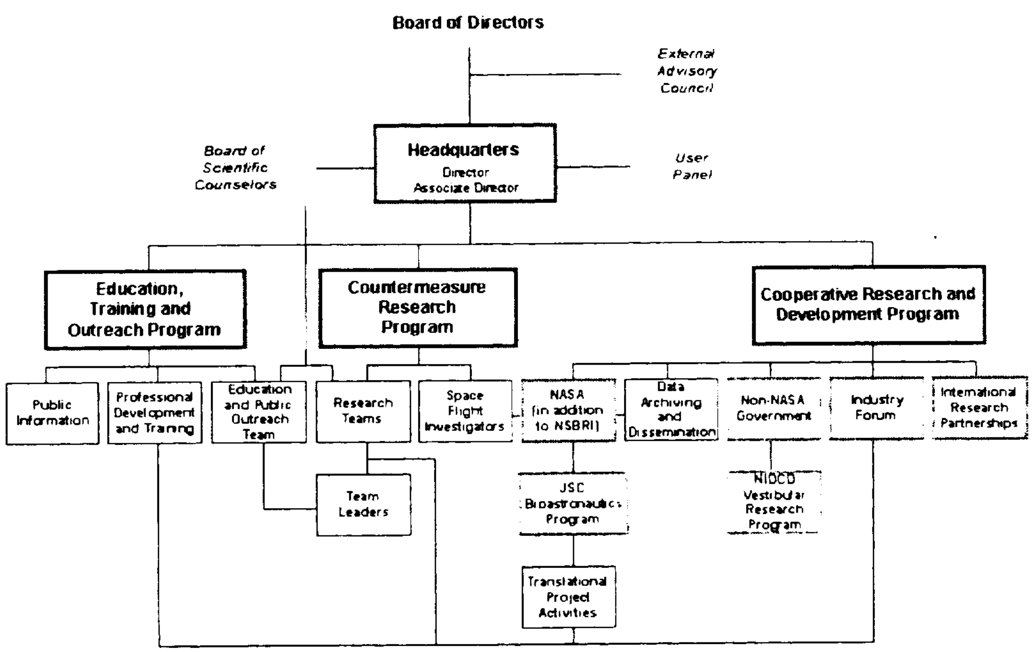
- **Goals and Objectives**;
- **Current Strategies** and how they are addressing the CAN objectives and augmentation guidelines;
- **Gaps and** the resulting **Modifications** to strategies required to address the gaps; and
- **Resource Requirements** to implement the proposed strategies.

2.7. PROGRESS AND VALUE

During the first five-year period, NASA and the NSBRI have planned, initiated and demonstrated that an integrated and multidisciplinary **team approach** to space biomedical research, engaging the best of the scientific community to collaboratively develop knowledge and technologies that lead to effective countermeasures, is a successful model. In five short years, the NSBRI has moved from a paper concept to a world leader in applied space biomedical research. The Institute has made substantial progress towards achieving many of its objectives and has brought a new focus into some areas of research. The endeavor is no longer an experiment, but represents a proven paradigm shift in how NASA can successfully implement a program to significantly advance biomedical research for the human space program, as well as support the President's Management Agenda. The Institute's mission remains of high priority, as stated in the International Space Station Management and Cost Evaluation Task Force report (November 2001), which was "unanimous in that the highest research priority should be solving problems associated with long-duration human space flight."

Figure 1. NSBRI Organizational Structure

(Strategic Programs shown in red)



In going forward, the NSBRI seeks to build on the unique value it brings to NASA, including:

- A **new approach to scientific management** that successfully integrates some of the best aspects of research management by NASA and other federal agencies such as the National Institutes of Health (NIH) and the Department of Defense (DoD). This is accomplished by integrating peer-reviewed research projects by individual scientists in medicine, biology, physics and engineering into focused programs, with the scientists working together in teams to solve high priority biomedical problems for NASA. Those teams include the members from NASA's intramural science program and are connected directly to NASA's operational activities in medicine and health-related areas.

- **Rapid development of countermeasures** by research teams of exceptional scientists led by outstanding scientists/managers who coordinate efforts and foster collaborations and integration within and between teams, to achieve solutions that might not be obtainable by a single project or within a single team.
- Demonstrable **achievements delivered ahead of schedule**, capitalizing on the team approach, on leveraging and on the use of capabilities not obtainable by alternative government or privately sponsored sources.

2.8. CORRESPONDENCE WITH THE PRESIDENT'S MANAGEMENT AGENDA

The NSBRI is an outstanding example of how a private, goal-directed scientific enterprise, which engages the academic community and resources of the nation's leading research institutes, can partner with government (i.e., NASA) to rapidly achieve outstanding results at low relative cost, and with significance for the human space program and the American people. NASA has therefore aggressively embraced the elements of the President's Management Agenda in the establishment of the NSBRI. This Strategic Plan ensures that the elements of the President's Management Agenda are implemented as follows:

Strategic Management of Human Capital - The NSBRI is a private entity that engages outstanding researchers to work together on coordinated and integrated teams to solve problems of high priority for NASA without adding a single civil servant to the government payroll.

Competitive Sourcing - The competitively-selected NSBRI provides an excellent example of how government can outsource a results-driven program to take advantage of distributed expertise, and improve the quality, and reduce the time to development, of deliverables.

Improved Financial Performance - The NSBRI has a streamlined accounting process operating with minimal bureaucracy, a handful of personnel and cost savings through master agreements that apply more money for direct research expenditures.

Expanded Electronic Government - Almost all business transactions among the distributed institutions, including grant proposal submissions, are conducted electronically.

Budget and Performance Integration - The NSBRI is task oriented with the ability to shift resources, as guided by the prioritization of projects to risk mitigation, as set forth by the NASA Critical Path Roadmap and by the assessment of Countermeasure Readiness Levels and Countermeasure Development Phases.[3]

[3] These terms are explained in Section 3.

3. COUNTERMEASURE RESEARCH PROGRAM

3.1. GOALS AND OBJECTIVES

Nearly all the CAN objectives and more than half of the augmentation guidelines provided to the NSBRI by NASA relate directly or indirectly to countermeasure research. Those objectives and guidelines include the following:

Objective 1.	Knowledge Integration and Risk Evaluation
Objective 2.	Countermeasure Development
Objective 3.	Science Management Plan
Objective 4.	Scientific Knowledge Dissemination
Objective 5.	Science Community Access
Objective 6.	Industry Partnerships
Objective 7.	Research Optimization
Guideline 1.	Original Team Growth
Guideline 2.	New Team Formation
Guideline 3.	Space Flight
Guideline 4.	Critical Path Roadmap
Guideline 7.	Data Consolidation

The NSBRI intends to accomplish these objectives and follow these guidelines by making the NSBRI's **primary goal** to lead an integrated research effort focused on development of countermeasures that eliminate, ameliorate, or mitigate the biomedical risks of long-duration space flight, that enable safe and productive exploration and development of space and that improve healthcare on Earth.

3.2. CURRENT STRATEGIES

3.2.1. Overview

When the Institute was created, a strategy was implemented in order to fully accomplish the original CAN objectives. Although it was impossible to accomplish those objectives within the originally specified budgetary profile, it was possible to develop a science management approach that enabled the NSBRI to contribute to focused areas of countermeasure development. When the budget was increased, and the NSBRI's research portfolio increased in breadth and depth, it became clear that the NSBRI was establishing itself as a unique national resource within the human space program. Over the next five years, the Institute intends to build upon its successful strategy for developing countermeasures using a set of coordinated and integrated methods that have been designed, tested and proven in the Institute's first five years. These methods are described in this section relative to the CAN objectives and augmentation guidelines listed above.

3.2.2. Critical Path Roadmap

Within the first year of the Institute's existence, NASA and the NSBRI used their new partnership to jointly develop the Critical Path Roadmap (CPR).[4] This formal, controlled document identifies and

[4]. The CPR is provided as a separate document accompanying this Strategic Plan. The CPR is also available online at http://criticalpath.jsc.nasa.gov.

makes publicly known the biomedical risks of space flight and the research questions that must be answered to reduce those risks. The CPR is directly relevant to several of the CAN objectives and augmentation guidelines, particularly to ***Objective 1 (Knowledge Integration and Risk Evaluation)*** and ***Guideline 4 (Critical Path Roadmap)***. The CPR is an interdisciplinary approach to the assessment and management of the risks associated with long-term exposure to the space environment. It is derived from an overarching general strategy that integrates requirements, risks, risk factors, critical questions, tasks, deliverables, and risk mitigation with the intent of directing biomedical research in support of human space flight. The CPR is based in part on recommendations from internal NASA experts, NSBRI scientists, advisory committees, task forces, and published reports such as the National Research Council Space Studies Board's "A Strategy for Research in Space Biology and Medicine in the New Century," as well as numerous other reports.

The current CPR is a product that has identified 55 risks, which are categorized into four groups: I, II, III and IV, I being the most severe. The risks are rank-ordered, based on their severity, within each of the 12 discipline areas underlying the CPR. Additionally, the risks are associated with 343 critical questions, where 250 are unique, reflecting both the breadth and interactive nature of each of the risk areas (see Table 1 for an example of a typical critical question list).

Table 1. Example of a Chart from the CPR

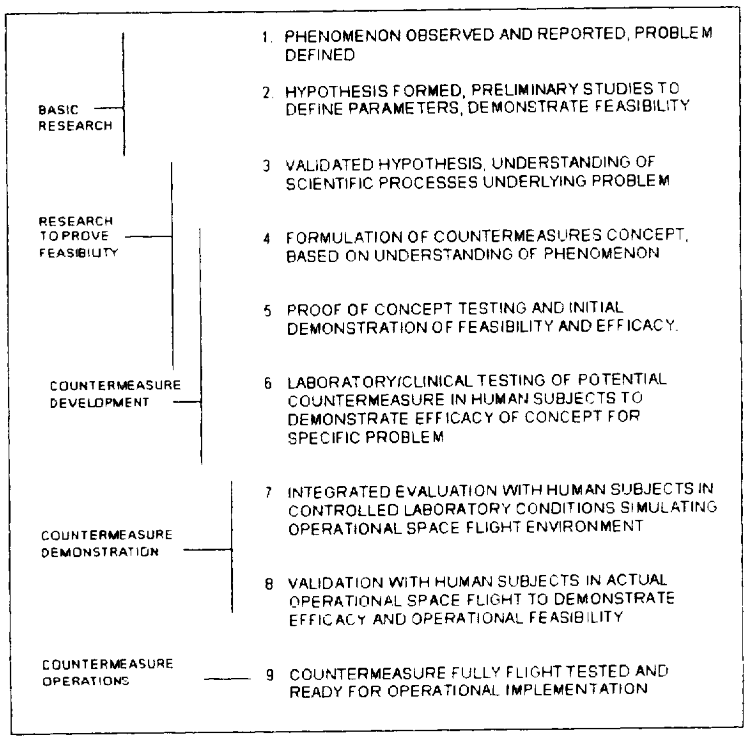
6.10 Radiation Effects

Risk[1]	CQ No.[2]	Critical Question[3]	CQ Priority[4]	Critical Question & Risk Mitigation/ CM Category[5]
Carcinogenesis Caused by Radiation (Risk No. 38)	10 09	What are the cancer risks in humans from spaceflight?	1	Risk Assessment
	10 11	What is the acceptable accuracy for risks of acute and late effects in humans from photons to adequately extrapolate to space?	1	Risk Assessment
	10 05	Are there unique biological effects associated with HZE's?	[illegible]	Mechanisms
	10 07	How can animal and cell experiments be done and data best be used to extrapolate to the human risk from space radiation?	1	Mechanisms
	10 10	What are the risks from SPE's and what is their impact on operations, EVAs and surface exploration?	1	Risk Assessment
	10 08	How do the thickness, design, and material composition of space vehicles affect the internal radiation environment and biological assessment?	1	Countermeasures
	10 06	Do we have strategies for calculating risks that are adequate if expected data are provided and what are uncertainties?	2	Countermeasures
	10 04	Are there differences in response to particles with similar LET, but with different atomic numbers and energies?	2	Mechanisms
	10 12	What are the effects of age, gender, and inter-individual diversity?	2	Mechanisms
	10 01	Are the biological effects for protons above 10 MeV sufficiently similar to photons that photon data can be used for their consequences?	3	Mechanisms
	10 03	Are there chemopreventive or biological agents which would mitigate acute or late effects?	3	Countermeasures

3.2.3. Countermeasure Readiness Levels

NASA has developed a scale to define, assess, and quantify the level of "countermeasure readiness." The use of this Countermeasure Readiness Level (CRL) scale allows NASA and the NSBRI to determine how each funded research project fits into the countermeasure development "flow" and to monitor progress in countermeasure development, in keeping with certain aspects of ***Objective 2 (Countermeasure Development) and Objective 3 (Science Management Plan)***. Figure 2 illustrates the CRL scale, which describes the level of scientific maturity of countermeasure research, from the fundamental studies that suggest potential countermeasures, to studies that allow the systematic evaluation and validation of countermeasures ready for operational implementation.

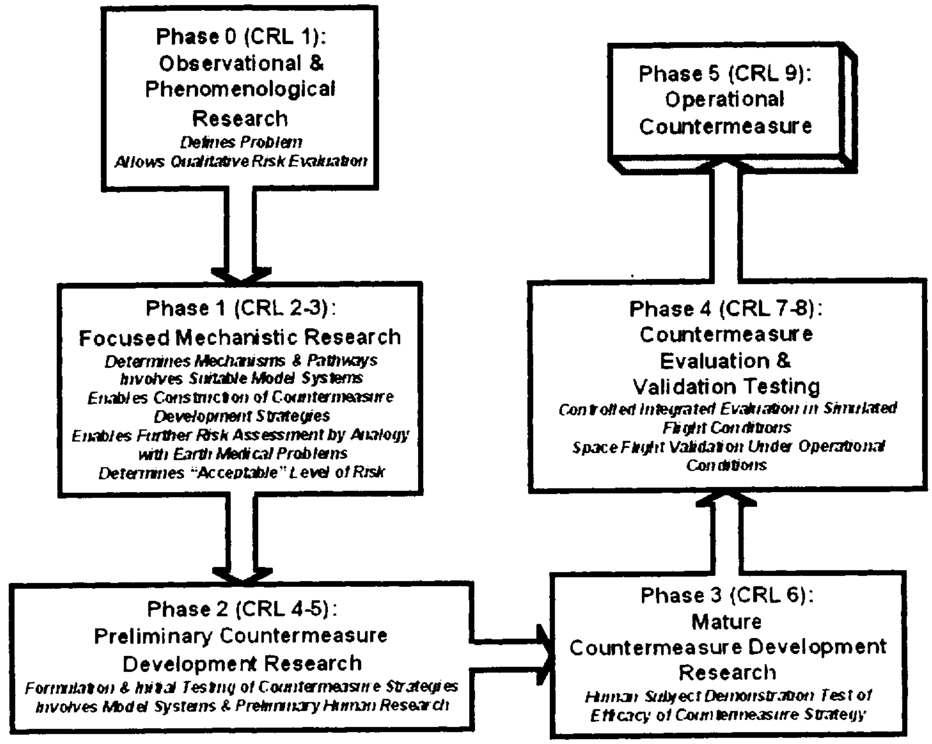
Figure 2. Countermeasure Readiness Levels



3.2.4. Countermeasure Development Phases

Although CRLs represent a useful management tool for the general NASA biomedical research program, the NSBRI has found that a complementary scale provides additional insight for managing its program of countermeasure development. That scale, termed Countermeasure Development Phases (CDP), has only six levels and is defined in Figure 3. Most NSBRI research activity takes place in phases one to three. In Volume II of this Strategic Plan, each research team uses this scale to show their schedule of progression to final operational countermeasures.

Figure 3. Countermeasure Development Phases



3.2.5. Countermeasure Development Strategy

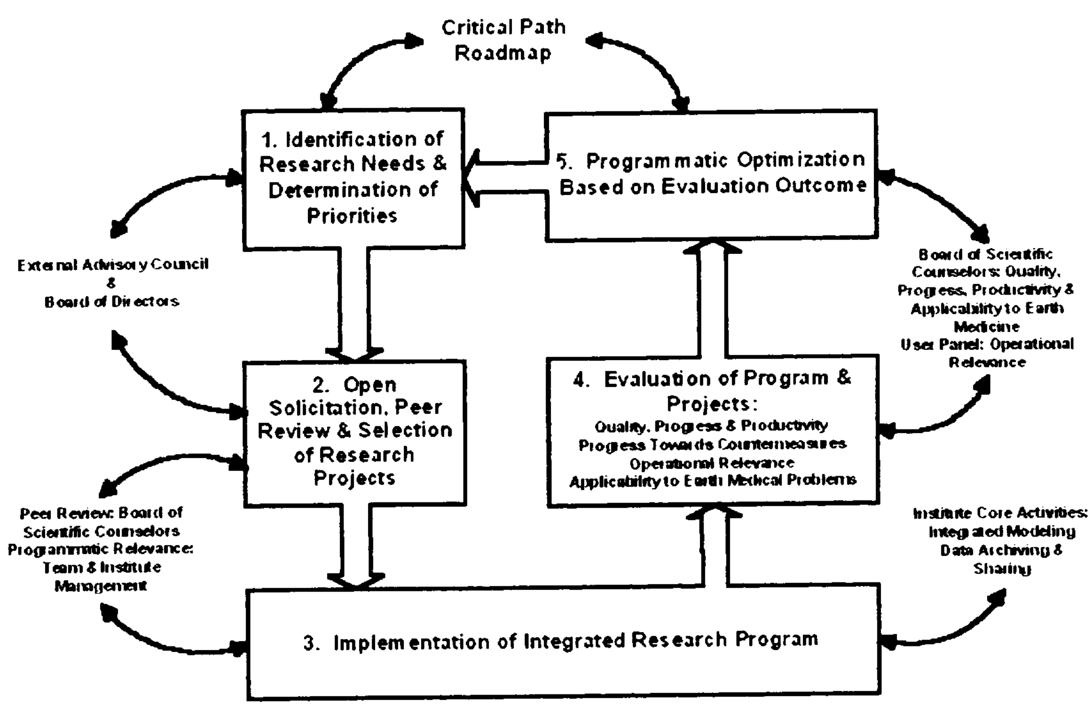
To achieve ***Objectives 2 (Countermeasure Development), 3 (Science Management Plan) and 7 (Research Optimization)***, the NSBRI follows a strategy involving five distinct, but related, steps in developing and managing a focused, integrated research program culminating in operational countermeasures:

1. Identification of research needs and determination of priorities;
2. Open solicitation, peer review and selection of research projects;
3. Implementation of integrated research program;
4. Evaluation of program and projects for
   - Quality and productivity,
   - Progress towards defined countermeasure goals and deliverables,
   - Operational relevance and contribution to an evidence-based approach to space medicine, and
   - Applicability to Earth-related problems; and
5. Programmatic optimization based on evaluation outcome.

The Institute carries out all of these steps, as depicted in Figure 4, using a special **team-based integrated research** infrastructure originally proposed and implemented in 1997. This approach has demonstrated its effectiveness during the first five years of NSBRI's existence, by enabling higher and higher levels of countermeasure readiness to be achieved in each of the Institute's research areas, and by drawing outstanding new investigators to space-related problems.

Currently, the NSBRI's biomedical research program is implemented through **nine discipline research teams**: Bone Loss; Cardiovascular Alterations; Human Performance Factors, Sleep and Chronobiology; Immunology, Infection and Hematology; Muscle Alterations and Atrophy; Neurobehavioral and Psychosocial Factors; Neurovestibular Adaptation; Nutrition, Physical Fitness and Rehabilitation; and Radiation Effects. A tenth Institute team, Smart Medical Systems, aims to allow for **health assessment and evidence-based medical care support** for the astronaut in flight, reducing the risks associated with the occurrence of medical events during the mission and optimizing medical countermeasures. An eleventh team, Technology Development, provides a strong **technological base** for the research program on Earth and in space. The Smart Medical Systems and Technology Development Teams relate closely to the activities of the discipline teams. Three of these teams (Neurobehavioral and Psychosocial Factors; Nutrition, Physical Fitness and Rehabilitation; and Smart Medical Systems) were instituted in FY 2001 in order to fulfill augmentation ***Guideline 2 (New Team Formation)***.

Figure 4. Countermeasure Development Strategy



3.2.6. Team Strategic Plans

Each of the research teams carries out a countermeasure-focused research program containing individual projects tied tightly together by a Team Strategic Plan. These plans are contained in Volume II of this Strategic Plan. These plans unify and guide each team's research program and summarize the steps that the teams are taking to develop the specific countermeasures required to eliminate, ameliorate and/or mitigate the biomedical risks in question. They also provide the schedule each team intends to follow in completing their tasks. These team strategic plans represent one of the major research management tools of the Institute and contribute significantly to achieving ***Objectives 1 (Knowledge Integration and Risk Evaluation), 2 (Countermeasure Development), 3 (Science Management Plan), 5 (Science Community Access) and 7 (Research Optimization)***.

In each team's Strategic Plan, there are, among other things:

- Identification of the CPR risks addressed by the team; [5]
- Listings of risk-based goals and non-risk based goals addressed;
- A description and evaluation of the current program;
- Objectives and strategic activities for each goal, with clearly delineated objectives of how and when each goal will be accomplished; and
- An executive summary.

Table 2. Example of Project Research Activities from Team Strategic Plans
(Cardiovascular Alterations Team)

Table 4.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
COHEN Effects of Space Flight on Cardiovascular Stability	Orthostatic hypotension Exercise Dysrhythmias	• Pharmacological (Midodrine and Spironolactone) • Diet (Electrolytes)	Pre and post flight humans	Effects of microgravity on • CV regulation (CV System Identification) • Dysrhythmias (T-Wave Alternans)	Pre and post flight in humans of • Midodrine • Spironolactone • Diet (Electrolytes)	Pre and post flight in humans of • Midodrine • Spironolactone • Diet (Electrolytes) • Spironolactone
COOLAHAN Distributed Simulation of Integrated Human Function	Orthostatic hypotension Dysrhythmias Cardiac function CV Disease Exercise	Simulation of effects of wide variety of different potential countermeasures including exercise	Computer model of the cardiovascular system integrated with other systems	Develop and validate accurate model of myocyte and heart	•Develop integrated CV model •Develop integrated model incorporating other systems •Simulate effects of space flight and potential CMs	Analyze data from animal and human tests of countermeasures
DELP Circulatory Remodeling with Simulated Microgravity	Orthostatic hypotension Cardiac function Exercise	Peripheral vascular countermeasures	• Hindlimb unloading (HU) of rats • Shuttle flight (STS-107) of rats	Measure effects and mechanisms of HU and shuttle flight on cerebral & peripher vascular beds, lymphatics, cardiac mass	Evaluate data to identify and then test potential countermeasures	Test countermeasures in human studies

[5] In the case of the Technology Development Team, the identification concerns technological needs of the other teams rather than the CPR. The Technology Development Team leads a working group involving the other teams to identify technological needs to advance the research of the Institute.

Table 2 provides an example of some of the project research activities of the Cardiovascular Alterations Team. Each project on the team addresses specific CPR risks, with clear systems to develop countermeasures to reduce those risks. The pathway through the Countermeasure Development Phases (see Figure 3) is summarized in the chart. Most countermeasure-focused team research activities are aimed at developing one or more countermeasures of the following types:

- Training;
- Exercise;
- Diet and nutrition;
- Environmental manipulation;
- Daily rhythm and schedule manipulation;
- Pharmacological agents;
- Selection and retention requirements;
- Monitoring and diagnostic assessment; and
- Medical and surgical procedures.

Vigorous Institute core activities support all of the teams by preserving and integrating the knowledge obtained through each of the team research programs into a unified picture of the interrelated changes occurring within the body during space flight. Two of these core activities are Institute-wide modeling and data archiving (see Section 5.2.1). In addition, certain strategic partnerships between the NSBRI, NASA, industry and other entities play an important role in supporting the achievements of the Institute (see Sections 5.2.2, 5.2.3 and 5.2.4).

Table 3. Example of Project Integration Activities from Team Strategic Plans

(Smart Medical Systems Team)

Table 11.2. Integration Activities

	CRUM HIFU for mission critical care	DAVIES Vascular genomics in g transitions	KLEMPNER Smart microorganism detection sys	PLETCHER Microcapsule drug formulation	SOLLER Non-invasive blood & tissue chemistry	SUTTON Near infrared brain imaging for space med	THOMAS Diagnostic 3D ultrasound for space	THOMAS Echo-cardiographic resource
Internal Communication	Monthly team telecon Biannual team meeting NSBRI retreat Biannual NASA meetings National scientific meetings	Monthly team telecon Biannual team meetings NSBRI retreat Biannual NASA meetings National scientific meetings	Monthly team telecon Biannual team meetings NSBRI retreat Biannual NASA meetings National scientific meetings	Monthly team telecon Biannual team meetings NSBRI retreat Biannual NASA meetings National scientific meeting	Monthly team telecon Biannual team meetings NSBRI retreat Biannual NASA meetings National scientific meetings	Monthly team telecon Biannual team meetings NSBRI retreat Biannual NASA meetings National scientific meetings	Monthly team telecon Biannual team meetings NSBRI retreat Biannual NASA meeting National scientific meeting	Monthly team telecon 3 annual team meetings NSBRI retreat Biannual NASA meeting National scientific meetings
Integrated Experiment Development	Sensor aspects link to both THOMAS projects	Vascular studies link Cardiovascular Alterations team	Algorithms link to SUTTON project. [illegible] studies link to [illegible] team	[illegible] development links to Neurovestibular Adaptation team	Sensor links to SUTTON project. Applications link to Muscle team	Sensor links to SOLLER project. Algorithms link to KLEMPNER and THOMAS projects	Sensor links to CRUM project. Algorithms link to SUTTON project. Echo links to CV team	Sensor links to CRUM project. Algorithms link to SUTTON project. Echo links to CV team
Sample Sharing			Specimen sharing with JSC microbiology	—	Collaborative with CABRERA project	Cognitive tests shared with [illegible] groups	Vascular investigations link to DAVIES project	Resources shared with NSBRI and NASA
Synergistic Studies of Opportunity	Studies with DoD - DARPA	Bioengineering Center, U Penn	SRI Biosystems biotechnology industry	Pharmaceutical industry collaborations	Medical assessment for diabetics surgical patients	Neuro monitoring in ICU [illegible]	Cardiac, renal [illegible] applications in [illegible] practice [illegible]	Resources of National [illegible]
Development of Computer Model of Integrated Human Function	Large model guided surgery	Data mining	Neural nets for pattern recognition	—	Algorithms for pattern identification	Neural nets software connectivity [illegible]	3D algorithms for individualized astronaut model	Modeling for training purposes

Table 3 summarizes some of the integration activities of the Smart Medical Systems Team, which has multiple collaborations in core modeling efforts, systems engineering for the design of common (reconfigurable) hardware platforms that will support and integrate multiple medical sensors and effectors, and pathways to the biotechnology, medical device and pharmaceutical industries. All teams have integration activities for internal communication, experimental development, sample sharing, synergistic studies of opportunity and participation in the development of a systems model of integrated human function.

In the Institute, countermeasure development is accomplished by answering critical questions in a timely manner using a logical, **science-driven strategy**, with ongoing dissemination of advances in knowledge to the scientific community through publication and other means, contributing to the accomplishment of ***Objective 4 (Scientific Knowledge Dissemination)***. An example of the time course of objectives and strategic activities to accomplish goals for the Muscle Alterations and Atrophy Team is provided in Table 4.

Table 4. Example of Time Course of Objectives and Strategic Activities to Accomplish Goals

(from Team Strategic Plans - Muscle Alterations and Atrophy Team)

Table 7.3 Achieving Goal 1 Reduce Risk of Loss of Muscle Mass, Strength and Endurance

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Understand muscle protein degradation • Determine slow-to-fast phenotype shift • Discern role of reactive oxygen species • Define loading-sensitive muscle genes													
• Determine how resistive exercise reduces atrophy of human muscle • Determine effects of artificial gravity on muscle • Identify acceptable target levels of risks in humans													
Phase 2: Preliminary Countermeasure Development Research													
• Test activity paradigms that create anabolic state and reduce atrophy in animals and humans • Test pharmacological interventions for muscle degradation and other muscle unloading effects • Study role of antioxidants as nutritional countermeasure strategy													
• Determine whether artificial gravity is a feasible countermeasure to muscle atrophy in humans													
Phase 3: Mature Countermeasure Development Research													
• Develop integrated exercise, nutritional, and pharmacological countermeasure and test in humans													
• Determine whether artificial gravity, in conjunction with the exercise, nutritional, and pharmacological countermeasure above, further reduces muscle atrophy in humans													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of integrated exercise, nutritional, pharmacological countermeasure with artificial gravity													
Phase 5: Operational Implementation of Countermeasure Strategy													

Many steps may be required to identify where in the physiological cascade of events to apply countermeasures and what form countermeasures should take. These steps, which may include performing basic research to decipher the mechanisms underlying the hazardous physiological changes induced in a microgravity environment and preliminary testing of candidate countermeasures on animal or human models of microgravity, are part of the distinct phases of countermeasure development (see Figure 3). As the countermeasures mature, the level of integration among the various countermeasure candidates increases through the sharing of protocols and data, and through common modeling and technological approaches. Ultimately, the **performance** and **effectiveness** of the Institute Countermeasure Research Program is assessed, in part, by the research teams' abilities to reduce the severity and number of risks in the CPR through countermeasure development in a given period of time, thereby achieving ***Objective 2 (Countermeasure Development)***.

3.2.7. Institute Science Management

Managing the NSBRI's ongoing focused research program involves the cyclical steps described in Section 3.2.5 and shown in Figure 4, augmented by periodic NASA-sponsored reviews. This section summarizes the Institute's Science Management Plan, designed to satisfy ***Objective 3 (Science Management Plan)***. For an overview of the Institute's management structure, see Figure 1.

3.2.7.1. Evaluation of Current Program and Determination of Programmatic Needs

Program evaluation is an ongoing process involving several distinct steps. First, the Institute's Board of Scientific Counselors annually evaluates the quality, productivity and progress of each project and of each research team as a whole. This evaluation is provided to NSBRI senior management and the External Advisory Council (EAC), team leaders, and investigators, as appropriate. Second, at its semiannual meetings, the EAC advises senior management of the effectiveness of the research program and of corrections necessary to fill gaps related to the CPR. Third, when countermeasure strategies have reached a sufficient level of maturity, the User Panel, consisting of present and former astronauts and flight surgeons, evaluates the operational suitability of the resulting countermeasure. Fourth, the Industry Forum, provides advice to Institute management concerning the applicability and suitability of new technologies for Earth benefit. Finally, at its semiannual meetings, the Institute Board of Directors reviews the major fiscal and programmatic issues confronting the Institute and provides advice and direction to senior management on necessary high-level actions.[6]

In order to develop a fully independent assessment of NSBRI's programs and activities, NASA intends to carry out a series of external reviews. While the Cooperative Agreement specifies that NASA would conduct a major review at the end of the third year of each five-year term, it was a recommendation of the Site Visit Report of the National Space Biomedical Research Institute in 2000 that there be separate NASA reviews of the teams every three to five years, as well as the Institute-wide third year reviews.

Table 5 presents a projected review schedule for all of these various reviews. The entries in the table show how many times per year, over the next five years, that the teams and the Institute as a whole will be reviewed. Note that the NASA reviews include all teams over the first three years (2003 – 2005) and reviews the Institute as a whole in 2006. No NASA reviews are conducted in 2007, but the cycle of NASA reviews begin again in FY 2008. The culmination of these evaluations will identify strengths and

[6] A complete listing of membership on these expert panels is provided in the Appendix 4 of the accompanying Progress Report.

weaknesses in the program. This is important in linking performance and budget, and filling gaps in the program with open solicitation of proposals in focused research areas, as appropriate.

Table 5. Review Schedule for Teams and for the Institute as a Whole

	FY 2003				FY 2004				FY 2005				FY 2006				FY 2007			
	EAC	BOD	BSC	NASA	EAC	BOD	BSC	NASA	EAC	BOD	BSC	NASA	EAC	BOD	BSC	NASA	EAC	BOD	BSC	NASA
BL	2		1	1	2		1		2		1		2		1		2		1	
CVA	2		1	1	2		1		2		1		2		1		2		1	
HPF	2		1	1	2		1		2		1		2		1		2		1	
IIH	2		1		2		1	1	2		1		2		1		2		1	
MAA	2		1		2		1	1	2		1		2		1		2		1	
NPF	2		1		2		1		2		1	1	2		1		2		1	
NVA	2		1		2		1	1	2		1		2		1		2		1	
NPFR	2		1		2		1		2		1	1	2		1		2		1	
RE	2		1	1	2		1		2		1		2		1		2		1	
SMS	2		1		2		1		2		1	1	2		1		2		1	
TD	2		1		2		1	1	2		1		2		1		2		1	
EO	2		1		2		1		2		1	1	2		1		2		1	
NSBRI	2	2			2	2			2	2			2	2		1	2	2		

Teams

BL - Bone Loss
CVA - Cardiovascular Alterations
HPF - Human Performance Factors
IIH - Immunology, Infection and Hematology
MAA - Muscle Alterations and Atrophy
NPF - Neurobehavioral and Psychosocial Factors
NVA - Neurovestibular Adaptation
NPFR - Nutrition, Physical Fitness and Rehabilitation
RE - Radiation Effects
SMS - Smart Medical Systems
TD - Technology Development
EO - Education and Outreach

NSBRI - Institute as a whole, including management

Review Panels

EAC - External Advisory Council
NASA - NASA External Reviews
BOD - Board of Directors
BSC - Board of Scientific Counselors

3.2.7.2. Selection of Research Projects and Investigators

Institute research is recruited through the use of **open solicitations** to the entire biomedical community. In general, if available funds permit, these solicitations would be issued annually by the Institute, either alone or in partnership with NASA, and would be focused on the gaps and issues identified in the evaluation process discussed above. Thus, the research solicitation would have the relative priorities of the various Institute elements built into it. The review and selection criteria would be spelled out clearly in the research announcement and diversity would be encouraged. This assures the potential involvement of any member of the scientific community in the Institute's program and optimizes the NSBRI's ability to recruit outstanding biomedical researchers to lead and participate in the research program.[7]

Research proposals have been and would continue to be reviewed by independent peer panels of experts. Those scoring within the competitive range are assessed by the appropriate Team Leader(s) for programmatic relevance. Then, each Team Leader recommends selection options to NSBRI senior management, who are responsible for selection.

The solicitation, review and selection process is fully coordinated with NASA to avoid inappropriate and wasteful duplication of effort, and to assure programmatic alignment. If NASA and the NSBRI are utilizing a single NASA Research Announcement (NRA) to recruit investigations for their programs, then it is also important that all aspects of the joint solicitation process be coordinated to ensure uniformity, fairness and program optimization for all parties, with the aim of supporting the most meritorious proposals that meet both NASA's and the NSBRI's requirements.

The NSBRI is aware that Team Leaders play a pivotal role in the success of the Institute. They are required to be practicing scientists with funded Institute projects, as well as manage their teams. Their expertise and "hands-on" approaches add value across projects and across teams. While the Team Leaders are not responsible for the executive decisions regarding team composition, their vision and input can be valuable in strategic directions that the teams take in carrying out their tasks. They must therefore be protected from any real or apparent conflicts of interest. especially with respect to inputs that may influence, either directly or indirectly, team selection by NSBRI senior management. The goal is to maintain the highest level of fairness, integrity and credibility for all investigators, including the Team Leaders, as well as for the Institute and for NASA.

These issues have been discussed among the NSBRI senior management, Team Leaders and EAC members. The Institute plans to obtain recommendations on this matter, as well as the issue of Team Leader selection (Section 3.2.7.3) from an **outside committee of experts**. This activity will be completed in a timely manner, namely early in FY 2003, to enable the Team Leaders and others to be aware of the approach and criteria that will be used in future selections.

3.2.7.3. Team Leader Selection

As noted in the previous section, Team Leaders play an important role in the management of the Institute's research program. Up to now, Team Leaders have been identified by NSBRI senior management based on recommendations from the Board of Directors. Most, but not all, of the current Team Leaders are from consortium institutions.

3.2.8. Current Program Funding Levels and Prioritization

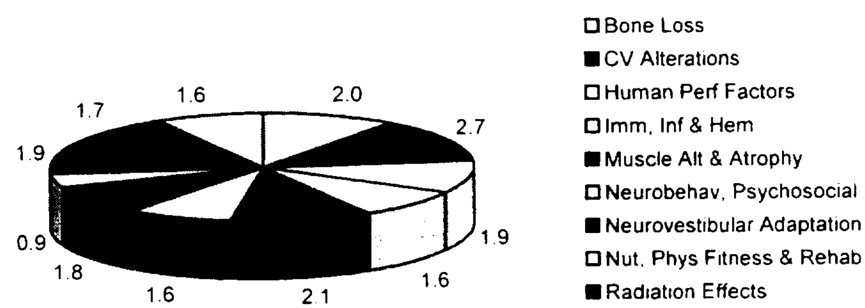
The original Institute research program consisted of three-year projects that began in October 1997 (FY 1998) and ended in September 2000. After much discussion between NASA and the NSBRI, it was

[7] NSBRI investigator accolades include the Nobel Prize in Physiology or Medicine, membership in the National Academies and Chair of the NASA Biological and Physical Research Advisory Committee. The NSBRI Director and 5 of 11 (45%) of the research Team Leaders are M.D.-Ph.D. scholars. In total, there are more than 260 investigators (with diverse expertise in medicine, biology, chemistry, physics, engineering, space flight (e.g., former astronauts), etc.) from academia, government and industry involved in 88 ground based research projects and 7 education and outreach projects, with funding at 75 institutions across 21 states. More than 58% of the PIs are not from consortium member institutions and 53 are new investigators to NASA. Five flight proposals have been received for definition and feasibility reviews.

agreed that the program would be enlarged in October 2000 (FY 2001) and the NSBRI released two, open, competitive research announcements. These announcements followed 12 intensive workshops involving the external community. One announcement was to expand the original teams by (on average) doubling the number of projects, and the other to add new teams to the Institute. Flight projects were included in both solicitations. These actions followed augmentation ***Guidelines 1 (Original Team Growth), 2 (New Team Formation), and 3 (Space Flight)***. The current research program involves eleven teams, ranging in size from 3 to 12 projects, with an average of 8 projects/team. A breakdown of team research support is shown in Figure 5.

Most of the current research projects were initiated during FY 2001 and will be completed during FY 2004. The annual budgetary requirement to support the 88 current ground-based projects is approximately \$25.6 M. However, the amount available during FY 2002 for project support was only \$19.8 M, with an additional \$0.6 M of contingency funds having been set aside to support five candidate flight proposals received in 2000 (they are presently undergoing final selection review).

Figure 5. Current Distribution of Team Funds for Ground Research (2002)
(Millions of Dollars)



Total Funding = \$19.8 M

3.2.9. Research Optimization

The Institute science management plan and countermeasure development strategy implement a "best value" program for a given set of resources, per ***Objective 7 (Research Optimization)***. The program is focused by the CPR, by the Team Leaders, and by the annual NSBRI reviews. It involves high caliber investigators from some of the best biomedical research institutions in the nation, including a significant number of investigators from well-funded, productive laboratories. In addition, the NSBRI program is built upon institutional infrastructure already developed within the biomedical research community, allowing research to be carried out at a substantially reduced rate if that infrastructure had to be developed again. This, coupled with the strong productivity of the investigators, argues strongly that the NSBRI's research program is a "best-value" program, thereby fulfilling this objective.

3.3. GAPS AND MODIFICATIONS

This section discusses the level to which the current program strategy addresses the CAN Objectives and augmentation guidelines, and presents the required modifications to the current program in order to effectively address any gaps that exist.

3.3.1. Funding Gap to Support the Current Program

Since the remainder of this section addresses the ability of the current NSBRI countermeasure research program to achieve the CAN Objectives, it is important to discuss the potential gap between the current program and the minimal program that NASA has notified the Institute it might have in FY 2003. In April 2002, NASA notified the NSBRI that:

> The current anticipated funding profile for the Core budget for years 6-10 is as follows, but is subject to change dependant on the outcome of the aforementioned discussions:
> FY03 - $16.179M
> FY04-FY07 - $10M/year

The current program was selected in FY 2001 when the NASA budget profile for the Institute was approximately $30 M/year and that is still the approximate cost of supporting the current program. In FY 2002, NASA reduced the Institute's budget to $22.1 M, but the Institute had a one-time unexpended balance of $3.7 M that it could use to reduce the problem to one that could be dealt with through a 25% reduction in the research program. Although this had a significant impact on the Institute's ongoing operation, this level of one-time reduction could be absorbed through three-month no-cost extensions applied to most projects, without descoping the current program.

However, if a reduction of the $30 M program to $16.2 M occurs in FY 2003, with no unexpended balance carryover from previous years, then the current program could not survive. In fact, the current strategy involving eleven research teams focusing on the CPR would no longer be viable, particularly if the ultimate budget level for FY 2004 – 2007 is $10 M. This amount ($10 M/year) was the initial funding level of the Institute, and it soon became very clear that this funding level was incompatible with the scope of the Institute's mission. That fact ultimately became the foundation for the NASA Bioastronautics budget augmentation request to Congress for the NSBRI for FY 2001, a request that was granted then, but is currently being re-evaluated.

The remainder of this section provides evidence that even the current program of approximately $30 M/year is inadequate to achieve the entire set of CAN Objectives. Thus, a $16 – 10 M/year Institute program would have a significantly reduced scope from the current program and would be able to achieve even fewer of the CAN Objectives.

3.3.2. Countermeasure/Risk Gaps .

The countermeasure development strategy discussed in Section 3.2.5, and illustrated in Figure 4, together with the Institute science management plan, discussed in Section 3.2.7, have provided an effective approach to recruiting the scientific community to work together to reduce the health risks associated with space flight. The detailed team strategic plans in Volume II, with their clear goals and defined schedules, demonstrate the utility of this approach, and work towards achieving ***Objectives 2 (Countermeasure Development) and 3 (Science Management Plan).*** However, the current program has two important limitations: (1) not all risks are addressed and (2) most countermeasures will take about ten years to develop at the current rate of funding.

Table 6 summarizes the coverage of the risks in the CPR by the current NSBRI program. Note that the current team research cover less than 80% (43/55) of risks in the CPR. Furthermore, not all 43 of these risks have entire research projects aimed at developing countermeasures to mitigate their effects. The coverage of critical questions is even less. Thus, there is not only room for program expansion in terms of number of risks covered, but perhaps more importantly, in terms of resources used to expeditiously develop countermeasures to mitigate risks with high likelihood, high consequences and low mitigation status.

The second limitation of the current program is the long development time associated with the individual countermeasures. This is due, to a significant extent, to limitations in funding that prohibit certain activities to proceed in parallel. Increases in team funding that would permit progressive funding of promising research paths and investigation of multiple critical questions at the same time by different investigators working together. These enhancements should enable some research to move forward at a faster pace, allowing more rapid convergence to operational countermeasures.

Table 6. Mapping Between NSBRI Research Teams and CPR Risks Addressed

RESEARCH TEAM	NUMBER OF UNIQUE RISKS	CPR RISK NUMBERS
Bone Loss	4	9, 10, 11, 12
CV Alterations	5	13, 14, 15, 16, 17
Human Perf Factors	1	19
Imm, Inf & Hem	5	22, 23, 25, 26, 27
Muscle Alt & Atrophy	5	28, 29, 30, 31, 32
Neurobehav, Psychosocial	3	18, 20, 21
Neurovestibular Adaptation	5	33, 34, 35, 36, 37
Nut, Phys Fitness & Rehab	3	7, 54, 55
Radiation Effects	5	38, 39, 40, 41, 42
Smart Med Systems	6	43, 44, 45, 46, 47, 48
Tech Development	N/A	
	1	49 (cross-risk)
TOTAL	**43**	

3.3.3. Team Member Selection

As pointed out in Sections 3.2.7.2 and 3.2.7.3, there is a gap in the procedures for team selection that expose the Team Leaders to a potential conflict of interest. Moreover, there is a need to make the Team Leader selection process more transparent. Since the Team Leaders' NSBRI grant support generally runs out in September 2003, there is an opportunity to develop guidelines concerning their selection. An expert outside committee will be convened to examine these issues and make recommendations to NSBRI senior management.

3.4. RESOURCE REQUIREMENTS

3.4.1. Baseline Research Program

The current NSBRI research program consists of 88 tasks grouped into 11 teams. The total annual requested budgets for all of these activities amounts to $26.2 M. Thus, the average team consists of eight tasks with a total budget of approximately $2.4 M. An average single project has a budget of approximately $300 K. These averages will be used to estimate project costs in this plan.

A close examination of the tasks in the current research program reveals that it is possible to reduce program costs by approximately $2.4 M to **$23.8 M** (about 9%) without impacting the current scope and CPR risk coverage significantly. This, then, represents the true baseline, or **critical mass**, for the current research program.

This is an appropriate minimal level of support for the current program for at least three reasons:

1. The level of support maintains a commitment by NASA and the NSBRI to a strong collaborative partnership with the academic research community, giving confidence to those outstanding scientists that have been recruited through an open, competitive solicitation to participate in a new and unique research program designed to solve important space biomedical problems;
2. The level of support represents the cost of a minimal team effort that addresses the most severe of the space biomedical risks. Reducing this minimal program in any significant way would concomitantly reduce the effectiveness of the Institute's countermeasure strategy; and
3. The level of support represents the minimal funding required to fund the current team strategic plans (Volume II) that are designed to produce sound, fundamentally based countermeasures over the next eight to ten years. Significant reduction of support will interrupt the flow of planned team activities and the schedules in major ways.

Thus, the baseline NSBRI research program will begin at $23.8 M for FY 2003. A small annual program cost increase (2%) is included to account for the effects of inflation. The budget plan for the baseline program is shown in Table 7.

3.4.2. Budget Augmentation

In Section 3.3.2, it was pointed out that the current countermeasure development program has two important limitations, namely not addressing many significant risks in the CPR, and taking approximately ten years to fully develop most countermeasures. A minimal approach to dealing with these limitations is to gradually increase the number of projects supported, increase support for highly successful projects and factor in increasing costs as countermeasures move through the phases of development.

The NSBRI has received 51 project proposals in response to the joint NASA/NSBRI Research Announcement (NRA 01-OBPR-07) that was issued on October 31, 2001. These proposals have been peer reviewed and 24 are in the competitive range for selection. A modest selection from this group would involve six projects, and at an average budget of $300 K/year. This would lead to a budget of $1.8 M for FY 2003. Once again, a small annual program cost increase is included to account for the effects of inflation.

After FY 2003, a flat growth rate of $2.5 M/year will lead to addition of approximately eight projects/year to the Institute's research portfolio. This is minimally sufficient to allow the program to increase scope or depth by adding projects, or by "fast-tracking" high payoff projects (with appropriate merit review).

Table 7. Countermeasure Research Program Budget Plan

(Millions of Dollars)

	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Baseline Program	19.8	23.8	24.3	24.8	25.3	25.8
Research Program Augmentation		1.8	4.3	6.9	9.4	12.0
TOTAL	**19.8**	**25.6**	**28.6**	**31.7**	**34.7**	**37.8**

4. EDUCATION, TRAINING AND OUTREACH PROGRAM

4.1. PROGRAM GOALS AND OBJECTIVES

Many of the NASA-provided CAN objectives and augmentation guidelines apply to the Education, Training and Outreach Program. They include:

Objective 4. Scientific Knowledge Dissemination
Objective 5. Science Community Access
Objective 8. Education and Public Outreach

Guideline 5. Education and Public Outreach Expansion
Guideline 6. Training Program

Associated with these objectives and guidelines are the following NSBRI **secondary goals**:

- To develop coordinated multi-institutional graduate and postgraduate training programs designed to produce the next generation of space biomedical researchers; and
- To transfer the medical and biomedical findings of space research to the scientific community, the home and the classroom, particularly by stimulating interest in the life sciences in students of all ages.

4.2. CURRENT STRATEGIES

The Institute has created a strong basis for education, training and outreach during its first five years and plans to build further on this foundation over the next five years. Scientists, professional educators, and NSBRI management personnel work together to carry out these current and ongoing activities.

4.2.1. Education and Public Outreach Team

The mission of this NSBRI team is to communicate the significance and excitement of space life sciences to local, national and international audiences, while transferring and disseminating knowledge gained via the biomedical advances achieved by the NSBRI Research Teams. This mission is being accomplished through an integrated array of programs focusing on students and educators at the **primary, secondary and undergraduate levels**, as well as the **general public**. In this regard, the Team works towards CAN ***Objectives 4 (Scientific Knowledge Dissemination), 5 (Science Community Access) and 8 (Education and Public Outreach).***

The Team's Strategic Plan is available, along with the Research Team Plans, in the Supporting Documentation (Volume II).[8] The team currently consists of seven projects that were selected following external peer review. There are focused team objectives that address five major programmatic goals. These goals were developed jointly by Team partners, in coordination with the NSBRI leadership, and are to:

- Design and conduct a variety of teacher professional development programs to help teachers understand space life sciences and change their practices and behaviors to improve the learning experiences they provide students.
- Develop curricular materials that:

[8] Recent accomplishments of the Team are also provided in the accompanying Progress Report.

  - span the educational continuum.
  - are aligned with national science standards.
  - provide accurate, balanced, effective and inquiry-based instruction.
  - expand students' understanding of on-going NSBRI research.
- Increase science literacy and public awareness of the real-life impacts of NSBRI research through media, informal science activities, direct mailings and magazine stories.
- Promote educational access and career awareness in space life science fields among high school and undergraduate students as well as high school teachers.
- Integrate NSBRI-focused teacher professional development, curricular materials, scientific literacy initiatives, and educational and career access activities among all projects on the Educational and Public Outreach Team, other NSBRI Teams and public venues.

The Education and Public Outreach Team is well aligned and engaged in activities with the Educational Outreach Program of the Office of Biological and Physical Research. The Team's activities and progress are monitored within the NSBRI by the EAC, BOD and BSC according to the schedule laid out in Table 5. The same Table also provides the timetable for external review of the Team by NASA.

4.2.2. Professional Development and Training for Scientists and Engineers

Training of scientists and engineers beyond the undergraduate level is necessary to broaden and diversify the future workforce in space biomedical research and operations. With its strong national academic base of 75 funded institutions, and an outstanding governing consortium of academic institutions of higher learning, the NSBRI possesses one of the strongest collective entities for focused biomedical training in the country.

Currently, the NSBRI supports two programs in Professional Development and Training. **Short Research Internships** have been, and will continue to be, offered at the NSBRI, NASA field centers and Industry Forum member laboratories to train advanced undergraduates, graduate students and medical students in the specific techniques of space biomedicine. This program has been in existence since the beginning of the Institute.

This **Visiting Scientist Program** actively recruits visiting senior scientists to spend up to one year at any of the Institute campuses, at JSC, or at an Industry Forum member facility and participate in ongoing research activities. Access to all laboratories in the Institute is open to these scholars to encourage interactions between Institute investigators, JSC scientists, and scientists outside of the Institute. A special part of this program focuses on providing opportunities for JSC scientists to spend sabbaticals at the Institute and other laboratories and for Institute scientists to spend sabbaticals at JSC and elsewhere. The Intergovernmental Personnel Agreement program provides a well-established mechanism for such exchanges and will continue to be used as appropriate.

4.2.3. Scientific Community Outreach

The Visiting Scientist Program is one way to reach out to professionals involved or interested in space biomedical research. Other strategies include hosting major symposiums, didactic continuing education courses and space-related sessions at general scientific meetings, such as meetings of the American Association for the Advancement of Science, FASEB, the Society for Neuroscience and the American Medical Association. These outreach sessions, begun in 1998, address ***Objectives 4 (Scientific***

Knowledge Dissemination), 5 (Science Community Access) and 8 (Education and Public Outreach), and seek to involve a mixture of scientists and astronauts in describing the biomedical problems of space flight in a way that the state of the field can be understood by the community at large.

4.2.4. Community Education and Public Outreach

Through public information, the Institute will continue to promote scientific literacy and share with a new audience an appreciation for the opportunities that space life sciences research presents. The NSBRI will continue to develop a multimedia approach to reaching out to diverse populations of the general public with information related to the mission and activities of the Institute (***Objective 8***).

This is being accomplished by continuing its use of a NSBRI Headquarters-based public relations plan to facilitate the dissemination of the biomedical advances made by[9]

- Institute researchers
- Continued development of the award-winning NSBRI World Wide Web site
- A national outreach program with PBS television
- Magazine stories that disseminate space biomedical knowledge
- Hands-on museum exhibits
- The preparation of exhibits for scientific and industrial events
- Brochures for public distribution
- Continued development of personal contacts with space and science reporters.

4.3. GAPS AND MODIFICATIONS

4.3.1. Funding Gap for Education and Public Outreach Team

The downturn in the NSBRI budget affected all the teams, including the Education and Public Outreach Team (Section 3.3.1). The Team's reduced budget of 25% had significant impact on its ability to carry out its mission. Many teachers who had planned on participating in the program were unable to do so because of the budget reduction.

4.3.2. New Program Opportunities

There is an opportunity to introduce high impact programs for Professional Development and Training for Scientists and Engineers and expand current strategies listed in Section 4.2.2. These programs would not only foster the Institute in meeting ***Objectives 4 (Scientific Knowledge Dissemination), 5 (Science Community Access) and 8 (Education and Public Outreach),*** but would provide strengthened ties to the Countermeasure Research Program, with its ***Objectives 1 to 7***. The added support of Professional Development and Training for Scientists and Engineers would therefore cut across **all** the objectives of the Institute (Section 2.4) and is viewed as a critical Institute endeavor. Moreover, the expansion in this area is consistent with overall NASA strategy, wherein the Administrator has made education a priority. The NSBRI is strategically well positioned in this area, based on the fact that the Institute is comprised of an academic consortium, with leading teachers and professors engaged in a variety of scholarly pursuits with diverse students at all levels.

[9] Details are provided in the accompanying Progress Report.

New NSBRI programs under development include the following:

- **Summer Graduate Training Program** – Starting in 2003, the NSBRI plans an 8-10 week intensive program in Space Biomedicine at JSC and nearby research laboratories. Designed to accommodate 15 to 20 graduate students, the program will include morning lectures and afternoon laboratories, and will be taught by members of the different NSBRI research teams and JSC personnel, including astronauts.
- **Postdoctoral Fellowship Program** – Beginning in 2003, the Institute plans a competitive postdoctoral program providing two years of support for 10 to 15 new fellows each year. Prospects must propose new and independent research ideas and protocols in space biomedical research. Fellows must be associated with a well-established and funded laboratory group carrying out research that is appropriate to the NSBRI's mission. A panel of leading, non-NSBRI scientists in space biomedicine will select fellows on the merit of their applicant proposals.
- **Graduate Student Fellowship Program** – In 2004, the Institute plans to create a nationally competitive program similar to the postdoctoral program above. In this case, however, students must work with NSBRI-funded investigators on some facet of their ongoing research. Selection will be based on merit and the likelihood of success in a graduate program.
- **Space Biomedical Curriculum** – The Institute plans to expand its efforts in the development of graduate courses in space biomedicine. These courses will involve a "knowledge station" that allows learners to interact with curricular materials via state-of-the-art information technology and a physical platform designed to facilitate human interaction and learning.

4.4. RESOURCE REQUIREMENTS

As in the determination of resource requirements in Section 3.4, any requirements are based on assumptions and ultimately driven by NASA.

4.4.1. Baseline Education, Training and Outreach Program

The current NSBRI Education, Training and Outreach Program consists of the seven peer-reviewed tasks making up the Education and Outreach Team, a small public relations office at NSBRI Headquarters, a small program of summer research internships, and a Visiting Scientist Program at Johnson Space Center. The total annual budget for the team tasks is $1.8 M, with an average single project budget of about $260 K/year. The total cost of the public relations office is approximately $200 K/year. The summer internship program costs about $30 K/year for 10 students, while NASA funds the Visiting Scientist Program separately.

Although the focus of the Education and Outreach Team is teacher training and curriculum development for elementary and high school, projects also include college undergraduate and graduate course development and community outreach. The Headquarters public relations office is extremely important to the NSBRI, enabling important direct communication links to various normal and scientific news organizations. The summer internship program is a low cost, high return program that the Institute has maintained since its first year of existence.

All of these tasks and activities are vital to the NSBRI, to NASA, and to the Nation. Any reduction in funding to this important program would have unfortunate negative consequences. Therefore, the baseline program will maintain the current program's full funding level. A small annual budgetary increase (2%)

is included to account for the effects of inflation. The budget plan for the baseline program is shown in Table 8.

4.4.2. Budget Augmentation

Section 4.3 identifies a number of new NSBRI activities, but not all of them require additional funds beyond the baseline program. The Institute strategy in this area is to: enhance the current Team program slowly, at the rate of two projects/year, beginning in FY 2004, at an annual cost of $250 K/project; develop a new Institute two-year postdoctoral fellowship program beginning in FY 2003; develop a new Institute three-year graduate student program beginning in FY 2004; and develop a new summer graduate training program beginning in FY 2003.

The two-year postdoctoral fellowship program will select 15 students/year beginning in FY 2003. Estimated costs for this program are $700 K for FY 2003 and $1.4 M thereafter. The three-year graduate student program will select 20 students/year beginning in FY 2004. Estimated costs for this program are $650 K for FY 2004, $1.3 M for FY 2005, and $2.0 thereafter. We expect both of these programs will be larger than this because of support from industrial partners. Both of these programs will be managed for the Institute by Morehouse School of Medicine. The summer graduate training program, beginning in FY 2003, will last eight weeks and competitively select 20 already enrolled graduate students/summer. Estimated costs for this program are modest, amounting to approximately $100 K/year.

Table 8. Education, Training and Outreach Program Budget Plan

(Millions of Dollars)

	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Baseline Program	1.5	2.0	2.1	2.1	2.2	2.2
Education Team Augmentation			0.5	1.0	1.5	2.0
Postdoctoral Fellows Augmentation		0.7	1.4	1.4	1.4	1.4
Graduate Fellows Augmentation			0.7	1.3	2.0	2.0
Summer Training Augmentation		0.1	0.1	0.1	0.1	0.1
TOTAL	**1.5**	**2.8**	**4.8**	**5.9**	**7.2**	**7.7**

5. COOPERATIVE RESEARCH AND DEVELOPMENT PROGRAM

5.1. GOALS AND OBJECTIVES

The **goal** of the Cooperative Research and Development Program is to create mechanisms for integrating knowledge and technologies, addressing operational requirements early in research development and translating discoveries for possible commercialization. To achieve this goal, the following CAN objectives and augmentation guidelines are relevant:

Objective 1. Knowledge Integration and Risk Evaluation
Objective 2. Countermeasure Development
Objective 3. Science Management Plan
Objective 4. Scientific Knowledge Dissemination
Objective 5. Science Community Access
Objective 6. Industry Partnerships
Objective 7. Research Optimization

Guideline 3. Space Flight
Guideline 6. Training Program
Guideline 7. Data Consolidation
Guideline 8. Consortium Growth

Unlike the Countermeasure Research Program and the Education, Training and Outreach Program, the Cooperative Research and Development Program is not a core program. Its function is to facilitate the activities of the other two (core) programs in ways that enhance the overall effectiveness of the Institute in achieving its mission.

5.2. CURRENT STRATEGIES

5.2.1. Data Integration and Archiving

In addition to generating countermeasures that focus on certain biomedical risks, the NSBRI's research program as a whole, in conjunction with NASA's own ground-based and space-flight research activities, generates valuable data sets. These data are used to develop a sufficient understanding of human function to enable a reliable evaluation of an astronaut's current health and a prediction of the effect(s) of individualized countermeasures or medical treatments on future health. This requires the development of quantitative and sophisticated **models** and techniques, leading to structured planning for adequate and timely responses to medical and psychological challenges in space.

The NSBRI has initiated a strategic effort based at its Headquarters and at JSC to coordinate and fully develop a central Institute/NASA modeling and data system, in accordance with ***Objectives 1 (Knowledge Integration and Risk Evaluation) and 2 (Countermeasure Development)*** and ***Guideline 7 (Data Consolidation)***. This activity cuts across the Institute's research teams (see Volume II) and aims at producing an integrated repository of medical and research data for the scientific community, including appropriate access to NASA's flight data archive. This initiative advances progress to meet ***Objectives 4 (Scientific Knowledge Dissemination) and 5 (Science Community Access).***

5.2.2 Translational Research for Space Medicine

The NSBRI's Countermeasure Research Program is a results oriented, cooperative venture with NASA, that has a developmental pipeline summarized by the CDPs of Figure 3. To foster success through countermeasure development phases (***Objective 2 - Countermeasure Development)***), it is important to engage the consumers of such NSBRI deliverables as knowledge, interventions and new technologies, early in the developmental process. Moreover, it is mutually and strategically advantageous to have interactive clinical involvement between the NSBRI and the Space Medicine and Health Care Systems Office at JSC. This activity provides NSBRI participants with exposure to the space medicine operations environment, where the countermeasures ultimately have to work (***Guideline 3 - Space Flight***). At the same time, the interactions provide the flight surgeon and astronaut communities with exposure to NSBRI-provided NASA extramural expertise, in line with ***Objectives 1 (Knowledge Integration and Risk Evaluation), 2 (Countermeasure Development), 4 (Scientific Knowledge Dissemination) and 7 (Research Optimization)*** and ***Guidelines 3 (Space Flight) and 7 (Data Consolidation).***

In addition to linking NSBRI research and development to the Space Medicine community for clinical reasons, it is also important to establish links to ensure that technological advances are able to interface with engineering and human factors constraints and platforms. Operational considerations built in early in the CDP evolution with ensure more favorable outcomes and increase the probability of NSBRI countermeasure developments actually being used to mitigate health risks in space (***Objective 2 - Countermeasure Development and Guideline 3 - Space Flight).***

While the NSBRI Countermeasure Research Program (Section 3) is a peer-reviewed program supported by NASA, the joint NASA – NSBRI initiative in space medicine just described is operationally driven, with the **goal of advancing the field of space medicine**. To this end, the emphasis is on direct clinical applications of countermeasures to space medicine and the translational requirements, results and resources needed to prepare investigations for clinical readiness in a flight environment.

5.2.3. Partnerships

This supporting activity recognizes that the NSBRI shares many of its goals and objectives with established elements of the world's scientific and technological establishment and that the limited resources of the NSBRI can be increased through effective partnerships. Clearly NASA has and continues to be a strong Institute partner. The NSBRI also has and continues to develop and maintain partnerships with other federal agencies, including the institutes of the NIH (e.g., National Institute on Deafness and Other Communication Disorders) and elements of the DoD. The strategy is to enable appropriate discussions and collaborations directed at facilitating rapid transfer of research findings on analogous medical problems, achieving aspects of ***Objectives 4 (Scientific Knowledge Dissemination), 5 (Science Community Access) and 7 (Research Optimization).***

In addition to strategic relationships with federal partners, the NSBRI has productive and appropriate partnerships with scientific and academic institutions and organizations, industry and international organizations. Developing and nurturing such partnerships are the responsibilities of every part of NSBRI. There is no one group designated to carry out this activity. It is singled out here to emphasize the central role that such activities should play in the future. The partnerships span all three Strategic Programs of the Institute and help in building community cceptance for space research and space medicine as emerging disciplines. In some instances, these have led to expansion of the Institute's consortium, through open competition ***(Guideline 8 - Consortium Growth)***.

5.2.4. Industry Forum

The members of the NSBRI Industry Forum are representatives of space and biomedically-related industries who keep the Institute in touch with the industrial community and aid in technology transfer.[10] The Forum serves as a mechanism for achieving ***Objective 6 (Industry Partnerships)***, largely through an advisory role rather than providing active participation in technology transfer of NSBRI research for earth-based spin off advances. Recently, the Industry Forum members have expressed an interest in a more active role in technology transfer and in supporting graduate and post-doctoral fellowship training (Section 4.3.2).

5.3. GAPS AND MODIFICATIONS

5.3.1. Risk Evaluation

In addition to knowledge and data integration activities described in Section 5.2.1, the Institute plans to address the risk evaluation component of ***Objective 1 (Knowledge Integration and Risk Evaluation)*** by expanding its efforts with NASA in several areas. One area concerns coordinated efforts among JSC, the NSBRI, NASA's Office of Space Flight and Office of Biological and Physical Research, and the Chief Health and Medical Officer, to work on the:

- Top-level mission requirements for Crew Health and Safety from the Office of Space Flight;
- Status of research deliverables from the Office of Biological and Physical Research, including the NSBRI; and
- Risk mitigation stoplight charts for preparedness.

These efforts address ***Objective 7 (Research Optimization)*** and ***Guideline 3 (Space Flight)***. They are important because they allow the NSBRI to contribute to a NASA-wide initiative to have one overarching risk mitigation program. Moreover, the Institute is best prepared to have impact in meeting ***Objectives 1 (Knowledge Integration and Risk Evaluation) and 2 (Countermeasure Development)*** if the high likelihood, high consequence risk with low risk mitigation status health concerns are adequately supported in prioritizing research efforts.

Part of the challenge in adequately assessing risk is to continue, and to enhance, the integration of data and to adjust the CPR accordingly. This activity builds on Section 5.2.1. The NSBRI's activities in this area occur through coordinated initiatives between NSBRI Headquarters and JSC (Section 5.2.1) and with the NSBRI research teams (Strategic Plan Volume II). However, there are two gaps.

First, it is important to develop, in partnership with NASA, a comprehensive, integrated and systematic risk management approach applicable to space flight crews. In part, this means developing a quantitative risk assessment and management model similar to that used to estimate risk level in various Earth populations engaged in endeavors with risk. The Institute has begun to explore this approach with the Baylor College of Medicine Risk Management Department and consultants from industry (***Objectives 1 (Knowledge Integration and Risk Evaluation) and 6 (Industry Partnerships)***, and ***Guidelines 3 (Space Flight) and 7 (Data Consolidation)***.

Second, it is important to form advanced data systems for archiving space life sciences information from human missions dating back to Skylab and to make the information available to the scientific community, in accord with ***Objectives 4 (Scientific Knowledge Dissemination) and 5 (Science Community Access)***, and ***Guideline 7 (Data Consolidation)***.

[10] A list of NSBRI Industry Forum members is provided in Appendix 4.F of the accompanying Progress Report.

5.3.2. Capitalizing on Industry Partnerships

To formalize the process of transferring technology, developed in whole or part with NASA/NSBRI support, the Institute plans to work with the Industry Forum to establish an intermediary entity to foster further development, application and potential commercialization of promising research deliverables (***Objective 6 - Industry Partnerships***). There are a number of venture models in current practice that successfully bridge the gap between academic discovery, with protection of intellectual property, and the process of due diligence, licensing and concept/seed support to establish feasibility and potential commercialization of a product driven by technological innovation and market forces.

Some of the services required of an intermediary commercial entity are:

- Creation of a formal process to perform early due diligence on NSBRI discoveries prior to or following protection of intellectual property through investigators' institutions;
- Establishment of a pipeline to bring potential new discoveries into the evaluation process;
- Development of an expert panel of advisors, who work as part of or with the Industry Forum, to assess commercialization potential of innovations;
- Possible seed or matching support to augment government investment in NASA/NSBRI research and technology (countermeasure) development;
- Licensing of promising discoveries, either individually or in partnership with others, to move innovation(s) out of the academic, and into the industrial, area; and
- Sharing of entity support, risk and gain by members of the Industry forum and others who invest in the effort.

5.4. RESOURCE REQUIREMENTS

5.4.1. Program Resources

Data integration and archiving activities described in 5.3.1. are anticipated to increase over time at a rate of approximately $200 K per annum, as countermeasure research generates more data and there is further bilateral sharing of information, including astronaut health data, between the NSBRI and JSC. In response to the risk management gap, it is proposed to initiate a small, focused risk modeling effort in FY 2004. This effort, budgeted at $500 K for the first two years and $600 K for the next two years, would explore the feasibility of using Earth-based risk models to estimate space-based risks.

To allow for "fast track" develop and the ability to expeditiously refocus or initiate research on high priority risk evaluation and mitigation efforts, discretionary funds can allow the Institute to perform a variety of tasks to enhance deliverables to NASA. These funds scale modestly over five years but enable research funds to be available for high priority projects that must be acted upon quickly (i.e., before the next round of solicitations that also serve to prioritize research efforts).

5.4.2. Operational Resources

The successful NSBRI/JSC initiative in space medicine is proposed to increase to address operation needs as set forth by NASA. A proposed budget is shown in Table 9.

Table 9. Cooperative Research and Development Program Budget Plan

(Millions of Dollars)

	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Data Integration and Archiving	1.4	1.4	1.6	1.8	2.0	2.6
Discretionary *	1.0	1.0	1.5	1.5	2.0	2.0
Risk Modeling Augmentation			0.5	0.5	0.6	0.6
PROGRAM TOTAL	**2.4**	**2.4**	**3.6**	**3.8**	**4.6**	**5.2**
JSC / NSBRI Space Medicine	0.5	1.0	1.0	1.5	1.5	2.0
TOTAL	**2.9**	**3.4**	**4.6**	**5.3**	**6.1**	**7.2**

* Discretionary funds used to support flight proposals in 2002.

6. BUDGET AND RESULTS

6.1. ADMINISTRATIVE INFRASTRUCTURE

As outlined in Section 2.8, the NSBRI is an exemplary, performance driven partnership with NASA that embodies the President's Management Agenda. In working towards its goals and objectives, the approaches taken by the Institute in each of its Programs are focused and of high value, both scientifically and fiscally. The NSBRI can be tasked by NASA to increase its Countermeasure Research Program and the Institute is readily scalable. The administrative costs are kept in check by outsourcing and utilizing the infrastructure that is already in place at the academic institutions. Moreover, the extensive use of e-business requires only a modest increase in NSBRI Headquarters personnel if the Institute were to expand. At present, the Institute's administrative infrastructure costs $2.2 M/year. A modest inflation is factored into this number in future years.

6.2. BUDGET PLANS

Table 10 summarizes the baseline program, where the first three rows are obtained from the Program budgets in Tables 7 to 9. The **critical mass** of the Institute is the Program Total for FY 2003, which is **$30.4 M**. This figure is made up, in part, of the critical mass figure of $23.8 M for the Countermeasure Research Program (Section 3.4.1). Table 11 gives the Institute augmentation budget and Table 12 provides the full program budget plan.

Table 10. Institute Baseline Program Budget Plan

(Millions of Dollars)

	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Countermeasure Research	19.8	23.8	24.3	24.8	25.3	25.8
Education, Training & Outreach	1.5	2.0	2.1	2.1	2.2	2.2
Coop Research & Development	2.4	2.4	3.1	3.3	4.0	4.6
Administration	2.2	2.2	2.3	2.4	2.5	2.6
PROGRAM TOTAL	**25.9**	**30.4**	**31.8**	**32.6**	**34.0**	**35.2**
JSC / NSBRI Space Medicine	0.5	1.0	1.0	1.5	1.5	2.0
GRAND TOTAL	**26.4**	**31.4**	**32.8**	**34.1**	**35.5**	**37.2**

Table 11. Institute Augmentation Program Budget Plan

(Millions of Dollars)

	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Countermeasure Research		1.8	4.3	6.9	9.4	12.0
Education, Training & Outreach		0.8	2.7	3.8	5.0	5.5
Coop Research & Development			0.5	0.5	0.6	0.6
PROGRAM TOTAL		**2.6**	**7.5**	**11.2**	**15.0**	**18.1**

Table 12. Institute Full Program Budget Plan

(Millions of Dollars)

	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Countermeasure Research	19.8	25.6	28.6	31.7	34.7	37.8
Education, Training & Outreach	1.5	2.8	4.8	5.9	7.2	7.7
Coop Research & Development	2.4	2.4	3.6	3.8	4.6	5.2
Administration	2.2	2.2	2.3	2.4	2.5	2.6
PROGRAM TOTAL	**25.9**	**33.0**	**39.3**	**43.8**	**49.0**	**53.3**
JSC / NSBRI Space Medicine	0.5	1.0	1.0	1.5	1.5	2.0
GRAND TOTAL	**26.4**	**34.0**	**40.3**	**45.3**	**50.5**	**55.3**

6.3. EXPECTED RESULTS

The following outcomes are expected from the implementation of this Strategic Plan:

- Clear identification and assessment of the biomedical risks of space travel;
- Comprehensive understanding of the molecular, cellular and organ-level responses of humans to weightlessness;
- Development of high-quality integrated research program focused on targeted risks and countermeasure development;
- Involvement of the biomedical research community in the Institute's program through open solicitations and independent merit review, promoting the highest quality space biomedical research;
- Development of innovative methods and advanced systems and technology for the provision of inflight astronaut medical care;
- Development of direct links between the biomedical research community and NASA's operational medical and biomedical communities that assures effective communication and development of a more complete understanding of the space-flight operational experience;
- Multidisciplinary coordination and integration of various research activities to promote the rapid, efficient, multi-directional exchange of ideas, minimize duplication of effort and develop an integrated understanding of the human physiological response to space flight;
- Integrated assessment of the effects of countermeasure candidates on human physiology using modeling, simulation and multidisciplinary experimentation;
- Development of mechanisms for appropriate access to past and future astronaut data by the active biomedical research community;
- Improved research community understanding of and access to special NASA facilities;
- Strong scientific and technical partnership with industry in space biomedical research;
- Development of international community participation in cooperative biomedical research related to countermeasure development;
- Rapid transfer of the scientific, technical and medical knowledge gained from space research to corresponding Earth-related problems;
- Ensured development of future space biomedical scientists and engineers with training beyond the undergraduate level;
- Informed scientific community concerning space biomedical issues;
- Increased scientific literacy of teachers, students and the general public because of the excitement of space life sciences;
- Establishment of internet-based distance education for younger and older students of the space life sciences;
- Larger numbers of students attracted to science careers in life sciences, engineering and technology-based fields;
- Enhanced scientific skill and technological readiness of educators;
- Development of healthy behaviors and attitudes among students and families and increased family involvement in a child's learning; and
- Increased public awareness and support for space life science research.

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

STRATEGIC PLAN

Volume II

May 24, 2002

1.0 RECAPITULATION: MISSION AND STRATEGIC PROGRAMS

As discussed in Section 2 of the Strategic Plan:

> **The Mission of the NSBRI will be to lead a National effort for accomplishing the integrated, critical path, biomedical research necessary to support the long term human presence, development, and exploration of space and to enhance life on Earth by applying the resultant advances in human knowledge and technology acquired through living and working in space.**

To carry out this mission, the NSBRI focuses its activities on three Strategic Programs:

Strategic Program 1: Countermeasure Research
Strategic Program 2: Education, Training and Outreach
Strategic Program 3: Cooperative Research and Development

This document contains the detailed Team Strategic Plans for the 11 research teams focused on Strategic Program 1, and the Education and Outreach Team focused on Strategic Program 2. There is overlap and integration among the Programs and Team Strategic Plans, as described in each of the Plans.

2.0 GENERAL INFORMATION

Critical Path Roadmap

In order to identify and make publicly known the biomedical risks of space flight and the research questions that must be answered to reduce those risks, NASA and the NSBRI have developed the Critical Path Roadmap (CPR). The CPR is an interdisciplinary tool to assess, understand, mitigate and manage the risks associated with long-term exposure to the space environment. It assumes an overarching strategy that integrates requirements, risks, risk factors, critical questions, tasks, deliverables and risk mitigation with the intent of directing biomedical research in support of human space flight, especially human missions of exploration. The CPR is based in part on recommendations from internal NASA experts, NSBRI scientists, advisory committees, task forces and published reports, such as the National Research Council Space Studies Board's "A Strategy for Research in Space Biology and Medicine in the New Century," as well as numerous other reports.

The current CPR is a product that has identified 55 risks and 250 unique critical questions. A more extensive overview as well as a list of all the risks and critical questions are available on the Web site http://criticalpath.jsc.nasa.gov/. Each of the 11 research team strategies addresses specific risks in the CPR in developing countermeasures to reduce the risk of space flight and satisfy NSBRI's primary goal. Figure 2.1 shows the general types of countermeasures that are available for use.

Countermeasure Readiness Levels

NASA has developed a scale to define, assess and quantify the level of "countermeasure readiness." The use of this scale allows NASA to determine how each funded research project fits into the countermeasure development "flow" and to monitor progress in countermeasure development. Figure 2.2 illustrates the Countermeasure Readiness Levels (CRL) scale, which describes the level of scientific maturity of countermeasure research, starting from the fundamental studies that suggest potential countermeasures to studies that allow the systematic evaluation and validation of countermeasures ready for operational implementation.

Countermeasure Development Phases

Although the CRL scale represents a useful management tool for the general NASA biomedical research program, the NSBRI finds that a different scale is more useful in managing its program of countermeasure development. That scale, termed countermeasure development phases, has only six levels and is defined in Figure 2.3. Most NSBRI research activity takes place in phases one to three. Each research team will use this scale to show their schedule of progression to final operational countermeasures.

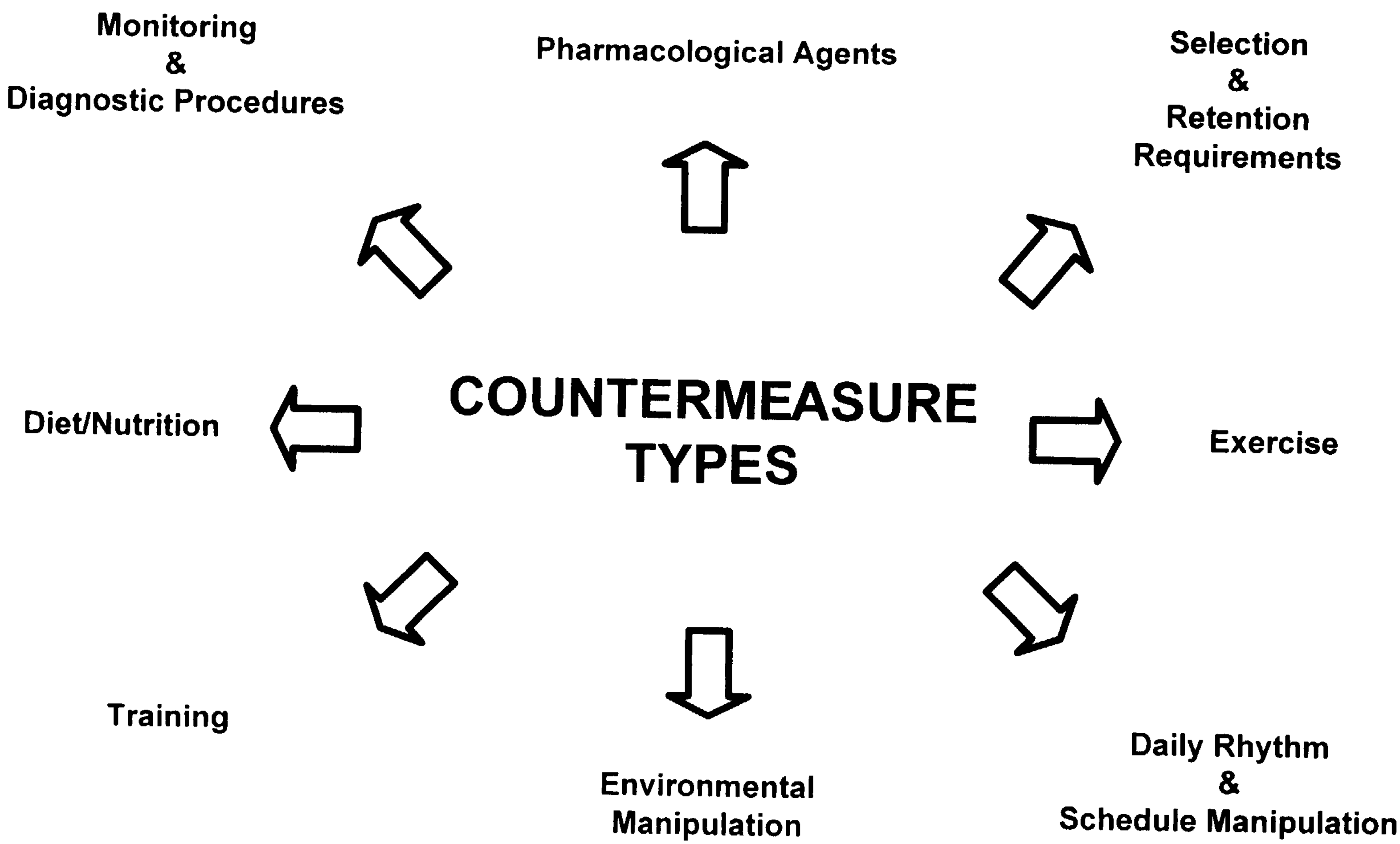


Figure 2.1. General countermeasure types.

Figure 2.2. COUNTERMEASURE READINESS LEVELS

BASIC RESEARCH

RESEARCH TO PROVE FEASIBILITY

COUNTERMEASURE DEVELOPMENT

COUNTERMEASURE DEMONSTRATION

COUNTERMEASURE OPERATIONS

1. PHENOMENON OBSERVED AND REPORTED, PROBLEM DEFINED.
2. HYPOTHESIS FORMED, PRELIMINARY STUDIES TO DEFINE PARAMETERS, DEMONSTRATE FEASIBILITY.
3. VALIDATED HYPOTHESIS, UNDERSTANDING OF SCIENTIFIC PROCESSES UNDERLYING PROBLEM.
4. FORMULATION OF COUNTERMEASURES CONCEPT, BASED ON UNDERSTANDING OF PHENOMENON.
5. PROOF OF CONCEPT TESTING AND INITIAL DEMONSTRATION OF FEASIBILITY AND EFFICACY.
6. LABORATORY/CLINICAL TESTING OF POTENTIAL COUNTERMEASURE IN HUMAN SUBJECTS TO DEMONSTRATE EFFICACY OF CONCEPT FOR SPECIFIC PROBLEM.
7. INTEGRATED EVALUATION WITH HUMAN SUBJECTS IN CONTROLLED LABORATORY CONDITIONS SIMULATING OPERATIONAL SPACE FLIGHT ENVIRONMENT.
8. VALIDATION WITH HUMAN SUBJECTS IN ACTUAL OPERATIONAL SPACE FLIGHT TO DEMONSTRATE EFFICACY AND OPERATIONAL FEASIBILITY.
9. COUNTERMEASURE FULLY FLIGHT TESTED AND READY FOR OPERATIONAL IMPLEMENTATION.

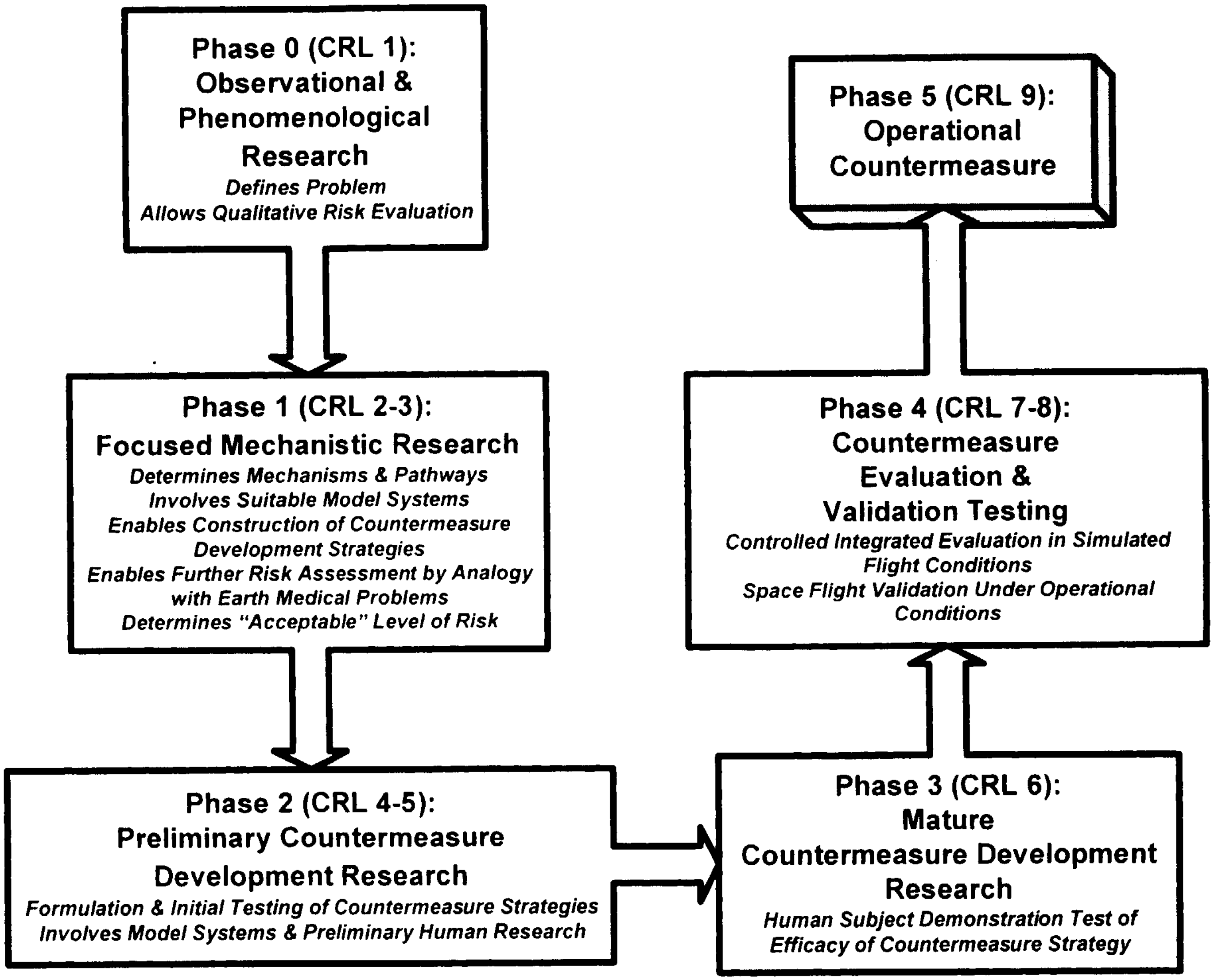


Figure 2.3. Phases of countermeasure development and their relation to countermeasure readiness levels (CRLs)

3.0 BONE LOSS

Team Leader: Jay R. Shapiro, M.D.
Professor, Department of Medicine
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road, Rm. A3068
Bethesda, MD 20814-4799
301-295-3600
301-295-3557 FAX
jshapiro@usuhs.mil

3.1 INTRODUCTION

The musculoskeletal system is uniquely dependent on Earth's gravity. Although human adaptation to the microgravity environment has allowed astronauts to maintain overall function, the musculoskeletal system rapidly degrades once the force of gravity is removed. Muscle atrophy has been documented by biopsy after 11 days in flight. The loss of cortical and trabecular bone follows the loss of mechanical strain normally transmitted from muscle. Several studies, American and Russian, have demonstrated that bone loss during flights lasting 4 to 6 months approximates 1-2% per month. However, some researchers have reported the range of bone loss in Mir cosmonauts varies from 0% to 24% per month when measured in cancellous and cortical bone in the tibia. Bone loss of this magnitude has been observed in human bed rest studies and in individuals following spinal cord injury. The loss of bone mass compromises bone strength, and diminished bone strength increases the risk of fracture, presenting a hazard to astronaut health and function and a threat to mission success.

The NSBRI Bone Loss Team aims to develop an effective countermeasure to bone loss. Countermeasures applied to date, including current in flight exercise regimens, dietary and vitamin supplements, and pre-flight conditioning, have not prevented bone loss during long duration flights such as those on Mir. Exercise regimens are currently being re-evaluated. Pharmacological interventions are also under investigation. However, as discussed below, progress in these areas will require a better understanding of the basic mechanisms that alter bone cell function in a microgravity environment. The current Bone Team research program includes basic and applied research targeted at countermeasure development and testing; each project focuses on issues relevant to mechanisms of bone loss, as well as, means that may be employed in the near future to mitigate the negative effects of microgravity on bone cells.

3.2 RISKS

The following risks in the Bone Loss Discipline Area have been identified in the Critical Path Roadmap (CPR) (risk number in parentheses):

- Development of Osteoporosis (9)
- Fracture and Impaired Fracture Healing (10)
- Injury to Soft Connective Tissue, Joint Cartilage, and Intervertebral Disc Rupture w/ or w/o Neurological Complications (11)
- Renal Stone Formation (12)

The majority of astronauts/cosmonauts have delayed return of bone density to normal following prolonged space fight causing two postflight health hazards: 1) prolonged fracture risk during active post-flight re-conditioning and 2) a life long increase in fracture risk and the risk of related soft tissue injury if bone density fails to attain pre-flight levels. As a result, the Bone Team has added an additional risk to the list currently found in the CPR:

- Delayed Return of Bone Mass to Normal Mass and Strength Following Extended Exposure to Weightlessness.

3.3 GOALS

The Bone Loss Team has the following goals for its program:

Risk-Based Goals

Goal 1: *Reduce the risk of accelerated bone loss leading to osteoporosis.*

Goal 2: *Reduce the risk of fracture and evaluate the potential for impaired fracture healing*

Goal 3: *Reduce the risk of injury to soft connective tissue, joint cartilage, and intervertebral disc rupture*

Goal 4: *Reduce the risk of renal stone formation*

Goal 5: *Promote the return of bone mass and strength to normal following an extended exposure to weightlessness*

Non Risk-Based Goals

Goal 6: *Collaborate with the NSBRI Muscle, Radiation and Technology Development Teams on the development of methods for inflight assessment of bone health and the appropriate monitoring, diagnosis and treatment for bone loss, fractures and soft tissue injury. Develop methods for the inflight assessment of renal stone risk and the prevention and treatment of renal calculi developed during flight.*

Goal 7: *Develop Earth-based applications of countermeasures to reduce increased bone loss and fracture risk found in health hazards, such as in children with non-weight bearing disorders and in adults following CNS and spinal cord trauma*

Goal 8: *Develop Earth-based applications of low weight, sensitive bone density machine*

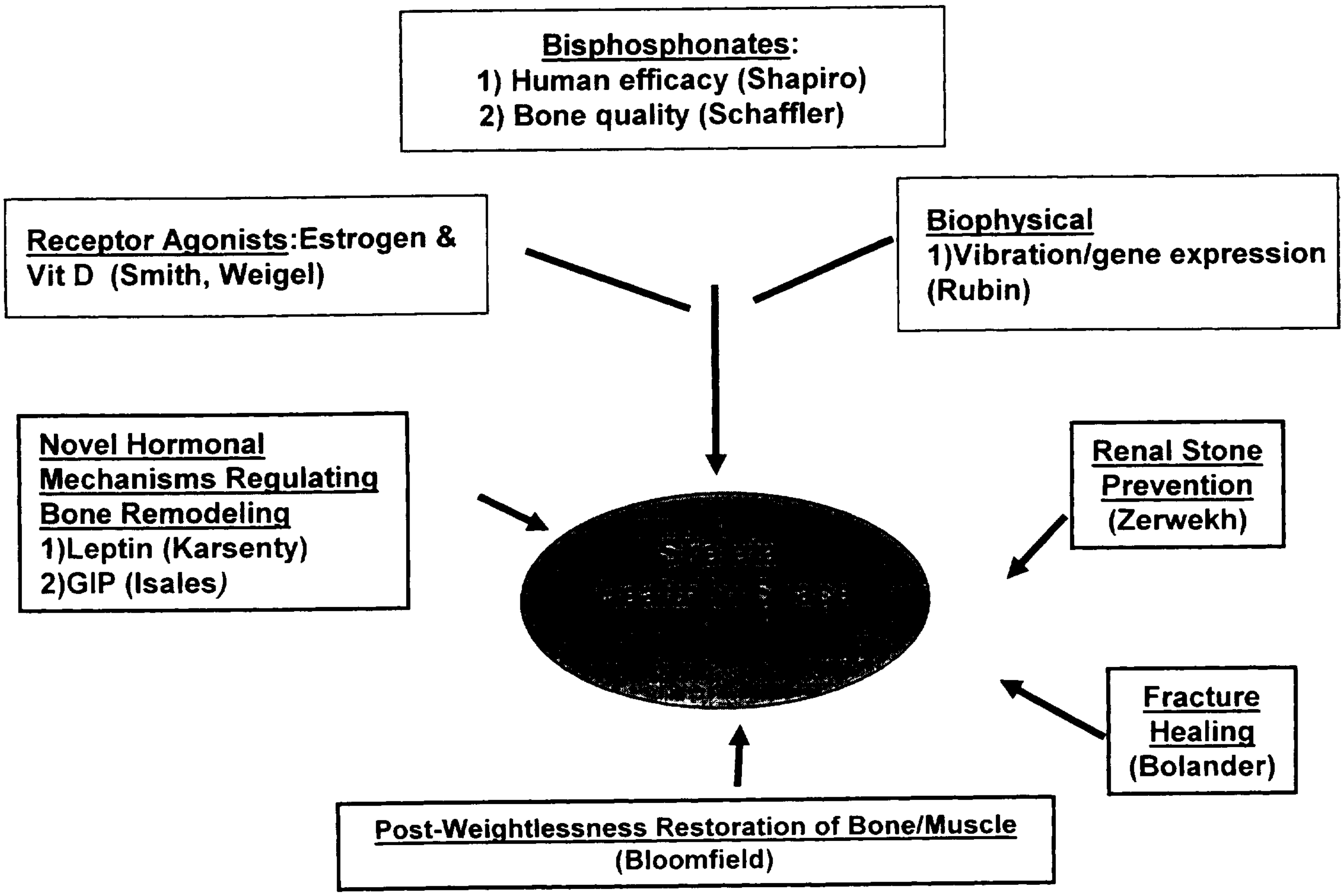
Goal 9: *Integrate research and analysis*

3.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

Current Research Projects

The current NSBRI program in bone includes both basic research and clinical research aimed at the development of countermeasures that may be tested during flight of animals or crew within the next 3-5 years. Project Countermeasure Readiness Levels (CRL) range from Level 2 for a basic research investigation of leptin and GIP function as potential hormonal targets for countermeasure development to Level 6 for testing of new intravenous bisphosphonates in spinal cord injury patients as a model of microgravity in parallel to testing of use of intravenous bisphosphonate prior to spaceflight and testing of KMgCit for renal calculus prevention. Current and anticipated future countermeasures include exercise, pharmaceuticals, mechanical methods, and nutritional methods. Figure 3.1 summarizes the different approaches taken by the projects in the Bone Loss Program.

Figure 3.1.



Operational Bone Team Activities

Members of the Bone Team are active participants in operational programs and planning at JSC. For instance, Dr. Shapiro serves on the Integrated Products Team for Bone, Muscle and Exercise. Recently, he has advised JSC flight surgeons on the evaluation and potential treatment of astronauts whose bone mass may have been negatively impacted by multiple flight exposures. This effort is joined with physicians at the MD Anderson Hospital in Houston. Additional efforts in this area have involved participation in a NASA/NSBRI committee planning the evaluation of clinical biochemical testing in astronaut crew before, during and after flight. As another example, Dr. Sue Bloomfield, Texas A & M University, is an active member of the Critical Path Roadmap development team which has revised and expanded issues of relevance to the Critical Path Roadmap program.

Each project is briefly summarized here and Table 3.1, presenting the basic research focus and experimental design, countermeasure focus, and contribution to achievement of team goals:

Basic Research Projects (Countermeasure Readiness Levels 2-4)

1. *Leptin as a Regulator of Bone Formation in Microgravity Bone Loss*: Karsenty Elefteriou, Dacquin, (Baylor): Leptin is a recently defined polypeptide hormone produced by adipocytes which binds to hypothalamic receptors and which decreases bone formation rate. Increased bone mass in obesity, a condition in which leptin levels are diminished, has led to studies showing that the absence of leptin can lead to high bone mass even in hypogonadal and hypercortisolemic states. In addition, it appears that leptin must bind to a hypothalamic receptor to control bone formation. Leptin indirectly appears to control bone formation by acting on the osteoblast via an yet undefined factor(s). The study seeks to :1) determine whether leptin controls bone mass by releasing a humoral substance following its binding to hypothalamic receptors, 2) to determine if the sympathetic nervous system is involved in mediating leptin control of bone formation, and 3) to determine whether a naturally occurring soluble form of the leptin receptor can prevent leptin inhibitory action on bone.

Significance: This research is focused on the relationship of the CNS to peripheral multifunctional hormones, which are now recognized to modulate osteoblast function and thus to influence bone mass. It addresses Goal 1, Reduce risk of accelerated bone loss leading to osteoporosis. Understanding the mechanism of leptin action promises to open a new route for the therapeutic control of bone mass, suggesting potential new countermeasures. Furthermore, the role of the CNS in the regulation of bone mass may have important implications for the problem of bone loss during spaceflight. The countermeasure development focus of this project, therefore, addresses central regulation of hormonal modulation of bone remodeling.

2. *Therapeutic Modulation of Systemic Glucose-Dependent Insulinotropic Peptide Levels to Counteract Microgravity-Induced Bone Loss*: Isales, Bollag, Mulloy (Medical College of Georgia): mRNA for the GIP receptor (GIPR) has been found in osteoblast cell lines and in isolated rat osteoclasts. Also, GIP appears to promote osteoblast differentiation and maturation, to stimulate type I collagen mRNA expression and to increase alkaline phosphatase activity in SaOS2 cells. GIP inhibits PTH-induced bone resorption. Transgenic mice over expressing GIP show increased bone mass. Intermittent GIP injection prevents bone loss in ovarectomized mice. The study will determine: 1) whether elevations in endogenous GIP leads to an increase in bone formation in GIP over expressing mice, including observing GIP effects in bone loss associated with estrogen and androgen deficiency and the effects of nutritional alterations on GIP effects on bone and 2) whether endogenous elevation in GIP prevents bone loss in GIP over expressing mice subjected to hindlimb suspension. These studies may establish GIP as the potential link between food intake and bone metabolism.

Significance: The problem of nutritional modification of bone loss during spaceflight has long been a subject of discussion and intervention but without success. Altering salt, protein or carbohydrate intake or caloric intake has not provided answers to control of bone loss. This project, directed at Goal 1, addresses a novel relationship between diet and bone cell function and may result in novel countermeasures that expand nutritional impact on bone mass during extended spaceflight.

3. *Receptor Countermeasures to Bone Loss in Microgravity*: Smith, Weigel, Bloomfield, Narayanan, Suva (Baylor, U. Arkansas): Space flight is associated with decreased gonadal steroid levels and 25(OH) D and 1,25(OH)D2 levels. This study examines specific pharmacological alternatives, estrogen and vitamin D receptor agonists, as countermeasures to bone loss. It is hypothesized that the appropriate administration and or combination of receptor active agent(s) will improve calcium absorption, promote bone formation and decrease bone resorption. These studies focus on novel vitamin D receptor agonists (VDR) such as EB189 and selective estrogen receptor modulator agents (SERMs) such as raloxifene. This study targets the ability of novel receptor agonists of the vitamin D receptor and estrogen receptor alone or in combination to modulate osteoblastogenesis, mature osteoblast function and osteoclastogenesis in vitro and in vivo. The study currently addresses these effects on preserving bone mass in the hindlimb suspended rat model of microgravity. Attenuation of disuse bone loss by estrogen and raloxifene in the hind limb suspended rat has been demonstrated. Altered osteoblast differentiation and preservation of bone mass during hindlimb suspension has been demonstrated using VDR agonists.

Significance: Hormonal alterations during spaceflight impact bone remodeling and potentiate bone loss. These changes assume greater significance as extended microgravity exposure is anticipated. Understanding the cellular mechanisms responsible for these changes are basic to defining and suggesting effective countermeasures to hormonal imbalance and thus bone loss. Flight testing with animal models is critical to correcting hormonal perturbations secondary to microgravity. This project addresses Goal 1. Countermeasure development involves receptor agonists used during spaceflight to correct gonadal/vit D imbalance.

Applied Research Projects (Readiness Levels 4-6)

4. *Muscle Bone Inbalance After Non-Weightbearing*: Bloomfield, Hogan Smith, Warren, Schultheis (Texas A & M): This study utilizes the hind limb suspended rat model to examine: 1) the time course of recovery of functional properties in a muscle bone pair of the hindlimb during reambulation after 28 days of skeletal unloading, 2) the mechanisms affecting the rate of recovery during periods of maximal mismatch between muscle and bone functional properties, 3) the effectiveness of two exercise regimens and a biomechanical intervention to promote return of bone strength during recovery, 4) the effectiveness of PTH treatment and growth hormone treatment as anabolic countermeasures during recovery.

Significance: Fracture risk, soft tissue injury and renal calculus formation continue into the post-flight period. This project addresses post-flight muscle/bone imbalance, and anticipates countermeasures to minimize continuing injury risk. It contributes to the achievement of Goal 5. Promote return of bone mass and strength to normal following an extended exposure to weightlessness. This project will develop countermeasures that may combine effective exercise regimens and medication to improve osteoblastic bone formation following flight.

5. *A Biomedical Countermeasure for Disuse Osteopenia*: Rubin, Hadjiargyrou, Zhi, Judex, Dowd, Donahue (State University of New York at Stony Brook and

Brookhaven National Labs). Whole body vibrational impact may provide an effective countermeasure to bone loss during exposure to microgravity. Using the tail-suspended rat and an oscillating plate to deliver mechanical strain, this study addresses 4 specific aims: 1) to correlate bone remodeling activity with spatial and temporal gene transcriptional activity in hind limb bone, 2) to correlate bone remodeling activity in the hind limb in the presence of 10 min. daily osteogenic mechanical stimulus (0.3 g @ 30 Hz) with the spatial and temporal transcriptional activity in the bone, 3) to correlate bone remodeling activity in the hind limb which arises from 23 h, 50 min of disuse interrupted daily by 10 minute osteogenic mechanical stimulus (0.3 g @ 30 Hz), 4) to correlate recovery of bone mass and transcriptional activity in the hindlimb following 28 days of disuse followed by 7 or 28 days of normal weightbearing vs. 28 days of disuse followed by 7 or 28 days of normal weightbearing plus 10 minutes/day of mechanical stimulus (0.3 g@ 30 Hz), vs. control. Evaluation will include histomorphometry, microtomographic imaging to present 3D models of the femur, gene expression patterns (actin, integrin β-3, osteopontin, collagen 1, connexin 43, BMP-2, MMP-1, MCSF, and ODF). IGF-1 levels in serum will be measured as indicative of coupled bone resorption and formation.

Significance: Several studies, animal and human have documented the beneficial effect of impact loading via vibrational stimuli on bone gene expression and bone mass. Impact loading in this manner may prove an effective countermeasure to bone loss in space. This project addresses Goal 1. Since this study requires early flight testing to facilitate the design of effective instrumentation, Dr. Rubin has submitted one plan for flight testing for review. Countermeasure development involves the design and construction of an effective device for vibrational mechanical loading.

6. *Resorption Suppression and Bone Health in Disuse Bone Loss*: Schaffler (Mt. Sinai School of Medicine): This protocol tests the hypothesis that long-term suppression of bone remodeling with bisphosphonate in a disuse situation will result in preserved bone mass and architecture but reduced resistance to fracture because of decreased osteocyte viability and integrity.

Significance: This study assesses potential risks in the utilization of chronic bisphosphonate as a countermeasure during extended duration spaceflight or following return to Earth after shorter microgravity exposure, and addresses Goals 1 and 5. Countermeasure plans include the eventual design of bisphosphonate with specific bone growth activities.

7. *The Effect of Microgravity on Fracture Healing/Ultrasound as a Possible Countermeasure*: Bolander, Turner, Greenleaf (Mayo Clinic): This program will determine the effect of hindlimb unloading on fracture healing in the rat model of microgravity. The study seeks to identify major cellular and molecular targets for the adverse effects of hindlimb unloading on fracture healing. Fracture healing will be evaluated by comparing histology and histomorphometry as well as by mechanical testing at different time points during fracture healing. The study explores the use of low intensity ultrasound to affect the rate of fracture healing during hind limb suspension. It is expected that ultrasound will promote cartilage callus formation and thus enhance the rate of fracture healing.

Significance: There exists no information about fracture healing in microgravity. This study will apply biomechanical testing and histomorphometry to fractured regions using the hindlimb suspended rat. Addressing Goal 2, Reduce risk of fracture and evaluate potential for impaired fracture healing, the results of this study will orient plans for medical care during flight and extraterrestrial exploration where fracture risk will be substantially increased and the issue of healing fractures will be a major concern. Countermeasure development includes the utility of ultrasound as a means to facilitate fracture healing.

8. *SCI as Model for Microgravity: Effect of Zoledronate*: Shapiro, Toerge, Ballard, Baldwin, Beck, Ruff, Burman, Mustapha (Unformed Services University, Johns Hopkins University and the National Rehabilitation Hospital). This protocol will utilize subjects with spinal cord injury (SCI, tetraplagia and paraplegia) as models of the muscle and bone loss experienced by astronauts during extended spaceflight. The essential elements of this program include 1) measurements of rates of bone loss during non-weightbearing, 2) measurements of rates of loss of muscle mass, 3) determination of biochemical alterations in muscle tissue during prolonged non-weightbearing, 4) geometric and structural analysis of femur bone loss, including 3 D finite element analysis of femur bone before and after treatments for estimation of fracture risk, and 5) an evaluation of the effectiveness of the tertiary potent intravenous bisphosphonate, zoledronate, as a countermeasure to prevent bone loss in these subjects and in astronauts during space flight.

Significance: This study, which addresses Goals 1 and 5, has two achievable outcomes. The first is establishment of the spinal cord injured patient as an Earth-bound surrogate for space-induced bone loss. This task has been accomplished. The second is obtaining data about the effectiveness of a third level bisphosphonate on Earth and during spaceflight. Bisphosphonate testing during flight has not yet been initiated; however, such analysis is on the horizon. Countermeasure development involves the administration of long active bisphosphonate prior to, during and after flight.

9. *Prevention of Microgravity-Induced Stone Risk by KMgCitrate*: Zerwekh, Wuermeser, Pak, Antich. (UT Southwestern Medical Center at Dallas): Both clinical observations and evaluation of the composition of urine related to stone-forming factors indicate an increase risk of stone formation during and after extended spaceflight. The objective of this research study is: 1) to determine the effectiveness of potassium magnesium citrate (KMgCitrate) as a countermeasure to the propensity for stone formation and skeletal mineral loss sustained during spaceflight, 2) to evaluate the effect of KMgCit in averting the diminished muscle Mg and K concentrations that may occur during microgravity-related muscle atrophy, and 3) to assess the efficacy of KMgCit supplementation in reducing microgravity-induced increase in bone resorption and urinary calcium. These specific aims will be studied in healthy volunteers on chronic bed rest for 5 weeks. Study phases will include 1 week of ambulatory evaluation (A), 2 weeks of bed rest (weeks 2-6) (B) and 2 weeks of reambulation (weeks 7-8) (C). Subjects will receive Relyte tablets, 3 tabs with breakfast, and 3 with dinner to equal 42 mEq K, 21 mEq Mg, and 63 mEq citrate. Placebo controls are included in the study design.

Significance: Renal calculus formation has occurred in cosmonauts, and this study addresses Goal 4, Reduce risk of renal stone formation. Stone formation is a major health hazard, and previous clinical studies point to the utility of KMgCit as a useful countermeasure. KMgCit is currently under consideration or in use for flight testing. KMgCit may offer additional benefits now under study in the bed rest model. Flight-testing is appropriate for this agent.

Achieving Non Risk-Based Goals

The team's activities towards achieving Goal 6, which includes the development of monitoring methods for bone loss inflight, involve the development and utilization of the AMPDEXA machine for measurement of bone mineral density during extended flight. The instrument will be of use on the ISS to measure sequentially and in real time changes in bone mass, estimated at 1-2%/month during flight. These types of measurements are of value because they permit: 1) recording differences in rates of bone loss of individual astronauts and the correlation of changes in bone biomarkers and hormones related to rates of bone loss, and 2) development of specific countermeasures applied at the time bone loss is evident. This complements preventive measures applied prior to flight. This machine is ready to be used in healthy volunteers. Plans will be made for its utilization at the Johns Hopkins Applied Physics Laboratory and for chronic bed rest studies at the National Rehabilitation Hospital using Dr. Shapiro's current protocol.

It should be emphasized that several components of the bone program impact the delivery of medical care on Earth (Goals 7 and 8). Investigating factors responsible for a potential muscle/bone functional gap during recovery from weightlessness (Bloomfield) addresses an issue of great significance to the rehabilitation community. In addition, it raises the question of factors responsible for the delay in recovery of osteoblast function following microgravity exposure. Definition of mechanisms involved in bone loss during weightlessness and treatment with a novel intravenous bisphosphonate (Shapiro) is relevant to pediatric and adult non-weightbearing populations at risk of fracture but currently untreated. Schaffler addresses the question of potential long term risk secondary to bisphosphonate treatment, a matter of importance to a large number of elderly currently under treatment for osteoporosis. These analyses and others on the team address Goal 7, Develop Earth-based applications of countermeasures for bone loss and fracture risk found in health hazards. Initial work towards achievement of Goal 8, Earth-based applications of low weight, sensitive bone density machine, involves completion of experiments in Spinal Cord Injury (Shapiro) project to provide a monitoring arm (AMPDEXA machine) to correlate bone loss rates with biomarker changes.

Achieving Goal 9, Program Integration, is summarized in Table 3.2: The members of the Bone Team maintain a constant level of contact through teleconferences, individual conferences and team meetings at national symposia and meetings. A current program at the Applied Physics Laboratory involves 3 D finite element analysis, which will be expanded for modeling purposes as fracture risk data is obtained.

Needs for Bone Loss Program

Bone loss during extended space flight and habitation on extra terrestrial bodies at reduced gravity poses a significant health hazard for Astronaut crews. This program is developing 3D finite element analysis for estimates of fracture risk. In view of a rate of bone loss during flight that is 10 fold that seen in postmenopausal women this risk of fracture that could approach a 10-15% level during extended spaceflight. This fact is emphasized in NASA Critical Path statement. The development of novel countermeasures directed at minimizing bone loss and thus fracture risk, requires a greater understanding of the responsible mechanisms at the cellular level. Our current understanding of bone loss however is limited to the level of the "effector" mechanisms, i.e., bone forming and bone resorbing cells. We do not understand what the mechanosensitive cells in bone actually experience as a result of microgravity, which in turn leads to responses from the effector cells. Accordingly, our ability to specifically target mechanical and exercise countermeasures and more effectively develop and utilize pharmacological intervention is limited. Critical issues for skeletal research, therefore, include issues as fundamental as the detailed characterization of the Earth-based loading environment of the skeleton. Central to this effort is developing a detailed understanding of how muscle loss alters function of bone cells, and whether countermeasures for prevention of muscle atrophy in space will also prevent bone loss. Unweighting effects and signal transduction mechanisms in bone warrant significant attention because of their importance in defining the optimal targets, both mechanical and biological, for countermeasure development. The current NSBRI Bone Loss Program strives to obtain some of this needed information, but more mechanistic studies are required.

The development of new and effective means for measuring bone mass during space flight, the application of effective resistive exercise for the maintenance of muscle and bone mass, and evaluation of biomechanical methods (vibrational impact loading) and new pharmacological agents all require evaluation under microgravity conditions. This analysis applies to both animal and human subjects. Unfortunately, the microgravity cannot be exactly approximated on Earth that may require revisiting the process under which certain projects are considered for flight testing. Targeted countermeasure research in this area in general is hampered by the problem of reproducing the microgravity environment for animal or human studies conducted on Earth. It is necessary that a coordinated effort between NSBRI Bone Team members and JSC staff facilitate flight testing for both animal models and human evaluation.

More research is needed in certain areas to achieve all the risk-based goals of the program. The currently (2000-2003) funded program of the Bone Team addresses Goals 1, 4, and 5 and to a insufficient extent, Goal 2. However, in spite of a broadly distributed request for proposals initiated in February 2000, only one proposal was received for Goal 2, fracture healing, and 2 proposals, neither judged fundable, were received for Goal 3, connective tissue injuries. These issues still need to be addressed. Accordingly, the current NSBRI solicitation again focuses on a call for research to address gaps in the bone program, specifically, fracture healing and soft connective tissue injury.

<u>Evaluation of Current Countermeasure Technologies and Ideas to Further Accelerate Development</u>

One objective of this strategic plan should be to conduct broad-based critical evaluations of current countermeasures nearing the stage of flight-testing. This process could serve to stimulate the search for new and novel methods of protecting Astronauts from the risk of fracture under hazardous conditions.

1) <u>In-Flight Exercise Programs</u>: Resistive/endurance exercise programs are currently being tested under protocols considered by the Integrated Product Team for Bone, Muscle and Exercise. Resistive exercise may be an important adjunct to maintaining muscle mass and bone mass; however, its efficacy in microgravity remains to be determined. At this time 2 methods are considered for flight testing, the Interim Resistive Exercise Device and the cycle ergometer (Tesch).

<u>Recommendations:</u> Critical evaluation of the potential usefulness of each method, in flight, is needed in a timely manner, so that modifications can be considered if the basic protocols are determined to not be effective during flight. A combined and focused NASA/NSBRI review to stimulate novel methods for effective-exercise regimens, under the aegis of the NSBRI Exercise team, is also recommended. Also, determination of the effectiveness of current resistive exercise

regimens by tracking changes in bone mineral density (BMD) with varying intensity, duration or frequency of training is suggested. Certain biomarker measurements such as serum CTX (a resorption biomarker) could be obtained concurrently to establish their usefulness in predicting changes in BMD.

2) Pharmacological agents: New bisphosphonates and receptor agonists (SERMs and Vit D receptor agonists) are among agents currently being developed by or in clinical study by NSBRI Bone Team members. It is necessary that NASA regulations regarding testing agents of potential usefulness be modified to allow flight experience to be gained within the limits of astronaut safety.

Recommendations: Bisphosphonate testing on short-term shuttle flights for determination of acute metabolic effects is recommended. The initial study should pre-treat astronauts with intravenous pamidronate, an extensively used agent about which extensive clinical and toxicological information exists. Completion of Earth-bound studies of chronic effects and drug safety is also required. Administration of potent intravenous bisphosphonates for immediate metabolic effects on shuttle fights and subsequently on the ISS is suggested. Animal studies, on mice or rats, to permit testing novel pharmacological agents, e.g., SERMs and VDR agonists, leptin and GIP in-flight is also encouraged. Note that commercial (Amgen) studies of osteoprotegerin have been completed.

3) Mechanical Methods: These techniques include human centrifuge methods to simulate gravity that are based on cycling or rotation of a sled or table and vibrational mechanical stimuli to provide osteogenic signals to bone in a weightless environment. These methods have been demonstrated in animals and humans to increase bone formation.

Recommendations: Funding for commercial development of a flight-ready device for providing vibrational strain to the lower extremities is suggested. The development for Earth testing of a suitable vibrational impact instrument that could be flight tested within 5 years is encouraged. In contrast to current commercially designed units, this instrument would be specific for use in flight.

4) Nutritional Methods: KMgCit is being tested to decrease renal propensity to calculus formation.

Recommendations: Once safety data have been acquired from bed rest studies, this compound should be tested on Shuttle flights and later on the ISS. Application of nutritional regimens for testing in bed rest protocols to improve spontaneous eating patterns during flight and to provide adequate nutritional supplements in preparation for testing during spaceflight is suggested.

Additional studies and monitoring to consider to initiate

- Biomechanical and radiological testing of fracture healing models during flight and postflight.
- Assessment of soft tissue injury during and after extended flight. This assessment would include radiological procedures (MRI) to define the anatomy of the intervertebral space, vertebral body, and joint space.

- Testing of the AMP DEXA machine now in preparation at the Johns Hopkins University Applied Physics Laboratory (JHU APL) on the ground in control and bedrest or spinal cord injured subjects. Testing on the ISS within 5 years.
- Testing of the mass spectrometer for biochemical analysis (R. Potember, JHU APL) in flight on the Shuttle. This testing would permit real-time assessment of blood, urine and saliva biochemistries.
- Animal studies to determine if reduced blood flow to the lower limbs (as observed during hind limb suspension in rats) impacts on interstitial fluid flow and hence on mechanotransduction in bone during (simulated or real) weightlessness.
- Identification of key molecular responses in bone which initiate bone loss in space flight. For example, definition of the signal transduction system that couples gravity-related muscle pull with bone formation/resorption could be made. This examination will facilitate development of optimally targeted pharmacological and mechanical countermeasures.
- Testing transgenic animal (specificity to be defined) models in flight. Considerations would include site-specific over-expression of locally acting osteogenic factors. Suitable agents could be those affecting osteoblast/osteoclast function in bone, application of the "coupling factor" when this is defined, identification through knock out experiments of critical transcription and growth factors to maintain bone mass in the face of microgravity.
- Advanced testing of novel pharmacological agents during ISS flight. These may be growth factors to maintain bone formation, novel antiresorptive agents, hormone receptor agonists, and agents such as leptin and GIP, whose role is yet to be defined.
- Genetic analysis of flight candidates for fracture risk. Family bone density survey, initial screening for specific osteoporosis related polymorphisms would initiate development of a data base to serve as a platform for expanded studies as new findings are available.
- Flight-based determination of bone mineral density. Includes application of analytic programs, including considerations of bone geometry, and modeling for fracture risk
- Correlation of new nutritional and optimized resistive exercise programs with bone mineral density changes during 6-month flight experience. In addition to bone density, this analysis would require the development of novel imaging methods for estimation of bone strength.
- Treatment for fracture healing tested under flight conditions in animals. This test could include current proposals (ultrasound), as well as, the dermal application or fracture-site use of instilled agents (e.g., bone morphogenetic protein-like agents)

<u>Post-flight Rehabilitation Suggestions</u>

Various conditioning training programs are currently in use to assist in the return of bone to normal levels post-flight. These programs extend for 6 weeks following return and evaluate conditioning programs with respect to post-flight alterations in bone mass and bone strength and the return of these parameters to pre-flight values.
<u>Recommendations:</u> Review of the effectiveness of current conditioning programs in American Astronauts in a joint NSBRI/NASA forum and from that data, design of a standardized rehabilitation program that will serve to highlight alterations in individual response to conditioning. This review, in turn, will permit analysis to determine mechanisms responsible for failure to regain pre-flight mineral mass (e.g., muscle bone mismatch).

<u>NSBRI/JSC Collaboration</u>

A short-term aim should be to increase the collaborative efforts between the NSBRI Bone Team and scientists at JSC and Ames. As currently structured, JSC has a limited capability to deal with countermeasure development for bone loss. Bone loss, as a Critical Path risk, is a matter of second priority at the Bone, Muscle, and Exercise Integrated Products Team because of the current emphasis on flight-testing exercise protocols. This may reflect: 1) failure on the part of investigators to bring bone related protocols forward, 2) the probability that certain countermeasures for bone loss are not ready to be flight-tested, and, 3) the slow process in bringing pharmacological agents to the stage of flight testing. Funding for bone loss research (HEDS Program) has been significantly hampered by budget problems within NASA as well as administrative issues. It is strongly recommended that the JSC/NSBRI program be critically reviewed so that program strategies provide the maximum collaboration between JSC scientists, engineers, flight surgeons and funded NSBRI investigators and their respective institutions. An initial step in this effort was taken at the NSBRI meeting at Del Lago, January 2002, where a combined NSBRI Bone Team/JSC staff meeting was held to open discussions about NASA targets and current NSBRI research program.

The recommendations presented in this plan are predicated on appropriate funding and the imposition of a countermeasure targeted research program. Members of this team recommend, that in contrast to "bottom up" NIH/NSF type funding programs, NASA/NSBRI research should be a "top down" system in which research funding follows mission requirements. In turn, mission requirements should reflect the best consensus about basic and applied priorities.

3.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Goal 1: *Reduce risk of accelerated bone loss leading to osteoporosis*

Objective 1A: Assess risk and target level of acceptable risk.

- Assess initial and sequential bone mass, bone biomarkers and genetic background, preflight in astronauts.

Objective 1B: Determine Mechanisms

- Determine mechanisms of bone loss using geometric/structural DEXA analysis pre flight and on interval flights if applicable.
- Determine mechanisms of bone loss using bone cell populations obtained from the hindquarter suspended rat or mouse model of microgravity. Mechanisms of bone cell response to microgravity such as altered signal transduction mechanisms are of critical importance in the eventual development of new countermeasures.

Objective 1C: Develop countermeasures.

- Study combined effect of related stressors such as radiation and weightlessness and countermeasures to lessen muscle loss
- Bring bisphosphonate administration and vibrational mechanical loading to point of flight testing. Achieving this feat may require short-circuiting established pre-flight testing currently required by NASA. Access exercise protocols.
- Study leptin, GIP, SERMs and Vit D analogues in flight experiments. Build on the database aimed at the development of new and novel countermeasures. Use a five-year window for development of new agents. Join with industry to facilitate new drug development.

Goal 2: *Reduce Risk of Fracture and Impaired Fracture Healing*

Objective 2A: Assess risk and target level of acceptable risk

- Using the initial data on fracture healing and callus strength now available through the Bolander study, recruit additional protocols to focus on these mechanisms and countermeasure development re: the integrity of the fracture callus.
- Collaborate with Hopkins Applied Technology Group to test the new AMP DEXA in humans with the aim of a flight model in 2004 for estimation of fracture risk
- Use 3-D finite element analysis derived from CT scans to model fracture risk during flight, in extraterrestrial environment and post-flight.

Objective 2B: Determine Mechanisms

- Determine mechanisms using cell models derived from fracture site. callus

Objective 2C: Develop Countermeasures

- Develop countermeasures including ultrasound, mechanical/electrical stimulation

Goal 3: *Reduce Risk of Injury to Soft Connective Tissue, Joint Cartilage, and Intervertebral Disc Rupture w/ or w/o Neurological Complications*

Objective 3A: Assess risk and target level of acceptable risk

- Initiate more funded studies. It is recognized that back pain presumably due to intervertebral disc disease is a significant problem with astronauts. The extent of cartilage impairment is undetermined. The risk must be determined using specific pre- and post flight studies of both animals and astronaut vertebrae and joints: biochemical and histopathological data is required.

Objective 3B: Determine mechanisms

- Study soft connective tissues in the hindlimb suspended model: sequential cartilage changes, expand the data base on intervertebral disc alterations. The mechanisms involved in these processes and their prevention/repair are significant issues.

Objective 3C: Develop Countermeasures

- Begin to assess potential countermeasures to injury to include: physical therapy, exercise programs.

Goal 4: *Reduce Risk of Renal Stone Formation*

Objective 4A: Assess risk and target level of acceptable risk.

- Review recent and current astronaut/cosmonaut experience re: stone formation and use of K Citrate.
- Zerwekh program addresses these issues.
- Re-evaluate urine stone propensity data collected by Drs Pak/Whitson

Objective 2A: Determine mechanisms

Objective 2A: Develop Countermeasures

- Test KMgCit in flight setting

Goal 5: *Reduce Risk of Delayed Return of Bone Mass to Normal Mass and Strength Following Extended Exposure to Weightlessness*

Objective 5A: Assess risk and target level of acceptable risk

- Review current data on stress fractures during re-conditioning.
- Evaluate data obtained in the Bloomfield study (bone/muscle mismatch)

Objective 5B: Determine Mechanisms

Objective 5C: Develop Countermeasures

- Work with the NASA IPT Committee for Bone, Muscle, and Exercise and JSC flight surgeons to formulate an effective and long duration rehabilitation program post-flight.

Goal 6: *Collaborate with the NSBRI Muscle, Radiation and Technology Development Teams on the development of methods for inflight assessment of bone health and the appropriate monitoring, diagnosis and treatment for bone loss, fractures and soft tissue injury. Develop methods for the inflight assessment of renal stone risk and the prevention and treatment of renal calculi developed during flight.*

- Collaborate with the Technology Team on developing and testing methods for monitoring of bone mass (e.g., AMPDEXA machine)
- Collaborate with the Muscle Team to correlate biochemical and genetic patterns of bone loss with changes in bone mass during weightlessness.
- Collaborate with the Radiation Team to evaluate the separate and interactive effects of radiation and weightlessness on bone cell functions.

Goal 7: *Develop Earth-based applications of countermeasures to reduce increased bone loss and fracture risk found in health hazards, such as in children with non-weight bearing disorders and in adults following CNS and spinal cord trauma*

- Complete experiments in Spinal Cord Injury project to provide treatments (such as bisphosphonates) that are useful to general public. (Shapiro et al)

Goal 8: *Develop Earth-based application of low weight, sensitive bone density machine*

- Complete experiments in Spinal Cord Injury project to provide a monitoring arm (AMPDEXA machine) to correlate bone loss rates with biomarker changes that are useful to general public. (Shapiro et al)

Goal 9: *Integrate Research and Analysis*

Objective 9A: Integrate Research Within the Muscle Alterations and Atrophy Team

- Teleconferences and team meetings at national symposia.

Objective 9B: Integrate Research With Other Teams, using modeling as well as other approaches

- Use Modeling (3-D finite element analysis, DEXA scan analysis)
- Collaborate with the Radiation Team to study independent and interactive effects of radiation on bone mass.

Objective 9C: Integrate Research with Scientists Outside of NSBRI

- This is in progress with scientists at the Armed Radiation and Radiobiology Institute, AFRRI.

3.6 SUMMARY

Two major hazards to human extended duration spaceflight are radiation exposure and bone loss. It is necessary to coordinate NSBRI research efforts with those of the NASA extramural HEDS program so as to create a focused, countermeasure development and testing program aimed at addressing problems of bone loss. In the current program, basic and applied protocols examine regulation of bone mass under weightlessness conditions, as well as, potential pharmacological, nutritional, exercise and biomechanical methods of countering bone loss. Questions related to accelerated bone loss, post-flight fracture, and renal calculus formation are addressed; however, some risks to astronaut health, such as inflight fracture risk and healing and soft tissue injury risk, are not being adequately addressed at this time. Investigation of cellular mechanisms modulating bone cell function should be a more prominent part of the program. Coordination of countermeasure development with in-flight and post-flight monitoring should be an integral part as well.

Table 3.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BLOOMFIELD/ Bone and Muscle Recovery from Simulated Microgravity	Post-flight fracture risk	• Pharmacological • Exercise	Hind limb suspended rat	Muscle/bone imbalance	Exercise regulation, PTH, growth hormone	
BOLANDER/The Effect of Microgravity on Fracture Healing: Ultrasound as a Possible Countermeasure	Microgravity impact on fracture healing	Ultrasound	Hind limb suspended rat	Integrity of fracture healing callus formation	Ultrasound action on fracture healing	
ISALES/Therapeutic Modulation of Systemic Glucose-Dependent Insulinotropic Peptide Levels to Counteract Microgravity-Induced Bone Loss	Accelerated bone loss leading to osteoporosis	Diet	Mice, transgenic mice	GIP effect on bone remodeling	Nutritional intervention to increase GIP levels and lesson bone loss	
KARSENTY/Leptin as a Regulator of Bone Formation in Microgravity	Accelerated bone loss leading to osteoporosis	Pharmacological	Mice	Leptin (humoral factors)/CNS inhibition role in bone remodeling; cntrl mechanisms	Test hindlimb suspended animals for this system and potential cms	
RUBIN/A Biomechanical Countermeasure for Disuse Osteopenia	Accelerated bone loss leading to osteoporosis	Mechanical stimulation	Mice	Gene expression related to vibratory stimuli	Mechanically stimulate bon via impact loading; operational features for testing in human	Flight protocol under review at JSC

Table 3.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
SCHAFFLER/Resorption Suppression and Bone Health in Disuse	Fracture risk after bisphosphonate treatment	Pharmacological	Dog with immobilized limb	Characterization of osteocyte integrity	Propose alterations in bisphosphonate drug dose, duration of administration	
SHAPIRO/Defining and Preventing Bone Loss: A Microgravity Model	• Accelerated bone loss leading to osteoporosis • Fracture risk after bisphospho-nate treatment	Pharmacological	Patients with spinal cord injury	Characterize rates and patterns of bone loss, muscle loss in non-weight bearing subjects	Administration of intravenous potent bisphosphonate (zoledronate) to protect bone loss	Flight testing of bisphosphonates under consideration
SMITH/Receptor Countermeasures to Bone Loss in Microgravity	Accelerated bone loss leading to osteoporosis	Pharmacological	Hind limb suspended rat	Characterize receptor agonist effects on bone cell and prevention of bone loss	Testing with SERMs and vitamin D agonist to decrease bone loss; in progress in hindlimb suspension model, flight testing anticipated.	
ZERWEKH/Prevention of Microgravity-Induced Stone Risk by KMgCitrate	Renal calculus prevention	Nutritional	Normal human volunteers at bed rest.		Effects of treatment with KMgCit on bone and muscle loss, renal stone propensity	Flight testing to be proposed.

National Space Biomedical Research Institute
BONE LOSS PROGRAM

Table 3.2. Integration Activities

	BLOOMFIELD	BOLANDER	ISALES	KARSENTY	RUBIN	SCHAFFLER	SHAPIRO	SMITH	ZERWEKH
Internal Communication	Monthly teleconferences, team meetings 2-3 times per year	same	same	Same	same	same	same	same	same
Integrated Experiment Development	Collaboration with Smith project								
Sample Sharing			Collaboration with Zerwekh bedrest project				Muscle team collaborates on this project		With Isales GIP project
Synergistic Studies of Opportunity							Collaborate with Technology Team for AMPDEXA evaluation		
Development of Computer Model of Integrated Human Function									

National Space Biomedical Research Institute
BONE LOSS PROGRAM

Table 3.3. Achieving Goal 1: Reduce Risk of Accelerated Bone Loss Leading to Osteoporosis

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research	■												
Phase 1: Focused Mechanistic Research		■	■	■									
• Understand gravity effects on leptin • Understand gravity effects on GIP • Complete evaluation of chronic bisphosphonate effect on bone cells • Determine how spinal cord injured (SCI) affects biochemistry of atrophy of human muscle													
• Model fracture risk in SCI with 3D finite element analysis • Evaluate alterations in fracture healing in weightlessness • Assess bone/muscle gap during reconditioning • Define geometric/structural parameters on bone loss in spinal cord injured patients													
Phase 2: Preliminary Countermeasure Development Research		■	■	■	■								
• Assess chronic bisphosphonates use on osteocyte integrity • Test SERM/Vitamin D agonist effects during flight in animals • Determine role of ultrasound in fracture healing in weightlessness													
• Assess role of exercise, PTH and growth hormone during reconditioning of hind limb suspended rats.													
Phase 3: Mature Countermeasure Development Research		■	■	■	■								
• Develop integrated exercise, nutritional, and pharmacological countermeasure and test in humans: test exercise activity on bone mass													
• Determine whether vibrational mechanical loading can be adapted to flight conditions: correlate engineering requirements for flight testing • Evaluate AMP DEXA apparatus with Technology Team													
Phase 4: Countermeasure Evaluation & Validation						■	■	■	■				
• Test intravenous bisphosphonate during flight • Test KMgCit during flight													
Phase 5: Operational Implementation of Countermeasure Strategy										▒	▒	▒	▒

4.0 CARDIOVASCULAR ALTERATIONS

Team Leader: Richard J. Cohen, M.D., Ph.D.
Whitaker Professor of Biomedical Engineering
Harvard-MIT Division of Health Sciences and Technology
Massachusetts Institute of Technology
45 Carleton Street, Rm. E25-335A
Cambridge, MA 02139-4301
617-253-7430
617-253-3019 FAX
rjcohen@mit.edu

4.1 INTRODUCTION

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to weightlessness and other factors, such as sleep disruption, confinement and additional environmental alterations. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume, and a modest decrease in arterial pressure. In addition, there are alterations in the lymphatic, neural and hormonal control systems. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. Furthermore, the extent of cardiovascular adaptation appears to increase with duration of space flight, and the magnitude and implications of these adaptations for long-duration space flight (that is, months to years) remain largely unknown.

Specific adverse effects of space flight on the cardiovascular system include:

1) **Impaired Cardiovascular Response to Orthostatic Stress.** Upon reentry into the Earth's gravitational field, astronauts experience orthostatic intolerance, which limits their ability to function during reentry. In many cases, the orthostatic intolerance is sufficiently severe that astronauts cannot stand erect for some time after landing and thus may interfere with the ability of astronauts to egress from the spacecraft under emergency conditions. Upon reentry into a gravitational field, blood pools in the dependent veins and arteries which leads to reduction in preload to the heart, resulting in a decrease in stroke volume, cardiac output and arterial blood pressure. Factors involved in the development of orthostatic intolerance may include structural and functional adaptations of the heart and arterial and venous blood vessels and lymphatics, alterations in volume control mechanisms, alterations leading to an inadequate or defective neural and hormonal regulatory response, alterations in local vascular reactivity, and mechanisms controlling regional distribution of blood volumes and flows. Factors, such as age, gender, genotype, as well as occupational, physical training and dietary history, may affect individual susceptibility to the development of post-flight orthostatic intolerance. Currently used countermeasures, such as oral administration of salt and water prior to reentry and application of anti-gravity suits, do not adequately prevent orthostatic intolerance, especially following long-duration space flight.

2) **Occurrence of Serious Cardiac Dysrhythmias.** A number of anecdotal reports suggest that long-duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. If space flight does in fact significantly decrease cardiac electrical stability, the effects could be catastrophic, potentially leading to sudden cardiac death. It will be important to determine the mechanisms underlying this phenomenon in order to develop appropriate countermeasures. Potential mechanisms that might lead to reduction in the stability of the electrical substrate include electrolyte changes, changes in the neural and hormonal milieu, and alterations of cardiac myocytes, myocyte connectivity and extracellular matrix resulting from space flight. These alterations may in turn lead to changes in cardiac conduction and repolarization processes that predispose the heart to sustained rhythm disturbances.

3) **Diminished Cardiac Function.** Long-term space flight may lead to a measurable reduction in cardiac mass, probably associated with cardiac remodeling. It is not known whether these cardiac alterations are reversible and whether they pose a long-term health risk to astronauts. Factors that may be involved in alterations in cardiac function include changes in myocyte number, size, and geometry; changes in myocardial matrix and microvasculature; alterations in myocyte and organ-level mechanical performance; changes in cardiac gene programming; stimuli and signals that lead to loss of cardiac mass and remodeling; factors affecting reversibility and recovery from these alterations.

4) **Manifestation of Previously Asymptomatic Cardiovascular Disease.** Long-duration space flight may exacerbate previously undetected cardiovascular disease, such as coronary artery disease. Little is known about what conditions of space flight may tend to make pre-existing disease symptomatic or accelerate the progression of the underlying disease. Also, we do not know what procedures should be applied to screen astronauts for the presence of asymptomatic cardiovascular disease prior to long term missions

5) **Impaired Cardiovascular Response to Exercise Stress.** Long-term space flight may impair cardiovascular response to exercise. Current inflight exercise programs appear adequate to maintain aerobic exercise capacity.

4.2 RISKS

In concert with the above described adverse effects of space flight, the following risks in the Cardiovascular Alterations Discipline Area have been identified in the Critical Path Roadmap (Risk number in parentheses):

- Impaired Cardiovascular Response to Orthostatic Stress (14)
- Occurrence of Serious Cardiac Dysrhythmias (13)
- Diminished Cardiac Function (15)
- Manifestation of Previously Asymptomatic Cardiovascular Disease (16)
- Impaired Cardiovascular Response to Exercise Stress (17)

4.3 GOALS

The Cardiovascular Alterations Team has the following goals for its program:

Risk-Based Goals

Goal 1: *Reduce risk of impaired cardiovascular response to orthostatic stress*

Goal 2: *Reduce risk of occurrence of serious cardiac dysrhythmias*

Goal 3: *Reduce risk of diminished cardiac function*

Goal 4: *Reduce risk of manifestation of previously asymptomatic cardiovascular disease*

Goal 5: *Reduce risk of impaired cardiovascular response to exercise stress*

Non Risk-Based Goals

Goal 6: *Develop new cardiovascular diagnostic and therapeutic technologies for space flight applications*

Goal 7: *Develop new cardiovascular diagnostic and therapeutic technologies for medical use on Earth*

Goal 8: *Integrate Research and Analysis*

4.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The overarching intentions of the Cardiovascular Alterations Team are to:

- Characterize and quantify the adverse effects of space flight on cardiovascular structure and function
- Determine the mechanisms of these adverse effects
- Develop effective countermeasures to these adverse effects
- Develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on Earth

The program's overall strategy is dictated by the relevant risks. The following risks are deemed to be high priority and are the focus of the team's efforts:

- Impaired Cardiovascular Response to Orthostatic Stress (14; Addressed in Goal 1)
- Occurrence of Serious Cardiac Dysrhythmias (13; Addressed in Goal 2)
- Diminished Cardiac Function (15; Addressed in Goal 3)

The remaining two risks are deemed to be of low priority:

- Manifestation of Previously Asymptomatic Cardiovascular Disease (16; Addressed in Goal 4)
- Impaired Cardiovascular Response to Exercise Stress (17; Addressed in Goal 5)

While some of the projects do address some aspects of these two risks, no one project principally addresses these risks.

Additional non risk-based goals include those associated with the development of new cardiovascular technologies for use in space (Goal 6) and for Earth-based applications (Goal 7). Integration of Research and Analysis is Team Goal 8.

The current program is summarized in the Figure at the end of this document. Table 4.1, entitled "Current Project Research Activities," summarizes for each current Cardiovascular Alterations Team project what risks are addressed, the experimental system, the countermeasure target and the planned progression of each project along the strategic steps of Phase 1, 2 or 3 Activities.

The Cardiovascular Alternations Team has recently been enlarged by the transfer of three projects (Bers, Coolahan, McCulloch) from the former Integrated Human Function Team. This transfer was the result of an NSBRI management decision that it was better for the computer modeling and simulation projects to reside in specific teams rather than to be grouped in a separate Integrated Human Function Team. An additional cardiovascular modeling project with Dr. Mark has been part of the Cardiovascular Alterations Team since its inception and is thus already very well integrated into the team's activities. A project with Dr. Murad was also just recently incorporated into the team. As a result, the Cardiovascular Alterations Team now has 16 projects (see Figure). While we have always attempted to have horizontal communication across all team projects, with the growth of the team to 16 projects we have decided to organize the projects into groups of Human Studies, Rodent Studies, and Cardiovascular Technologies. Projects within each group will have separate group meetings in addition to meetings of the entire team.

Progress Towards Risk-Based Goals

Projects addressing risk of Impaired Cardiovascular Response to Orthostatic Stress (Goal 1). Most of the effort of the Cardiovascular Alterations Team has been focused on the problem of post-flight orthostatic hypotension, for this is a well-known current operational problem. As a matter of fact, all the team projects are involved in this effort. In animal and human studies we have studied mechanisms and proposed and tested countermeasures. We are examining a wide range of factors including neural, vestibular, hormonal, vascular, cardiac, lymphatic, and genetic factors that may contribute to the development of orthostatic hypotension. We have also developed new non-invasive techniques to study alterations in cardiovascular regulation resulting from space flight. One such technique is Cardiovascular System Identification that involves mathematical analysis of spontaneous second-to-second fluctuations in physiological signals such as heart rate, arterial blood pressure, cardiac output, and respiration to create an individualized closed loop model of cardiovascular regulation. Finally, we have developed and utilized computer simulations of the cardiovascular system to analyze data, investigate mechanisms, evaluate proposed countermeasures, and refine hypotheses to be tested experimentally. The dynamic interplay between animal, human and computer simulations has already led to the proposal of the alpha-sympathetic agonist, midodrine, as a pharmacological countermeasure to the development of orthostatic hypotension, and the successful testing of this countermeasure in animal and ground based human studies. Flight studies of this countermeasure have been approved and will begin soon. We are also developing an innovative pulsatile G-suit as a new countermeasure.

Projects addressing risk of Occurrence of Serious Cardiac Dysrhythmias (Goal 2). Several of the team projects relate to the development of life threatening dysrhythmias in space (Bers, Cohen, Coolahan, McCulloch, and Williams). The focus here has been to establish specifically whether simulated microgravity increases the risk of these ventricular tachyarrhythmias. To test this hypothesis a new non-invasive technique has been developed for the identification of subjects at risk of developing ventricular tachyarrhythmias - measurement of microvolt T-wave alternans. This technique was developed under both NASA and NSBRI support. This technique has been validated in multiple studies of patients with increased sudden cardiac death. The technique has proven to be the best non-invasive predictor of susceptibility to ventricular tachyarrhythmias and sudden cardiac death. It has been successfully commercialized, cleared by the FDA, and approved by Medicare for reimbursement, and is in widespread clinical use. Initial bed rest data using microvolt T-wave alternans suggests that simulated microgravity increases the risk of ventricular tachyarrhythmias, and flight studies will shortly be initiated to test this in astronauts pre- and postflight. Mechanistic ground based studies will examine the effects of age and gender on susceptibility to ventricular tachyarrhythmias. Also, current studies plan to evaluate aldosterone antagonists (spironolactone) and alterations in dietary intake of electrolytes as potential countermeasures.

Projects addressing risk of Diminished Cardiac Function (Goal 3). One project (Lorell) deals primarily with the risk of diminished cardiac function and several other projects (Bers, Cohen, Coolahan, Delp, Mark, McCulloch, Shoukas, Thomas, and Williams) have this risk as a less primary focus. The aim here is to establish the development of atrophy and remodeling in ground based models and to study molecular and genetic mechanisms and functional sequelae. We require more flight data documenting the extent of space induced cardiac atrophy and remodeling that occurs during flight.

Projects addressing risk of Manifestation of Previously Asymptomatic Cardiovascular Disease (Goal 4). There are no current projects that really focus on this issue. A few projects are minimally associated with this problem (Coolahan, McCulloch, and Thomas). Although this is a lower priority risk than the first three, we are interested in the question of determining what is the optimum set of screening tests for astronauts to detect asymptomatic cardiovascular disease that may cause problems during long duration space flight. We plan to solicit proposals in this area in the future.

Projects addressing risk of Impaired Cardiovascular Response to Exercise Stress (Goal 5). Although several of the projects address exercise, this is not a primary focus of any of the current projects. The reason for this situation is that the current in-flight exercise regimen appears to be adequate to maintain aerobic exercise capacity.

Progress Towards Non Risk-Based Goals

Progress towards Development of New Cardiovascular Technologies for Space flight (Goal 6) and Earth-based Applications (Goal 7). The progress of the Cardiovascular Alterations Team has been heavily dependent on the development of new technologies which allow us to better understand, measure and alter physiological processes. Technologies that we have developed and applied include computer simulation technologies, Cardiovascular System Identification technology for the non-invasive quantification of closed cardiovascular regulation, measurement of Microvolt T-Wave Alternans to assess cardiac electrical stability, and ultrasound technologies for the non-invasive assessment of cardiovascular function. One of these technologies (Microvolt T-Wave Alternans) has already been successfully commercialized for clinical use here on Earth. We are just beginning to develop a novel pulsatile G-suit as a countermeasure to the development of orthostatic hypotension. Future progress of the Cardiovascular Alterations Team will continue to be dependent, in part, on the development of new diagnostic and therapeutic technologies. In the future we plan to solicit proposals which specifically focus on the development of novel cardiovascular technologies with applications to both space and Earth medicine.

Progress towards Integration (Goal 8) The cardiovascular team strives to have a dynamic interplay/integration between projects focused on animal studies, human studies, and cardiovascular simulations (Table 4.2 and Figure 4.1). This intra-team interaction has been facilitated by team retreats and telecons. With the recent enlargement of our team from 12 to 16 projects discussed above, going forward we will have projects within each of the three areas (animal studies, human studies, and cardiovascular simulations) also meet separately in addition to the team wide meetings.

In addition to our intra-team integration we interact with a number of other NSBRI teams including Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems. Two of our project leaders (Cassone, Thomas) are integrated into the functioning of other teams (Human Performance, Smart Medical Systems). We plan to further promote this inter-team interaction for the following reasons:

- In addition to microgravity, other conditions of space flight may also adversely affect the cardiovascular system, including sleep disruption, reduced physical stress, environmental factors, and psycho-social stresses.
- Countermeasures proposed by and/or affecting the other teams may include pharmacological, nutritional, and physical interventions (including artificial gravity) and modifications of behavior, activity and environment.

Additional Issues

Below are some important cross-cutting issues which affect multiple projects.

Experimental Models. Additional data from space flight is required to evaluate the degree of correspondence of data from ground-based animal and human models with space flight data. Previously, we have had very limited opportunity to obtain data for this validation, but we are now beginning to obtain both animal and human flight data.

Cardiovascular Space Flight Database. There is an urgent need to obtain and make available to investigators a systematic database of cardiovascular data from astronauts before, during and after space flight. We will be working with a NASA-NSBRI initiative to develop a cardiovascular physiological flight database from data collected routinely during ongoing flights.

Experimental Approaches. Investigations are required which range from the molecular, genetic and cellular level to the organ system level to the level of the entire organism. Our projects do span this spectrum and we are using computer simulations as a means of integrating the experimental data across these different levels of organization.

Individual Susceptibility. Investigation of factors that make an individual more susceptible to the adverse effects of space flight on the cardiovascular system may include age, gender, genotype, and dietary, occupational and physical conditioning history. We have begun to address these issues but more activity in this area is required.

4.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Presented here are the objectives underlying each goal and the strategic activities that we plan to use to achieve the goals and objectives of our program. The timelines for achievement of the activities underlying each goal are presented in Table 4.3.

Goal 1: *Reduce Risk of Impaired Cardiovascular Response to Orthostatic Stress*

Objective 1A: Assess Risk and/or Determine Level of Acceptable Risk

- Continue to collect data from ongoing flights to determine incidence and level of risk of orthostatic intolerance particularly during long term flights

Objective 1B: Determine Mechanisms

- Understand alterations in nitric oxide and prostacyclin systems
- Understand alterations in circadian physiology
- Study alterations in CV regulation using CV System Identification
- Develop accurate computer models of CV System
- Study effects of microgravity on blood vessels, lymphatics
- Study effects of adrenergic agents (midodrine)
- Study effects of soluble guanylyl cyclase gene disruption
- Study effects of vestibular stimulation
- Develop and apply relevant ultrasound technology
- Assess volume, electrolyte and hormonal responses
- Assess effects of sleep disruption
- Assess effects of gender and age
- Develop pulsatile G suit
- Assess effects of artificial gravity

Objective 1C: Develop Countermeasures

Preliminary

- Evaluate pharmacologic alteration of nitric oxide and prostacyclin systems
- Evaluate circadian intervention
- Use CV System Identification to evaluate countermeasures
- Utilize CV models to simulate effects of countermeasures
- Evaluate vascular and lymphatic interventions
- Evaluate adrenergic agents (midodrine)
- Evaluate soluble guanylyl cyclase intervention
- Evaluate vestibular intervention
- Utilize ultrasound technology to evaluate countermeasures
- Evaluate volume regulatory and electrolyte interventions
- Evaluate sleep control intervention
- Evaluate gender and age dependent interventions
- Evaluate exercise countermeasure
- Evaluate pulsatile G suit
- Evaluate artificial gravity countermeasure

Mature

- Test midodrine countermeasure in human ground studies
- Select and test most promising countermeasures and develop and test in human ground studies

Evaluation and Validation

- Flight test midodrine countermeasure
- Flight test other countermeasures successful in mature countermeasure development

Operational Implementation

- Implement midodrine countermeasure
- Implement other countermeasures successful in evaluation and validation of countermeasures

Goal 2: *Reduce Risk of Occurrence of Serious Cardiac Dysrhythmias*

Objective 2A: Assess Risk and/or Determine Level of Acceptable Risk

- Obtain and analyze ECG data from prior and future flights to determine incidence of dysrhythmias

Objective 2B: Determine Mechanisms

- Microvolt T-wave alternans (MTWA) studies in patient populations to validate MTWA as a non-invasive measure of susceptibility to ventricular dysrhythmias

- Measure effects of microgravity on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Measure effects of electrolyte alterations on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Measure effects of alterations in volume regulatory hormones on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Measure effects of age and gender on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Develop animal model of microgravity altered susceptibility to ventricular dysrhythmias
- Develop computer models of cardiac electrical activity in humans

Objective 2C: Develop Countermeasures

Preliminary

- Test aldosterone antagonist (spironolactone) as potential countermeasure in human studies
- Measure MTWA in pre and post flight astronauts
- Evaluate dietary countermeasure in human studies
- Evaluate pharmacologic countermeasures in animal studies
- Evaluate countermeasures developed for Goal 1 in human studies

Mature

- Select and test most promising countermeasures and develop and test in human ground studies

Evaluation and Validation

- Flight test countermeasures successful in mature countermeasure development

Operational Implementation

- Implement countermeasures successful in evaluation and validation of countermeasures

Goal 3: *Reduce Risk of Diminished Cardiac Function*

Objective 3A: Assess Risk and/or Determine Level of Acceptable Risk

- Obtain and analyze relevant data from prior and future flights to characterize and quantify to what extent space flight causes cardiac atrophy and remodeling, whether the alterations are reversible and whether they pose a long-term risk to astronauts.

Objective 3B: Determine Mechanisms

- Develop myocyte and cardiac computer models
- Measure effects of microgravity on cardiac mass
- Measure effects of microgravity on myocyte function
- Measure effects of microgravity on cardiac remodeling
- Measure role of calcium, hormones, genes, muscle degradation
- Develop ultrasound techniques to measure cardiac function

Objective 3C: Develop Countermeasures

Preliminary

- Use computer models to simulate potential countermeasures
- Evaluate growth hormone countermeasure
- Evaluate adrenergic countermeasure
- Evaluate dietary and exercise countermeasures
- Evaluate other pharmacological countermeasures
- Evaluate countermeasures developed for Goal 1 in human studies

Mature

- Select and test most promising countermeasures and develop and test in human ground studies

Evaluation & Validation

- Flight test countermeasures successful in mature countermeasure development

Operational Implementation

- Implement countermeasures successful in evaluation and validation of countermeasures

Goal 4: *Reduce Risk of Manifestation of Previously Asymptomatic Cardiovascular Disease*
Objective 4A: Assess Risk and/or Determine Level of Acceptable Risk

- Propose non-invasive screening protocol to detect asymptomatic cardiovascular disease and test in ground-based study where subjects are followed for several years for manifestations of cardiovascular disease.

Goal 5: *Reduce Risk of Impaired Cardiovascular Response to Exercise Stress*

- Since current inflight exercise regimens appear to accomplish this goal, we do not plan further activity in this area.

Goal 6: *Develop new cardiovascular diagnostic and therapeutic technologies for space flight applications*
Objective 6A: Solicit proposals

Goal 7: *Develop new cardiovascular diagnostic and therapeutic technologies for medical use on Earth*
Objective 7A: Solicit proposals

Goal 8: *Integrate Research and Analysis*
Objective 8A: Integrate Research Within the Cardiovascular Alterations Team.

- Continue scheduled discussions

Objective 8B: Integrate Research With Other Teams, Using Modeling as well as Other Approaches

- Integrate cardiovascular models with models of other organ systems to simulate integrated physiologic behavior of multiple systems
- Create models of individualized physiologic function from data collected on a single astronaut at a single point in time
- Develop shared research protocols with other teams such as Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems.

Objective 8C: Integrate Research with Scientists Outside of NSBRI

4.6 SUMMARY

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to weightlessness and other factors, such as sleep disruption, confinement and additional environmental alterations. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume, and a modest decrease in arterial pressure. In addition, there are alterations in the lymphatic, neural and hormonal control systems. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. Furthermore, the extent of cardiovascular adaptation appears to increase with duration of space flight, and the magnitude and implications of these adaptations for long-duration space flight (that is, months to years) remain largely unknown.

Adverse effects of space flight on the cardiovascular system include: 1) Upon reentry into the Earth's gravitational field, astronauts experience orthostatic intolerance, which limits their ability to function during reentry and after landing and possibly could interfere with the ability of astronauts to egress from the spacecraft under emergency conditions. Currently used countermeasures, such as oral administration of salt and water prior to reentry and application of anti-gravity suits, do not adequately prevent orthostatic intolerance, especially following long-duration space flight. 2) A number of anecdotal reports suggest that long-duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. If space flight does in fact significantly decrease cardiac electrical stability, the effects could be catastrophic, potentially leading to sudden cardiac death. 3) Long-term space flight may lead to a measurable reduction in cardiac mass. It is not known whether these cardiac alterations are reversible and whether they pose a long-term health risk to astronauts. 4) Long-duration space flight may exacerbate previously undetected cardiovascular disease, such as coronary artery disease. 5) Long-term space flight may impair cardiovascular response to exercise.

The aim of the Cardiovascular Alterations Team is to minimize these risks using the following approach:

- Characterize and quantify the adverse effects of space flight on cardiovascular structure and function
- Determine the mechanisms of these adverse effects
- Develop effective countermeasures to these adverse effects
- Develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on Earth

This approach involves an integrated team effort involving projects ranging from the molecular, cellular, organ system, and whole animal investigations as well as computer simulations.

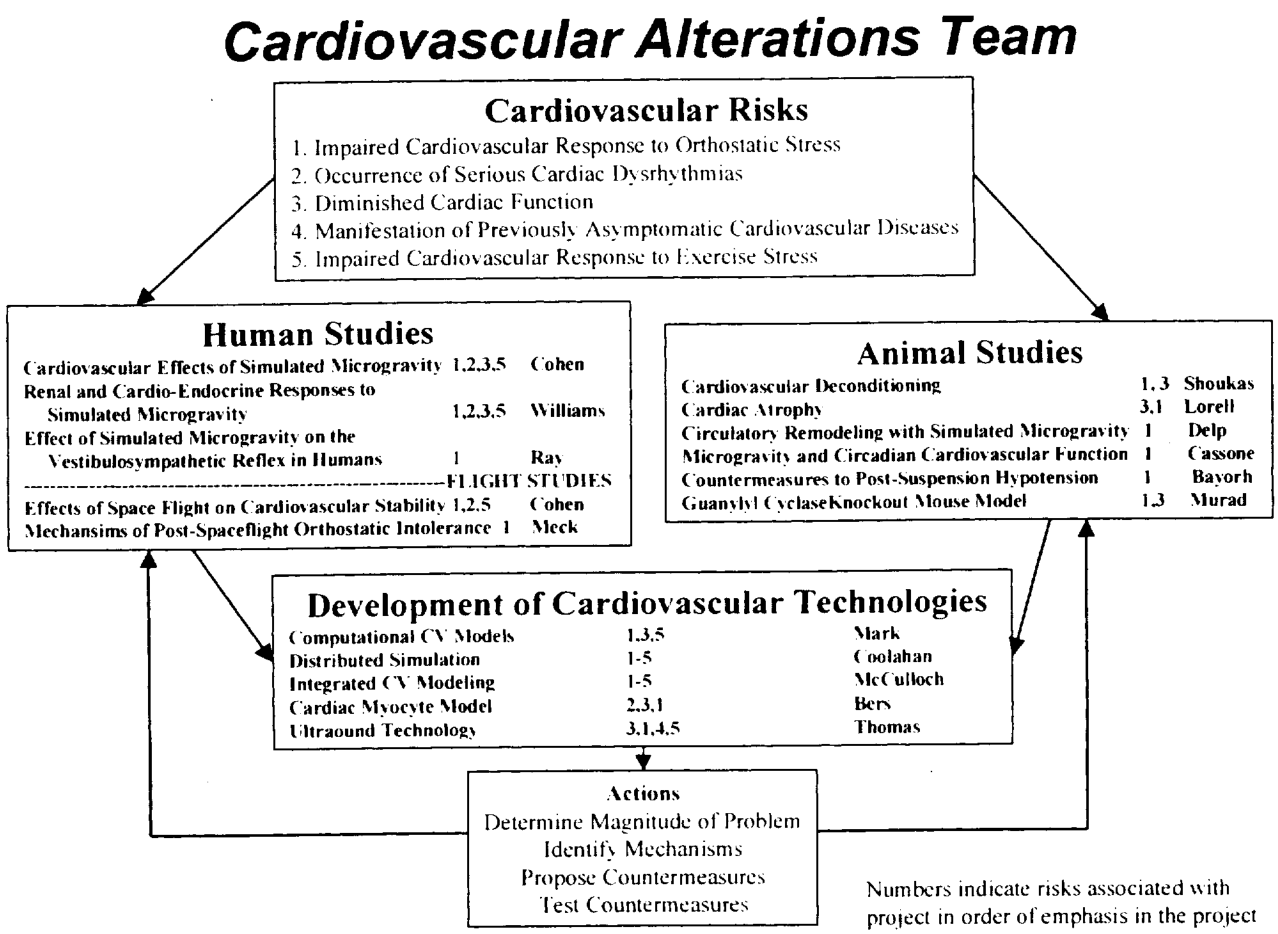
The team has already achieved advanced development of one countermeasure for orthostatic hypotension, the alpha agonist midodrine. The team has progressed from ground-based studies to having two flight studies approved, one of which will be testing the midodrine countermeasure, the other of which will focus on alterations in vascular control mechanisms.

The team has successfully developed two new technologies. One of these technologies, measurement of microvolt T-wave alternans is a non-invasive means of assessing risk of ventricular arrhythmias and sudden cardiac death. This technology is being used to determine whether microgravity predisposes astronauts to ventricular dysrhythmias. This technology has been successfully commercialized, cleared by the FDA, reimbursed by Medicare, and is in widespread clinical use to reduce sudden cardiac here on Earth, which claims 350,000 lives in the United States each year. The other technology developed by the team is Cardiovascular System Identification that non-invasively quantifies closed-loop cardiovascular regulation. This technology is being used to assess mechanisms of post flight orthostatic hypotension, and also has applications for diagnosis and management of heart failure, diabetes and hypertension on Earth.

The team has developed effective cardiovascular computer models that have been used to analyze and integrate data from multiple studies and evaluate potential countermeasures.

National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Figure 4.1 – Relationship and Integration of Projects



National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Table 4.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BAYORH/Possible Countermeasures to Post-Suspension Hypotension in the Head-Down Tilt Rat Model	Orthostatic hypotension	Pharmacological (Nitric oxide and prostacyclin inhibitors)	Head-down tilt rat model	Alterations in nitric oxide and prostacyclin systems	Interventional pharmacological studies	Test countermeasures in human studies
BERS/Integrative Cardiac Myocyte Model: Ion channels, Ca and Contraction	• Dysrhythmias • Cardiac function • Orthostatic hypotension	Simulation of effects of wide variety of potential countermeasures	Computer simulation of cardiac myocyte	Develop computer mode of cardiac myocyte	Simulate effects of space flight and potential countermeasures on myocyte function	Use computer model to analyze data from animal and human countermeasure studies
CASSONE/Microgravity and Circadian Cardiovascular Function	Orthostatic hypotension	• Environmental • Pharmacologic	Tail suspended rat	Effects of alterations in circadian physiol and microgravity on nervous and CV systems	Interventional studies: • Environmental • Pharmacological	Test countermeasures in human studies
COHEN/Cardiovascular Effects of Simulated Microgravity in Man	• Orthostatic hypotension • Exercise • Cardiac function • Dyshythmias	• Pharmacological (Midodrine and Spironolactone) • Diet (Electrolytes)	• Head down tilt bed rest - humans • Sleep disruption • Groups vary by age and gender	Effects of microgravity on: • CV regulation (CV System Identification) • Dysrhythmias (T-Wave Alternans)	Ground based testing in humans of • Midodrine • Spironolactone • Diet (Electrolytes)	Ground based testing in humans of • Midodrine • Spironolactone • Diet (Electrolytes)

Table 4.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
COHEN Effects of Space Flight on Cardiovascular Stability	• Orthostatic hypotension • Exercise • Dysrhythmias	• Pharmacological (Midodrine and Spironolactone) • Diet (Electrolytes)	Pre and post flight humans	Effects of microgravity on: • CV regulation (CV System Identification) • Dysrhythmias (T-Wave Alternans)	Pre and post flight in humans of • Midodrine • Spironolactone • Diet (Electrolytes)	Pre and post flight in humans of • Midodrine • Spironolactone • Diet (Electrolytes) • Spironolactone
COOLAHAN/Distributed Simulation of Integrated Human Function	• Orthostatic hypotension • Dyshythmias • Cardiac function • CV Disease • Exercise	Simulation of effects of wide variety of different potential countermeasures including exercise	Computer model of the cardiovascular system integrated with other systems	Develop and validate accurate model of myocyte and heart	• Develop integrated CV model • Develop integrated model incorporating other systems • Simulate effects of space flight and potential CMs	Analyze data from animal and human tests of countermeasures
DELP/Circulatory Remodeling with Simulated Microgravity	Orthostatic hypotension • Cardiac function • Exercise	Peripheral vascular countermeasures	• Hindlimb unloading (HU) of rats • Shuttle flight (STS-107) of rats	Measure effects and mechansims of HU and shuttle flight on: cerebral & peripheral vascular beds, lymphatics, cardiac mass	Evaluate data to identify and then test potential countermeasures	Test countermeasures in human studies

Table 4.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
LORELL/Cardiac Unloading: Biologic Mechanisms and Countermeasures for Cardiac Atrophy	• Cardiac function • Orthostatic hypotension	• Pharmacological countermeasures to: reduce cardiac atrophy, suppress muscle degradation, & restore cardiac function • Identify molecular targets to modify cardiac muscle growth and degradation	• Heterotopic cardiac transplantation rodent model: intact heart & adult myocyte •Transgenic mouse models and cultured myocytes	Study: cardiac remodeling, myocyte function, & role of calcium, hormones, muscle degradation, genes, kinases	Test: • Low dose growth hormone • Adrenergic agonist	Test countermeasures in human studies
MARK/Computational Models of the Cardiovascular System and its Response to Microgravity and Disease	• Orthostatic hypotension • Cardiac function • Exercise	Simulation of effects of wide variety of different potential countermeasures	Computer model of the cardiovascular system	Develop and validate accurate model of cardiovascular system	Simulate effects of space flight and potential countermeasures	Analyze data from animal and human tests of countermeasures
MCCULLOCH/Integrated Modeling of Cardiac Mechanical and Electrical Function	• Orthostatic hypotension • Dysrhythmias • Cardiac function • CV Disease • Exercise	Simulation of effects of wide variety of different potential countermeasures including exercise	Three dimensional finite element model of the heart	Develop and validate accurate three dimensional finite element model of the heart	Simulate effects of space flight and potential countermeasures	Analyze data from animal and human tests of countermeasures
MECK/Mechanisms of Post-Space Flight Orthostatic Intolerance	Orthostatic hypotension	Pharmacological (Nitric oxide system, Adrenergic system)	Pre and post flight astronauts	Study effect of space flight on: responses to adrenergic agents & nitric oxide system	Propose and test countermeasures in ground based models	Test countermeasures in human studies

Table 4.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
MURAD/A soluble guanylyl cyclase mouse knock-out model	Orthostatic hypotension	Pharmacological (affecting soluble guanylyl cyclase (sGC))	Tail-suspended knockout mouse	Study effect of sGC gene disruption on the CVsystem	Study effect of sGC gene disruption on development of orthostatic hypotension	Propose and test pharmacologic countermeasures
RAY/Effect of Simulated Microgravity on the Vestibulosympathetic Reflex in Humans	Orthostatic hypotension	Countermeasures affecting vestibulosympathetic reflex	Human bed rest studies	Study effects of vestibular stimulation and bed rest on sympathetics	Propose and evaluate feasibility of countermeasures in human studies	Test countermeasures in human studies
SHOUKAS/Mechanics of Cardiovascular Deconditioning	• Orthostatic hypotension • Cardiac function	• Pharmacological (Adrenergic agents) • Pulsatile G-suit	• Hindlimb unloading (HU) of rats • Shuttle flight (STS-107) of rats	Measure effects and mechansims of HU and shuttle flight on: • vascular beds • cardiac fctn	• Identify and test pharmacologic countermeasures in rodent model • Develop pulsatile G-suit	Test countermeasures in human studies
THOMAS/Echocardiographic Assessment of CV Adaptation and Countermeasures in Microgravity	• Orthostatic hypotension • Cardiac function • CV disease • Exercise	N/A	• Core lab analysis of ultrasound data •Development of new ultrasound techniques	Study effects of interventions & countermeasures using ultrasound techniques	Study effects of interventions & countermeasures using ultrasound techniques	Study effects of interventions & countermeasures using ultrasound techniques
WILLIAMS/Influence of Gender and Age on Renal and Cardio-Endocrine Responses to Simulated Microgravity	• Orthostatic Hypotension • Exercise • Cardiac Function • Dysrhythmias	• Pharmacological (Midodrine and volume regulating hormones) • Diet (Electrolytes)	• Head down tilt bed rest Head down tilt bed rest - humans • Sleep disruption • Groups vary by age and gender	Assess volume, electrolyte, hormonal responses	•Midodrine •Spironolactone •Diet (Electrolytes)	•Midodrine •Spironolactone •Diet (Electrolytes)

National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Table 4.2. Integration Activities

	Bayorh	Bers	Cassone	Cohen	Coolahan
Internal Communication	•Animal studies group •All	•CV technology group •All	•Animal studies group •All	•Human studies group •All	•CV technology group •All
Integrated Experiment Development	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Human Studies (Human studies group) •Animal and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)
Sample Sharing	•Tissue (Animal studies group) •Data (All)	•Computer Code (CV technology group) •Data (All)	•Tissue (Animal studies group) •Data (All)	•Blood and Urine (Human studies group) •Data (All)	•Computer Code (CV technology group) •Data (All)
Synergistic Studies of Opportunity	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)	•Animal Studies(Animal studies group) •Human and Computer Studies (All)	Human Studies (Humans studies group) Animal and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)
Development of Computer Model of Integrated Human Function	•CV technology group	•CV technology group	•CV technology group	•CV technology group	•CV technology group

Human Studies Group = Cohen, Meck, Ray, Williams, and collaborators from other Teams
Animal Studies Group = Bayorh, Cassone, Delp, Lorell, Murad Shoukas, and collaborators from other Teams
CV Technology Group = Bers, Coolahan, Mark, McCulloch, Thomas, and collaborators from other Teams
Collaborators from other Teams include members of Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems Teams

Table 4.2. Integration Activities (continued)

	Delp	Lorell	Mark	McCulloch	Meck
Internal Communication	•Animal studies group •All	•Animal studies group •All	•CV technology group •All	•CV technology group •All	•Human studies group •All
Integrated Experiment Development	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)	•Human Studies (Human studies group) •Animal and Computer Studies (All)
Sample Sharing	•Tissue (Animal studies group) •Data(All)	•Tissue(Animal studies group) •Data (All)	•Computer Cod e(CV technology group) •Data (All)	•Computer Code (CV technology group) •Data (All)	•Blood and Urine (Human studies group) •Data (All)
Synergistic Studies of Opportunity	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)	Human Studies (Humans studies group) Animal and Computer Studies (All)
Development of Computer Model of Integrated Human Function	•CV technology group	•CV technology group	•CV technology group	•CV technology group	•CV technology group

Human Studies Group = Cohen, Meck, Ray, Williams, and collaborators from other Teams
Animal Studies Group = Bayorh, Cassone, Delp, Lorell, Murad Shoukas, and collaborators from other Teams
CV Technology Group = Bers, Coolahan, Mark, McCulloch, Thomas, and collaborators from other Teams
Collaborators from other Teams include members of Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems Teams

National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Table 4.2. Integration Activities (continued)

	Murad	Ray	Shoukas	Thomas	Williams
Internal Communication	•Animal studies group •All	•Human studies group •All	•Animal studies group •All	•CV technology group •All	•Human studies group •All
Integrated Experiment Development	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Human Studies (Human studies group) •Animal and Computer Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Human and Animal Studies(All) •Computer Studies (CV technology group)	•Human Studies (Human studies group) •Animal and Computer Studies (All)
Sample Sharing	•Tissue (Animal studies group) •Data (All)	•Blood and Urine (Human studies group) •Data (All)	•Tissue (Animal studies group) •Data(All)	•Data (All) •Computer Code (CV technology group)	•Blood and Urine (Human studies group) •Data (All)
Synergistic Studies of Opportunity	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	Human Studies (Humans studies group) Animal and Computer Studies (All)	•Animal Studies Animal studies group) •Human and Computer Studies (All)	•Human and Animal Studies (All) •Computer Studies (CV technology group)	Human Studies (Humans studies group) Animal and Computer Studies (All)
Development of Computer Model of Integrated Human Function	•CV technology group	•CV technology group	•CV technology group	•CV technology group	•CV technology group

Human Studies Group = Cohen, Meck, Ray, Williams, and collaborators from other Teams
Animal Studies Group = Bayorh, Cassone, Delp, Lorell, Murad Shoukas, and collaborators from other Teams
CV Technology Group = Bers, Coolahan, Mark, McCulloch, Thomas, and collaborators from other Teams
Collaborators from other Teams include members of Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems Teams

National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Table 4.3a. Achieving Goal 1: Reduce Risk of Impaired Cardiovascular Response to Orthostatic Stress

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Obtain & analyze relevant data from prior and future flights													
Phase 1: Focused Mechanistic Research													
• Study alterations in CV regulation using CV System Identification • Study effects of adrenergic agents (midodrine) • Assess volume, electrolyte and hormonal responses													
• Understand alterations in nitric oxide and prostacyclin systems • Understand alterations in circadian physiology • Develop accurate computer models of CV System • Study effects of microgravity on blood vessels, lymphatics • Study effects of soluble guanylyl cyclase gene disruption • Study effects of vestibular stimulation • Develop and apply relevant ultrasound technology • Assess effects of sleep disruption • Assess effects of gender and age • Develop pulsatile G suit													
• Assess effects of artificial gravity													
Phase 2: Preliminary Countermeasure Development Research													
• Evaluate adrenergic agents (midodrine)													
• Evaluate pharmacologic alteration of nitric oxide and prostacyclin systems • Evaluate circadian intervention • Use CV System Identification to evaluate countermeasures • Utilize CV models to simulate effects of countermeasures • Evaluate vascular and lymphatic interventions • Evaluate soluble guanylyl cyclase intervention • Evaluate vestibular intervention • Utilize ultrasound technology to evaluate countermeasures • Evaluate volume regulatory and electrolyte interventions • Evaluate sleep control intervention													

National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Table 4.3a. Achieving Goal 1: Reduce Risk of Impaired Cardiovascular Response to Orthostatic Stress (continued)

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 2: Preliminary Countermeasure Development Research													
• Evaluate gender and age dependent interventions • Evaluate exercise countermeasure • Evaluate pulsatile G suit													
• Evaluate artificial gravity countermeasures													
Phase 3: Mature Countermeasure Development Research													
• Test midodrine countermeasure in human ground-based studies													
• Select and test most promising countermeasures and develop and test in human ground studies													
Phase 4: Countermeasure Evaluation & Validation													
• Flight test midodrine countermeasure													
• Flight test other countermeasures successful in Phase 3													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement midodrine countermeasure													
• Implement other countermeasures in Phase 4													

National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Table 4.3b. Achieving Goal 2: Reduce Risk of Serious Cardiac Dysrhythmias

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Obtain & analyze ECG data from prior and future flights													
Phase 1: Focused Mechanistic Research													
• Microvolt T-wave alternans (MTWA) studies in patient populations													
• Measure effects of microgravity on MTWA • Measure effects of electrolyte alterations • Measure effects of alterations in volume regulatory hormones • Measure effects of age and gender • Develop animal model • Develop computer models of cardiac electrical activity													
Phase 2: Preliminary Countermeasure Development Research													
• Measure MTWA in pre and postflight astronauts													
• Test aldosterone antagonist as countermeasure in human studies • Evaluate dietary countermeasures in human studies • Evaluate pharmacologic countermeasures in animal studies • Evaluate countermeasures developed for Goal 1 in human studies													
Phase 3: Mature Countermeasure Development Research													
• Select and test most promising countermeasures and develop and test in human ground studies													
Phase 4: Countermeasure Evaluation & Validation													
• Flight test countermeasures successful in Phase 3													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement countermeasures successful in Phase 4													

National Space Biomedical Research Institute
CARDIOVASCULAR ALTERATIONS PROGRAM

Table 4.3c. Achieving Goal 3: Reduce Risk of Diminished Cardiac Function

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Obtain & analyze relevant data from prior and future flights													
Phase 1: Focused Mechanistic Research													
• Develop myocyte and cardiac computer models													
• Measure effects of microgravity on cardiac mass • Measure effects of microgravity on myocyte function • Measure effects of microgravity on cardiac remodeling • Measure role of calcium, hormones, genes, muscle degradation • Develop ultrasound techniques to measure cardiac function													
Phase 2: Preliminary Countermeasure Development Research													
• Use computer models to simulate potential countermeasures • Evaluate growth hormone countermeasure • Evaluate adrenergic countermeasure • Evaluate dietary and exercise countermeasures • Evaluate other pharmacological countermeasures • Evaluate countermeasures developed for Goal 1 in human studies													
Phase 3: Mature Countermeasure Development Research													
• Select and test most promising countermeasures and develop and test in human ground studies													
Phase 4: Countermeasure Evaluation & Validation													
• Flight test countermeasures successful in Phase 3													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement countermeasures successful in Phase 4													

5.0 HUMAN PERFORMANCE FACTORS, SLEEP & CHRONOBIOLOGY

Team Leader: Charles A. Czeisler, M.D., Ph.D.
Professor of Medicine, Harvard Medical School
Chief, Division of Sleep Medicine
Brigham and Women's Hospital
221 Longwood Avenue, Room 438A
Boston, MA 02115
617-732-4013
617-732-4015 FAX
caczeisler@hms.harvard.edu

5.1 INTRODUCTION

Sleep and circadian rhythm systems are fundamental regulatory processes of the nervous system and the most ubiquitous endogenous controls of human biobehavioral functions-everyone is internally programmed to sleep every night. The need for sleep is a homeostatic drive that occurs regardless of time of day, but the endogenous circadian pacemaker also modulates it. Conversely, the endogenous circadian pacemaker oscillates regardless of the need for sleep, although its promotion of wakefulness can be overwhelmed by elevated homeostatic sleep drive. These two powerful neurobiological systems interact continuously to control brain state (i.e., waking vs. sleep) and the intensity of state (e.g., alert vs. sleepy). Sleep and circadian rhythmicity also temporally modulate a wide range of physiological functions (e.g., body temperature, cardiovascular activity, respiration, immune responses), hormonal functions (e.g., growth hormone, melatonin, cortisol, thyroid hormones), behavioral functions (e.g., movement, posture, reaction time), and cognitive functions (e.g., fatigue, alertness, vigilance, memory, cognitive throughput). No astronaut-no matter how much training, preparation, nutrition, psychosocial support, or environmental protection is provided-is immune from the daily control of physiology and performance by the homeostatic drive for sleep and the endogenous circadian timing system. Failure to take these two interactive neurobiological imperatives into account when planning human activities in space could have catastrophic consequences.

The success of human space missions therefore depends on each astronaut remaining alert and vigilant while operating sophisticated equipment and following complex procedures. During exploration class space missions, the space environment affects a number of physiological systems critically involved in human performance, and it is vital to mission success to understand the biological limits of human performance under such conditions. It has been demonstrated that both acute gravitational changes and space flight disrupt circadian rhythms and reduce sleep. Since circadian disruption and sleep loss result in both physiological and performance deficits, this team is focused on these issues and, in particular, is concerned with the following aspects of the space environment: microgravity, altered light-dark cycles and altered or reduced sleep/rest opportunities that may involve extended durations of wakefulness. The primary thrust of this team's research program involves altered circadian organization, sleep disruption and cumulative sleep loss, and the associated neurobehavioral decrements occurring during exploration class missions.

The need for sleep and the circadian pacemaker have a sustained influence over many biomedical systems essential for maintaining astronaut physical condition, mental health, and performance capability. Dysfunction of sleep and circadian systems can adversely affect an organism's ability to respond to environmental challenges and has been linked to physiological and psychological disorders. This area therefore has a high degree of relevance to a number of cardiovascular and immune changes, neurovestibular alterations and nutritional needs, and behavioral and psychological health in space flight.

5.2 RISKS

The following risks in the Human Behavior and Performance Discipline Area of the Critical Path Roadmap have been identified:

- Human Performance Failure Because of Sleep and Circadian Rhythm Problems (19)
- Human Performance Failure Because Of Human System Interface Problems and Ineffective Habitat, Equipment, Design, Workload, or In-flight Information and Training Systems

Risk number 19 includes both neurobehavioral performance failure as well as physiological performance failure due to sleep or circadian rhythm disturbances and is a very complex risk. For our research purposes, therefore, we have broken this risk down further into:

- Risk of Human Neurobehavioral or Physiological Performance Failure Due to Disruption of Circadian Phase, Amplitude, Period, or Entrainment During Space Exploration.
- Risk of Human Neurobehavioral or Physiological Performance Failure Due to Acute or Chronic Degradation of Sleep Quality or Quantity During Space Exploration

5.3 GOALS

The Human Performance Factors, Sleep and Chronobiology Team has the following goals for its program:

Risk-Based Goals

Goal 1: *Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration.*

Goal 2: *Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.*

Goal 3: *Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.*

Non Risk-Based Goals

Goal 4: *Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight.*

Goal 5: *Develop new methods for monitoring ambient and retinal light exposure (illuminance/photopic lux, broadband visible irradiance, and circadian effective illuminance/circadian lux) on board space shuttle and ISS during space flight and on planetary habitats.*

Goal 6: *Develop Earth-based applications of technologies for non-invasively monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance for industrial and medical use.*

Goal 7: *Develop Earth-based applications of high-fidelity mathematical models of performance based on circadian organization and sleep-wake history for industrial and medical use.*

Goal 8: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment.*

Goal 9: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to acute and chronic degradation of sleep quality or quantity.*

Goal 10: *Develop Earth-based applications of technologies developed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work.*

Goal 11: *Integrate research and analysis*

5.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

Current Research Program

The Human Performance Factors, Sleep and Chronobiology Team is focused on developing countermeasures for the sleep loss and circadian dysfunction and associated neurobehavioral performance decrements that occur during long-duration space flight. The team research objectives are driven by the Critical Path Roadmap related to Human Performance Failure because of Sleep and Circadian Rhythm Problems. The current research program involves nine ground-based research projects. The strategy of the Human Performance Factors, Sleep and Chronobiology Team is to develop a synergistic interaction between research projects at the molecular, cellular, organism, and human levels, and to integrate predictive biomathematical modeling of the sleep and circadian systems.

In 2001, the HPFSC Team was substantially restructured. The current team is comprised of nine PIs, six of whom are new NSBRI investigators. Three of these six new NSBRI investigators are new to the space science community, a direct result of the recruitment efforts made within the science community. In order to achieve the goals listed above, the Human Performance Factors, Sleep and Chronobiology Team has identified the following six interrelated themes within this research area:

A. **Effects of long-duration space flight on sleep and/or circadian rhythmicity.** The focus of this theme is to identify and understand the mechanism underlying the effect of long-duration space flight (microgravity, altered light intensity, loss of geophysical cues, isolation, altered physical activity, etc.) on neurobiologic, endocrinological, and behavioral functions (molecular, cellular and organismic) that control sleep and circadian systems.

B. **Effects of sleep loss and/or circadian dysfunction on physical and neurobehavioral performance.** The focus of this theme is to identify and to understand the mechanisms underlying the acute and chronic adverse effects that sleep loss, sleep disruption, and/or circadian dysfunction have on critical physiologic and performance parameters during long-duration space flight (e.g., neurophysiologic function, physiological alertness, vigilance, cognitive performance, mood/morale, problem solving and communication).
C. **Predictive modeling of performance based upon circadian organization and sleep homeostasis.** This theme is concerned with the development of analytical or phenomenological mathematical models that predict individual human performance capability by involving multiple subsystems (e.g., circadian rhythmicity, sleep homeostasis, work-rest schedules, etc.) as an integrated unit across levels of organization, and by estimating the impact of countermeasure use designed to optimize human physical and/or neurobehavioral performance.
D. **Countermeasures to optimize sleep and facilitate circadian adaptation in space and maintain optimal neurobehavioral performance**. The research program of this team will not only define the impact of the space environment on sleep and circadian rhythmicity and the effects of the sleep loss and circadian dysfunction on performance but also will develop methods to counter the adverse physiological and behavioral events. These countermeasures may include behavioral, pharmacological, environmental light or other adaptive approaches to maintain function and performance under the adverse conditions of long-duration space flight.
E. **Monitoring and assessment during space flight.** This theme deals with the development of methods for monitoring the status of sleep, sleep homeostasis and circadian organization, as well as technologies that monitor ambient lighting conditions on space shuttle and ISS and assess and update the current functional status or performance capability of the individual

The initial strategic research program for the Human Performance Factors, Sleep and Chronobiology Team addresses the five research themes described above and is focused on developing countermeasures for the sleep loss and circadian dysfunction and associated neurobehavioral and physiological performance decrements that occur during long-duration space flight. The schematic of the circadian and homeostatic regulation of sleep and alertness and physiological functions shown in Diagram 5.1 illustrates the relationships between the nine current ground-based experiments that comprise the Team, with the principal targets of each project indicated. This diagram illustrates the interrelated nature of the projects, designed to fill critical gaps in knowledge that need to be filled in order to develop effective countermeasures for long-duration space flight. Each of the individual projects is summarized below and in Table 5.1, including which goal(s) are addressed and countermeasure targets.

Brainard et al.: *Optimizing Light Spectrum for Long Duration Space Flight*
The physiological changes caused by disturbed circadian rhythms and altered sleep-wake patterns can result in decrements in alertness, concentration, and performance. This project addresses these risk factors, which threaten the safety of personnel and the objectives of space missions as stated in Goal 3.
Countermeasure targets include:
1. Identification of the optimum spectrum for photic resetting o f the circadian pacemaker:
2. Design specifications for space suit visors and the windows used in space vehicles and habitats; and
3. Engineering parameters for the ideal spectral distribution for illumination of general living quarters during space exploration.

Czeisler et al.: *Circadian Entrainment, Sleep-Wake Regulation & Performance during Space Flight*
The intent of this project is to develop countermeasures to facilitate adaptation of the human circadian pacemaker to the 24.65-h day length of Mars, which is outside the range of entrainment of the human circadian pacemaker given the weak synchronizing stimuli within the Martian habitat. This project applies to Goal 3.

The primary ***countermeasure target*** is to evaluate the efficacy of intermittent bright light pulses as a treatment to reduce the risk of the misalignment of circadian phase, sleep disruption, associated decrements in neurobehavioral performance and reduction in nocturnal growth hormone secretion experienced by individuals exposed to the 24.65h Martian day.

Dinges et al.: *Countermeasures to Neurobehavioral Deficits From Partial Sleep Loss*
Using a response surface experimental paradigm (RSM), this project seeks to reduce neurobehavioral deficits and fatigue due to inadequate sleep in astronauts by investigating how variations in sleep duration and its circadian placement relate to the return of performance per time invested in sleep. This project applies to Goal 2.

Countermeasure targets include determination of the amount of naptime necessary to compensate for interrupted nocturnal sleep periods for the prevention of cumulative sleepiness and performance deficits.

Fuller et al.: *Primate Circadian Rhythms in the Martian Environment*
This project is focused on the ability of the circadian time system to synchronize to the Martian photic (spectrum and period) by examining the effects of 1.0, 1.5 and 2.0G on the period of the circadian pacemaker. A G vs. period model will be developed to predict the effect of the 0.38 G Martian environment on the period of the circadian pacemaker. Long-term (4 months) physiological and behavioral responses will be examined.

Countermeasure targets include the use of timed bright light pulses on circadian entrainment. This program will develop a primate model to evaluate physiological and behavioral consequences of long-term exposure of males and females to altered lighting and gravitational environments. This project applies to Goals 1 and 3.

Jewett et al.: *Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure*
The intent of this project is to further develop and refine our mathematical dynamic stimulus processing model so that it can accurately predict the phase and amplitude of the human circadian system under any lighting system especially those which are in space. The mathematical Neurobehavioral Performance model validated against performance data collected will result in the development of a user-friendly Performance Simulation Software program. This project applies to Goals 1 through 4.

Countermeasure targets include the design of shift schedules to allow astronauts to receive available bright light at appropriate times for proper circadian alignment with their sleep/wake schedules.

Menaker et al.: *A Model of Circadian Disruption in the Space Environment*
This project proposes to evaluate the effects of "constant" conditions and shift work schedules on the maintenance of circadian rhythmicity when the central and peripheral structures are abnormally phased. The resulting abnormal circadian organization is "dysphasia." This project applies to Goal 1.

Countermeasure targets include an evaluation of meal timing, melatonin administration, forced exercise, and short pulses of complete darkness as a treatment to reduce the risk of circadian dysphasia.

Morin et al.: *Circadian and Vestibular Relationships*
This project seeks to determine the route by which a correlate of the non-photic stimulus, i.e., locomotion, might gain access to the circadian rhythm system and shift rhythm phase. It has also opened the possibility that the vestibular system is a specific route by which sensory information related to head movement might gain access to the circadian system. This project applies to Goal 1.

Countermeasure targets include an evaluation of a non-locomotor, non-photic three-dimensional motion stimulus to activate functionally the vestibular and circadian systems, laying the groundwork for the future development of novel approaches for the treatment of space motion sickness and for resetting circadian phase.

Tosini et al.: *Long-Term Exposure to Dim Light Desynchronizes the Circadian System of Rats*
The goal of this project is to understand the mechanisms responsible for the desynchronization of circadian rhythm in locomotion and the enzymes responsible for the production of melatonin. Investigating the effect that internal desynchronization has on the immune response and motor and cognitive performances. This project applies to Goal 2.

Countermeasure targets include an evaluation of the use of melatonin as a pharmacological agent to counteract desynchronization of the circadian rhythms.

Turek et al.: *Animal Model for Sleep Loss and Circadian Disruption*
This project will focus on determining the effects of 12 hours of imposed wakefulness on circadian rhythms, sleep-wake cycles, neurobehavioral and motor performance measures during normal active and inactive periods. This project applies to Goals 1 and 3.

Countermeasure targets include treatment exercise and with either physiological or pharmacological dose of melatonin reduce the effects of circadian disruption and sleep loss as well as alleviate the adverse effects associated with work at different times of day.

Achieving Non Risk-Based Goals

Goal 4: *Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight.*
To achieve this goal, current studies are being conducted to assess the potential of using the Actiwatch-L (a wrist-worn light and actigraphy recording device already approved for space flight) to monitor sleep and light exposure of individual crewmembers while in space. This device could replace more extensive polysomnography devices used in more recent studies of sleep in space. Studies are also underway that compare the wrist-level Actiwatch-L light recordings with eye-level light measurements. Work is progressing on the use of the Actiwatch-

L measurements as inputs to a mathematical model that can then predict the level of sleep homeostasis, phase of circadian rhythmicity and relative neurobehavioral performance levels.

Goal 5: *Develop new methods for monitoring ambient and retinal light exposure (illuminance/ photopic lux, broadband visible irradiance, and circadian effective illuminance/circadian lux) on board space shuttle and ISS during space flight and on planetary habitats.*
For measurement of retinal light exposure in space, please see Goal 4 above. For ambient light exposure, wall-mounted ambient light recording devices have been tested aboard the Space Shuttle in the Neurolab flight. The team's current studies will help determine the circadian effective illuminance and irradiance levels, and then these recording devices can be refined to measure circadian-activating light levels more precisely.

Goal 6: *Develop Earth-based applications of technologies for non-invasively monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance for industrial and medical use.*
The polysomnography device that was developed for the recording of sleep in space in the Neurolabb Shuttle flight has become a useful, wire-free device for recording polysomnography in lab-based and home-based basic science and clinical studies. This technology has the advantage of being appropriate for use when ambulatory and is straightforward enough for a trained person to apply to themselves.

The use of salivary melatonin as a marker of circadian phase has been applied in both space and on Earth and is a technology that allows the validation of experimental and modeling results in field studies in which plasma melatonin measurements would not be possible.

Mathematical models that are developed to predict neurobehavioral performance in space are also being used to determine appropriate shift scheduling, light exposure, sleep timing, and countermeasure applications for shift workers, pilots, military and medical personnel, and transportation workers who also face the challenges of restricted sleep and circadian misalignment here on Earth. Neurobehavioral test batteries that are developed for these projects are useful for the validation of mathematical models in field and laboratory studies as well.

Goal 7: *Develop Earth-based applications of high-fidelity mathematical models of performance based on circadian organization and sleep-wake history for industrial and medical use.*
The mathematical models of performance that are being developed in this project can be applied to any Earth-based situation in which it would be helpful to know the effects of a sleep/wake schedule and a light exposure pattern on resulting neurobehavioral performance (e.g., shift workers, pilots, military and medical personnel, and transportation workers). Therefore, the mathematical models developed here have been programmed into user-friendly simulation software that can be used by anyone to predict neurobehavioral performance given light exposure levels and sleep/wake history. This software is updated with model revisions and user-interface improvements on a regular basis.

Goal 8: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment.*
The studies conducted here improve our understanding of the effects of light on the human circadian system and the role that the circadian system plays in neurobehavioral performance. These findings are incorporated into our mathematical models on an ongoing basis. This allows us to then determine the best light schedule and intensities to reduce the risk of performance

failure by appropriately aligning the circadian system with the work/rest schedule. This technology is already currently in use in transportation, military and industrial settings here on Earth.

Goal 9: *Develop Earth-based application so technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to acute a chronic degradation of sleep quality or quantity.*
Our projects will help determine the amount and timing of sleep that best allows people to work extended and/or misaligned shifts with the least risk of performance failure. These findings will also be incorporated into the mathematical model being developed here. The model can then be used to help schedule rest/nap/sleep times so that they are the most effective in improving performance levels.

Goal 10: *Develop Earth-based applications to technologies developed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work.*
Studies investigating the effects of extended duration work schedules in these projects allow us to determine the best timing of countermeasures (light exposure, naps, melatonin, etc.) to improve performance. These findings are completely applicable to any extended duration work schedules used here on Earth.

Goal 11: *Integrate research and analysis*
Our goal is to integrate research within the Human Performance Factors, Sleep and Chronobiology Team, with other teams, and with work being done by Team investigators not directly supported by NSBRI. See a summary of our activities in Table 5.2.

Program Gaps
The Human Performance Factors, Sleep and Chronobiology Team has nine ground-based projects currently funded until 2003 or 2004. The External Advisory Council of the NSBRI rated the current research program of the Human Performance Factors, Sleep and Chronobiology Team as "excellent" in its initial evaluation in September 2000, and recommended that additional funding be set aside in the next research announcement "in order to solicit proposals in those areas identified as gaps in the current team". Therefore, in addition to the progress toward countermeasure development anticipated from the currently funded research projects, it is anticipated that the following four research questions will be addressed in the remaining years of the 5-year strategic plan.

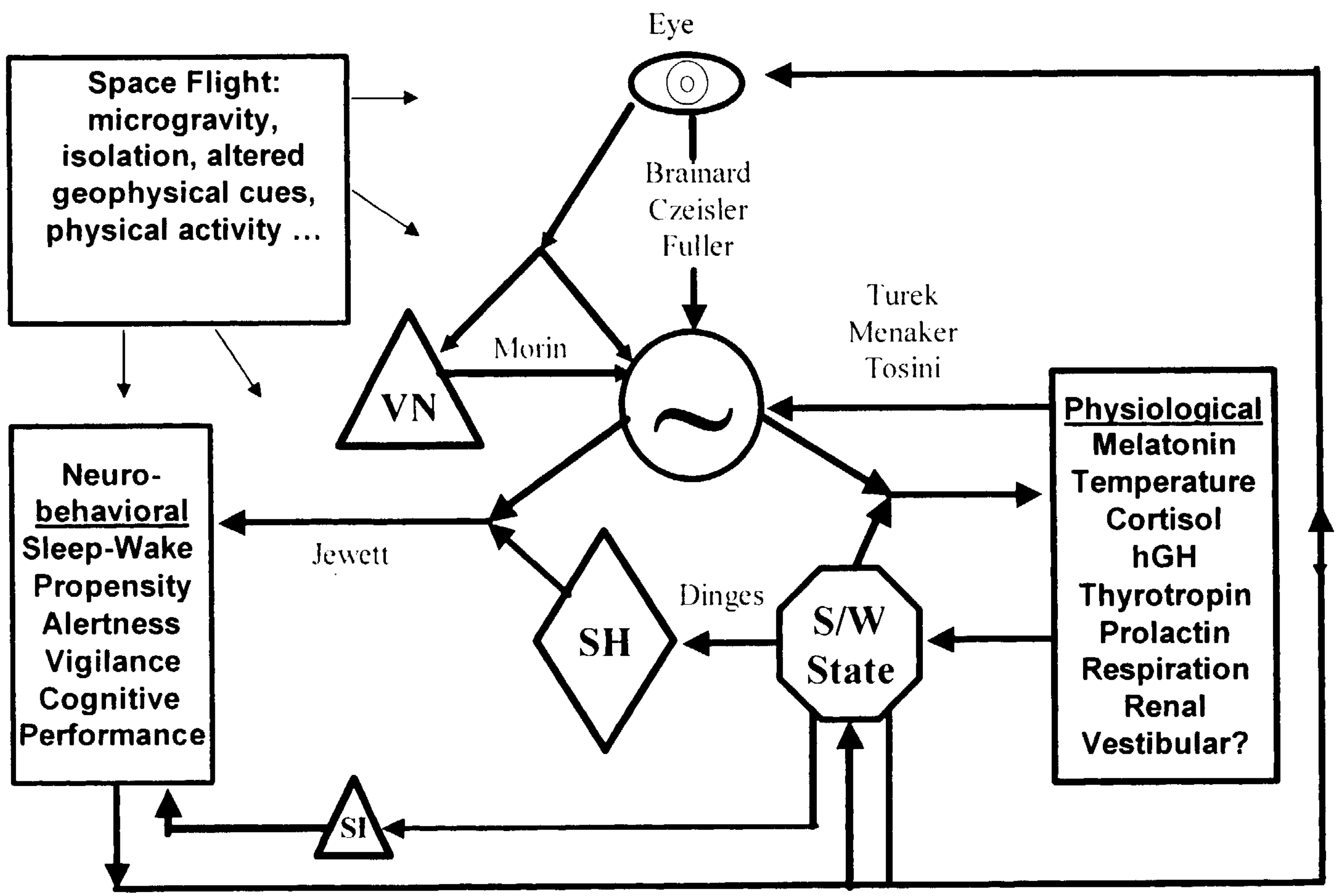
Physical effects. Proposal are sought to determine how space flight or exposure to chronic sleep restriction and/or circadian disruption affect sleep- and/or circadian-mediated neuroendocrine, metabolic, neurologic or autonomic functions, particularly those relevant to risk mitigation (e.g., growth factors, nutrition, glucocorticoids, monoamines) during extended duration missions.

Monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and/or neurobehavioral performance during space flight. Proposals are sought to validate methodologies that are portable and non-intrusive in the space flight environment to assess sleep and/or circadian rhythms and monitor light on space shuttle, ISS and other long duration space environments.

Novel countermeasure development. Proposal are sought to determine how recent advances in the neurobiology of sleep and/or circadian rhythms (orexin/hypocretin system, circadian photoreception, output pathways for regulation of sleep or circadian rhythms) can be used to develop countermeasures to facilitate adaptation to and thereby maintain optimal neurobehavioral performance during an exploration class space mission.

Age, gender and inter-individual differences. Proposals are sought to determine how age, gender and individual biological and behavioral characteristics alter sleep- and/or circadian-mediated physiologic responses to, and risk mitigation for, prolonged space flight.

Diagram 5.1. Description of Current (2001) Program for Human Performance Factors, Sleep and Chronobiology. This diagram illustrates the relationships between the different physiological systems investigated by the different projects on the team. Illustrated is the influence of the retinal light exposure on the human circadian clock (circle with the oscillator symbol ~) and the influence on the sleep-wake state (S/W), and their effect on a number of physiological variables (melatonin, temperature, etc.). A combined influence of the circadian clock and sleep-wake is exerted on neurobehavioral variables (sleep-wake propensity, alertness, etc.). The sleep-wake state influence is illustrated via the intermediary of the sleep homeostat (SH), and sleep inertia (SI). The global influence of factors associated to Space Flight (micro gravity, isolation, etc.) on the sleep and circadian systems is also represented. The interaction of the Vestibular Nucleus (VN) and its output pathways with the circadian pacemaker is being investigated by one project.



5.5 OBJECTIVES AND STRATEGIC ACTIVITIES

The objectives underlying each goal are presented below along with strategic activities that will be used to achieve the goals and objectives. Table 5.3 provides a timeline for the completion of these activities.

Risk-Based Goals

Goal 1: *Reduce the risk of human performance failure due to disruption of circadian phase, amplitude, period, or entrainment.*

Objective 1A: Assess risk and target level of acceptable risk

- Complete projects that characterize and quantify neurobehavioral performance decrements associated with circadian misalignment (Czeisler, Dinges, Jewett projects)
- Complete projects that quantify the impact of chronic circadian disruption on recovery sleep, circadian adjustment and/or neurobehavioral performance (Turek, Menaker and Tosini projects)

Objective 1B: Determine mechanisms

- Complete projects that investigate the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function in humans (Dinges project)
- Complete projects that fit stochastic and deterministic models to low-amplitude human temperature data to select lower- vs. higher-order models of human circadian amplitude recovery (Jewett project)
- Complete projects that determine the performance levels of desynchronized animals how desynchronized organisms respond to infections (Tosini project)
- Complete projects that validate refined circadian amplitude recovery dynamics of human light model (Jewett project)
- Complete projects that investigate the relationship between the degree of circadian disruption and the resulting impairment to neurobehavioral performance in mice (Turek project)

Objective 1C: Develop countermeasures

- Complete projects that test commercially available head-mounted light devices for circadian efficacy (Jewett, Brainard, Czeisler projects)
- Complete projects that test if bright light pulses facilitate entrainment to Martian day (Fuller project)
- Complete projects that determine the efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars (Czeisler project)
- Complete projects that determine the efficacy of intermittent bright light pulses of different intensities and/or wavelengths on circadian entrainment to non-24-hour work-rest schedules (Czeisler project)
- Complete projects that test pharmacological countermeasures (melatonin) to reduce the risk of internal desynchronization (Tosini project)
- Complete projects that apply knowledge gained with animal model to humans using measures of cognitive performance and physiological well-being to assess effectiveness (Menaker project)
- Complete projects that incorporate refined light model into circadian component of neurobehavioral performance model and predict

neurobehavioral performance in human phase shifting experiments (Jewett project)

- Complete projects that test neurobehavioral model predictions against circadian and performance data collected under field conditions (Jewett project)
- Complete projects that test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic circadian disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that test if access to a wheel during rest periods (exercise) reduces the impact of chronic circadian disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that determine what duration of exercise optimally reduces the impact of chronic circadian disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that test pharmacological wake-promoting countermeasures (caffeine, modafinil) to reduce the risk of neurobehavioral performance failure due to circadian disruption (Czeisler allied projects)
- Initiate project that integrates into biomathematical model the impact of wake- and sleep-promoting therapeutics (pharmacological or behavioral) on neurobehavioral performance in the presence of circadian misalignment
- Initiate projects that ground test the efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic circadian disruption in humans
- Initiate projects that ground test the efficacy of pharmacological (e.g., melatonin), nutritional, environmental (e.g., light or dark pulses) or behavioral (e.g., exercise) circadian countermeasures designed to maintain internal synchrony of circadian oscillators in diverse organ systems in humans
- Initiate project to conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep
- Initiate project to conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic circadian disruption
- Initiate project to conduct projects that implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment

Goal 2: *Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality and quantity.*

Objective 2A: Assess risk and target level of acceptable risk

- Complete projects to characterize and quantify neurobehavioral performance decrements associated with sleep restriction and disruption (Czeisler, Dinges, Jewett projects)
- Complete projects that quantify the impact of chronic sleep restriction/disruption on recovery sleep and circadian adjustment (Turek, Dinges projects)

Objective 2B: Determine mechanisms

- Complete projects that determine the nature of neurobehavioral and physiological changes induced by chronic sleep restriction at different circadian phases (Dinges project)
- Complete projects that test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases (Dinges project)
- Complete projects that investigate the relationship between the degree of sleep disruption and the resulting impairment to neurobehavioral performance in mice (Turek project)

Objective 2C: Develop countermeasures

- Complete projects that develop and test candidate sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Dinges Project)
- Complete projects that test optimal sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Dinges project)
- Complete projects that test neurobehavioral model predictions against circadian and performance data collected under field conditions (Jewett project)
- Complete projects that test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic sleep restriction/ disruption on performance and recovery sleep in mice (Turek project)
- Complete project that tests if access to a wheel during rest periods (exercise) reduces the impact of chronic sleep restriction/disruption on performance and recovery sleep in mice (Turek project)
- Complete project that determines what duration of exercise optimally reduces the impact of chronic sleep restriction/disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that test pharmacological wake-promoting countermeasures (caffeine, modafinil) to reduce the risk of neurobehavioral performance failure due to sleep loss (Czeisler allied projects)
- Complete projects that ground test the efficacy of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of microgravity on sleep in humans
- Initiate projects that integrate into biomathematical models the impact of wake- and sleep-promoting therapeutics (pharmacological or behavioral) on neurobehavioral performance in the presence of sleep restriction/disruption
- Initiate project to ground test the efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction in humans
- Initiate project to conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of microgravity on sleep
- Initiate project to conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction
- Initiate project that implements a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to sleep loss

Goal 3: *Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution*

Objective 3A: Assess risk and target level of acceptable risk

- Complete projects that describe disrupting effects of shifting schedules of light, food availability and exercise on phase relationships among circadian oscillators in brain and peripheral organs (Menaker project)
- Complete projects that characterize the effect of long-term exposure to constant conditions on the circadian system (Tosini project)
- Characterize and quantify the presumptive vestibular-circadian system anatomical connection (Morin project)
- Complete projects that determine how desynchronized organisms respond to infections (Tosini project)
- Initiate project to develop lighting monitoring system for inside of space shuttle and ISS
- Initiate projects that identify the effect of an altered circadian environment on the well being of the organisms

Objective 3B: Determine mechanisms

- Complete projects that develop human melatonin fluence-response curves below 440 nm and above 600 nm (Brainard project)
- Complete projects that quantify role of pupil dilation in circadian photic transduction in humans and that develop melatonin action spectrum in humans with freely reactive pupils (Brainard project)
- Complete projects that determine how desynchronized organisms respond to infections(Tosini project)
- Complete projects that describe disrupting effects of constant light on phase relationships among circadian oscillators in brain and peripheral organs (Menaker project)
- Complete projects that describe disrupting effects of shifting schedules of light, food availability and exercise on phase relationships among circadian oscillators in brain and peripheral organs (Menaker project)
- Complete projects that test entrainment to Martian day-length and both ambient and habitat lighting (Czeisler project)
- Complete projects that identify promising pharmacological countermeasures to reduce the risk of desynchronization (Menaker, Tosini, Turek projects)
- Complete project that determines effect of altered gravity on circadian period in primates (Fuller project)
- Complete projects that test human melatonin response to simulated ISS, EVA and lunar light environments (Brainard and Czeisler projects)
- Complete projects that determine functional activation of the vestibular and circadian systems by an optokinectic nystagmus stimulus (Morin project)

Objective 3C: Develop countermeasures

- Complete projects that determine the functional activation of the vestibular and circadian systems by a non-locomotor, non-photic, vestibular activating stimulus (Morin project)
- Complete projects that test human circadian phase-shifting with selected monochromatic wavelengths (Brainard project)
- Complete projects that ameliorate disruptive effects of constant light and shifting schedules using pulses of bright light, darkness, melatonin and applying regularized feeding and work schedules (Menaker project)

- Initiate projects that develop and ground test light sources that optimally stimulate human circadian responses and light sources that specifically do not stimulate human circadian responses
- Initiate projects that develop and ground test window and visor prototypes for optimal human circadian stimulation and prototypes that minimize human circadian responses
- Initiate projects that integrate current ISS and shuttle lighting with new light sources and window systems

Non Risk-Based Goals

Goal 4: *Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight.*

- Complete projects that assess the potential of using the Actiwatch-L (a wrist-worn light and actigraphy recording device already approved for space flight) to monitor sleep and light exposure of individual crew members while in space
- Complete projects that compare the wrist-level Actiwatch-L light recordings with eye-level light measurements
- Complete projects that use of the Actiwatch-L measurements as inputs to a mathematical model that can then predict the level of sleep homeostasis, phase of circadian rhythmicity and relative neurobehavioral performance levels
- Initiate projects that develop non-invasive electroencephalographic, electrooculographic and/or electromyographic monitoring techniques for recording the timing of the sleep-wake cycle during space flight
- Initiate projects that develop and evaluate new methods for monitoring sleep-wake fitness for duty during space flight
- Initiate projects that develop and evaluate new methods to monitor neurobehavioral performance during space flight without interfering with the operational demands of space flight
- Initiate projects that develop and evaluate new non-invasive methods for assessing circadian phase during space flight
- Initiate projects that develop and evaluate new non-invasive methods for assessing homeostatic sleep need during space flight

Goal 5: *Develop new methods for monitoring ambient and retinal light exposure (illuminance/photopic lux, broadband visible irradiance, and circadian effective illuminance/circadian lux) on board space shuttle and ISS during space flight and on planetary habitats.*

- Complete projects that analyze the data from the wall-mounted ambient light recording devices that have been tested aboard the Space Shuttle in the Neurolab flight
- Complete projects that determine the circadian effective illuminance and irradiance levels
- Initiate projects that refine these recording devices to measure circadian-activating light levels more precisely on board space shuttle and ISS during space flight and on planetary habitats

Goal 6: *Develop Earth-based applications of technologies for non-invasively monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neuro-behavioral performance for industrial and medical use.*

- Complete projects that develop neurobehavioral test for the validation of mathematical models in field and laboratory studies as well.
- Initiate projects that improve the polysomnography device that was developed for the recording of sleep in space in the Neurolab Shuttle flight
- Initiate projects that refine and develop current and new markers of circadian phase to be applied on Earth
- Initiate projects that develop non-invasive electroencephalographic, electrooculographic and/or electromyographic monitoring techniques for recording the timing of the sleep-wake cycle for industrial and medical use
- Initiate projects that develop and evaluate new methods for monitoring sleep-wake fitness for duty for industrial and medical use
- Initiate projects that develop and evaluate new methods to monitor neurobehavioral performance for industrial and medical use
- Initiate projects that develop and evaluate new non-invasive methods for assessing homeostatic sleep need for industrial and medical use

Goal 7: *Develop Earth-based applications of high-fidelity mathematical models of performance based on circadian organization and sleep-wake history for industrial and medical use.*

- Complete projects that refine mathematical models to predict neurobehavioral performance in space
- Complete projects that refine mathematical models to determine appropriate shift scheduling, light exposure, sleep timing, and countermeasure applications for shift workers, pilots, military and medical personnel, and transportation workers
- Complete projects that develop a user-friendly simulation software that can be used by anyone to predict neurobehavioral performance given light exposure levels and sleep/wake history
- Initiate projects that incorporate high-fidelity mathematical models of performance based on circadian organization and sleep-wake history into personal monitoring and display devices for industrial and medical use.

Goal 8: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment.*

- Complete projects to improve our understanding of the effects of light on the human circadian system, and the role that the circadian system plays in neurobehavioral performance.
- Complete projects that incorporate our findings into mathematical models to determine the best light schedule and intensities to reduce the risk of performance failure by appropriately aligning the circadian system with the work/rest schedule
- Initiate projects that produce technologies for medical and industrial use designed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment

Goal 9: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to acute a chronic degradation of sleep quality or quantity.*

- Complete projects to determine the amount and timing of sleep that best allows people to work extended and/or misaligned shifts with the least risk of performance failure
- Complete projects that incorporate our findings into the mathematical model to help schedule rest/nap/sleep times so that they are the most effective in improving performance levels
- Initiate projects that produce technologies for medical and industrial use designed to reduce the risk of human neurobehavioral or physiological performance failure due to acute chronic degradation of sleep quality or quantity.

Goal 10: *Develop Earth-based applications of technologies developed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work.*

- Complete projects that investigate the effects of extended duration work schedules to determine the best timing of countermeasures (light exposure, naps, melatonin, etc.) to improve performance
- Initiate projects that produce technologies for medical and industrial use designed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work

Goal 11: *Integrate research and analysis*

Objective 11A: Integrate research within the Human Performance Factor, Sleep and Chronobiology Team

- Continue current integration efforts among team PIs, and co-investigators.

Objective 11B: Integrate research with other teams

- Continue to build collaborative links between the Team projects and projects on other teams, especially other teams with a focus on Sleep and Circadian Physiology
- Coordinate with Neurobehavioral and Psychosocial Factors Team regarding the effects of sleep loss and circadian displacement, and countermeasures for these factors on cognition, mood and social interaction.
- Coordinate with the Neurovestibular Adaptation Team regarding the effects of space motion sickness and countermeasures for it on circadian entrainment
- Coordinate with the Nutrition and Rehabilitation Team regarding the potential for effects of chronic partial sleep loss on carbohydrate metabolism
- Coordinate with the Smart Medical Systems Team regarding the potential for neuroimaging to enhance objective detection of neurobehavioral dysfunction due to sleep loss during space flight.

Objective 11C: Integrate research being done by Team investigators with their other, related research projects that are not directly supported by NSBRI.

- Most of the investigators on the Human Performance Factor, Sleep and Chronobiology Team are conducting other research projects related to human performance factors, sleep and chronobiology that are supported by other federal and non-Federal agencies (Air Force, Department of Defense, NIH, NSF, NASA, etc.). We plan to integrate the results of that allied research with the results of their NSBRI projects to facilitate the development of countermeasures for exploration class missions.

5.6 SUMMARY

The success of human space flight depends on astronauts remaining alert while operating highly complex, state-of-the-art equipment. A crucial factor of mission success is that crewmembers do not get enough sleep. The loss of 24-hour day/light cycle, weightlessness, a confined environment and work demands make sleep difficult in space. Astronauts sleep only six hours each night, on average. Exploration crews will have to switch their "body clock" from the Earth day to the day/night cycle of another planet. These factors may lead to cumulative sleep loss, increased risk of accidents and possible mission failure. The Human Performance Factors, Sleep and Chronobiology Team is focused on developing countermeasures to reduce human mistakes and optimize neurobehavioral and physiological performance during exploration class space missions.

National Space Biomedical Research Institute
HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 5.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BRAINARD/Optimizing Light Spectrum for Long Duration Space Flight	Goals 1, 3	Optimum light spectral distribution	Healthy male and female human subjects	Develop melatonin fluence-response curves below 440 nm and above 600 nm in human subjects & develop action spectrum between 400 and 700 nm in subjects with dil./undilated pupils	Optimum light spectral character. for maintaining or adjusting circadian phase & sleep-wake cycle. Preliminary test of monochromatic stimuli for phase shifting human circadian rhythms	Assist in designing a novel light panel for circadian stimulation. Assist in developing protocols for comparing head mounted light therapy devices
CZEISLER/Circadian Entraining, Sleep-Wake Regulation & Performance During Space Flight	Goals 1, 2	Intermittent bright light pulses	Healthy male and female human subjects scheduled to non-24-hour day lengths in an environment shielded from periodic, 24-h time cues	Quantification of intrinsic period and the limits of entrainment of the human circadian pacemaker & investing. of the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function	Preliminary evaluation of the efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars	Full-scale clinical trial of age and gender matched astronaut surrogates living for extended durations on a non-24-hour work schedule while exposed to intermittent bright light at the most effective wavelength
DINGES/Countermeasures to Neurobehavioral Deficits from Partial Sleep Loss	Goals 1, 2, 3	Naps and split sleep schedules	Healthy male and female human subjects	Track neurobehavioral performance deficits associated with chronic sleep restriction & examine sleep efficiency and architecture (restricted sleep periods at diff. circadian phases)	Develop response surface map paradigms to further understand the interaction between sleep duration, sleep-wake placement and neurobehavioral functioning	Development of optimal sleep-wake schedules (including main and supplementary sleep episodes) to ensure maintenance of high level neurobehavioral functioning

Note:
Goal 1: Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration.
Goal 2: Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.**Goal 3:** Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.

FULLER/Primate Circadian Rhythms in the Martian Environment	Goals 1, 2	Bright light pulses	Rhesus monkeys as human surrogates. Long-duration studies in large-diameter Centrifuge with controlled lighting period, intensity and spectra.	Determine the effect of altered gravity on primate circadian rhythms, principally the endogenous clock perio	Enhance entrainment response to low light (ISS, Martian habitat), reddish light (Mars), and non-24 hour schedules by means of exposure to light pulses. Studies will address timing and efficacy of bright light exposure.	Projected application of bright light pulses to prevent loss of circadian entrainment, sleep and rhythm disturbances, performance decrements.
JEWETT/Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure	Goals 1,2	Design of rest/work and sleep/wake schedules	Previously collected human data;	Determine the nature of amplitude recovery dynamics of human circadian system.	Design shift and sleep schedules for proper circadian alignment. Validate refined circadian amplitude dynamics of light model.	Incorporate refined light model into circadian components of neurobehavioral performance model and predict the performance in human phase shifting.
MENAKER/ A Model of Circadian Disruption in the Space Environment	Goals 1,2	Coupling between multiple circadian oscillators	Transgenic rat incorporating a circadian luciferase reporter gene	Description of system disintegration under simulated space flight conditions	Repair system disintegration with timed application of light, food and melatonin	Transfer working countermeasures to humans
MORIN/Circadian and Vestibular Relationships	Goals 1,2	Anatomical & functional issues linking the vestibular & circadian systems	Anatomical tract tracin using retro and anterograde transport labels Study of brain regions for stimuli responses known to alter vestibular functions Phase shifts in circadian rhythms	Understanding the basic anatomical & functional pathways linking vestibular & circadian systems	N/A	N/A
TOSINI/Long-term Exposure to Dim Light Desynchronizes the Circadian System of Rats	Goals 1,2	Coupling between central and peripheral oscillators	Measuring expression of gene in peripheral tissues	Identification of the effects on the circadian system of prolonged exposure to constant conditions	Use of melatonin as synchronizing agent	
TUREK/Animal Model for Sleep Loss and Circadian Disruption	Goals 1, 2	Exogenous melatonin administration and exercise	Mice	N/A	Testing of the effectiveness of countermeasures (melatonin, exercise) using a mouse model	N/A

Note: Goal 1: Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration. **Goal 2:** Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration. **Goal 3:** Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.

National Space Biomedical Research Institute
HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 5.2. Integration Activities

	Brainard	Czeisler	Dinges	Fuller	Jewett	Menaker	Morin	Turek	Tosini
Internal Communication	Monthly team telecon. NSBRI January Retreat, informal discussions. Discussions with JSC staff: night lighting & and window design	Telecon and informal discussions with other team members	Czeisler et al, Jewett et al , Kosslyn et al, Lieberman et al	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members Czeisler et al, Dinges et al, Brainard et. al	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members
Integrated Experiment Development	Dr. Fuller and Peter Smith: lighting specifications for simulated Martian environment for current primate studies and future animal and human studies. Dr. Jewett: developing protocols for comparing head mounted light therapy devices	Dr. Dinges: standardize neurobehavioral assessment. Dr.Fuller: coordination of primate-human models. Dr. Jewett: use of biomathematical model predictions re. intermittent bright light cm. Dr. Brainard: spectral sensitivity of circadian phase resetting.	Neurobehavioral performance assessment Neurobehavioral performance assessment	Dr. Brainard: develop a specification for simulated Martian ambient lighting, test apparatus, and document spectrum. Potential integrated experiment facility, with animal centrifuges and both rodent and primate habitats	N/A	N/A	N/A	N/A	N/A
Sample Sharing	Accessed head mounted light stimulation systems from BioBrite Inc. and Leon Lack, MD, for Dr. Jewett's efficacy tests	Neurobehavioral and entrainment data with Jewett et al	Neurobehavioral data/ Jewett et al	N/A	Czeisler et al, Dinges et al	N/A	N/A	N/A	N/A
Synergistic Studies of Opportunity	Preliminary test of monochromatic	The results of our growth hormone measures will be shared with the	Neurobehavioral performance testing during chronic sleep	We are currently exploring interest in both	N/A	N/A	N/A	N/A	N/A

	stimuli for phase shifting human circadian rhythms with Drs. Czeisler and Lockley	Muscle and Bone Teams, given the potential impact of the hypothesized chronic reduction in sleep-related growth hormone secretion on maintenance of muscle and bone function	restriction and circadian displacement (stressful condition)/ Dinges et al (Neurobehavioral and Psychosocial) Circadian adjustment during chronic sleep restriction/ Czeisler et al (Sleep and Chronobiology)	the rhesus model and hypergravity					
Development of Computer Model of Integrated Human Function	N/A	Contributing neurobehavioral and entrainment data for biomathematical model development (Jewett et al/ Sleep and Chronobiology) with ultimate goal of integrating performance model into model of Integrated Human Function	Contributing neurobehavioral data for biomathematical model development (Jewett et al/ Sleep and Chronobiology) with ultimate goal of integrating performance model into model of Integrated Human Function	Our findings should help define parameters of circadian response to gravity in combination with altered lighting environments.	Development and validation of refined model the effects of light on human circadian system. Refinement and validation of mathematical model of human Neurobehavioral Performance	N/A	N/A	N/A	N/A

National Space Biomedical Research Institute

HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 5.3a. Achieving Goal 1: Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Quantify neurobehavioral performance decrements associated with circadian misalignment and/or sleep restriction/disruption (Goals 1 and 2) • Observation of a presumptive vestibular-circadian system anatomical connection													
• Identify the effect of an altered circadian environment on the well being of the organisms (Goals 1 and 3) • Characterize the effect of long-term exposure to constant conditions on the circadian system (Goals 1 and 3)													
• Quantify the impact of chronic circadian disruption and/or sleep restriction/disruption on recovery sleep, circadian adjustment and neurobehavioral performance in different strains of mice (x2) entrained to different light levels (low, medium and high intensity) (Goals 1 and 2)													
Phase 1: Focused Mechanistic Research													
• Fit stochastic and deterministic models to low-amplitude human temperature data to select lower- vs. higher-order models of human circadian amplitude recovery • Describe disrupting effects of constant light on phase relationships among circadian oscillators in brain and peripheral organs													
• Investigate the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function (Goals 1 and 2) • Determine how desynchronized organisms respond to infections (Goals 1 and 2) • Determine the performance levels of desynchronized animals (Goals 1 and 2)													
• Develop human melatonin fluence-response curves below 440 nm and above 600 nm (Goals 1 and 3) • Quantify role of pupil dilation in circadian photic transduction in humans • Develop melatonin action spectrum in humans with freely reactive pupils • Establish the anatomy of connectivity between the circadian rhythm system and the vestibular system													

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
• Investigate the relationship between the degree of sleep and/or circadian disruption and the resulting impairment to neurobehavioral performance in mice (Goals 1 and 2)													
• Describe disrupting effects of shifting schedules of light, food availability and exercise on phase relationships among circadian oscillators in brain and peripheral organs													
• Determine functional activation of the vestibular and circadian systems by an optokinectic nystagmus stimulus													
• Identify promising pharmacological countermeasures to reduce the risk of desynchronization													
Phase 2: Preliminary Countermeasure Development Research													
• Test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases (Goals 1 and 2)													
• Determine the functional activation of the vestibular and circadian systems bya non-locomotor, non-photic, vestibular activating stimulus													
• Efficacy of intermittent bright light pulses on circadian entrainment to non24-hour work-rest schedules, as required on Mars (Goals a and 3)													
• Validate refined circadian amplitude recovery dynamics of light modelAmeliorate disruptive effects of constant light and shifting schedules using pulses of bright light, darkness, melatonin and applying regularized feeding and work schedules													
• Test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2) • Test if access to a wheel during rest periods (exercise) reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2) • Determine what duration of exercise optimally reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2)													
• Test pharmacological countermeasures (melatonin) to reduce the risk ofinternal desynchronization (Goals 1 and 2)													
• Test human circadian phase-shifting with selected monochromatic wavelengths													

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 3: Mature Countermeasure Development Research													
• Incorporate refined light model into circadian component of neurobehavioral performance model and predict neurobehavioral performance in human phase shifting experiments				■	■	■	■						
• Efficacy of intermittent bright light pulses of different intensities and/or wavelengths on circadian entrainment to non-24-hour work-rest schedules (Goals 1 and 3)						■	■	■	■	■			
• Develop and test candidate sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Goals 1, 2 and 3)							■	■	■	■			
• Apply knowledge gained with animal model to humans using measures of cognitive performance and physiological well-being to assess effectiveness								■	■	■	■		
• Ground test efficacy of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep in humans (Goals 1 and 2) • Ground test efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption in humans (Goals 1 and 2) • Ground test efficacy of pharmacological (e.g., melatonin), nutritional, environmental (e.g., light or dark pulses) or behavioral (e.g., exercise) circadian countermeasures designed to maintain internal synchrony of circadian oscillators in diverse organ systems in humans								■	■	■	■		
Phase 4: Countermeasure Evaluation & Validation													
• Test neurobehavioral model predictions against circadian and performance data collected under field conditions							■	■	■	■	■	■	
• Test optimal sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Goals 1 and 2)								■	■	■	■	■	
• Conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep (Goals 1 and 2) • Conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption (Goals 1 and 2)												■	■
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1,2 and 3)													■

National Space Biomedical Research Institute

HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 3b. Achieving Goal 2: Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Quantify neurobehavioral performance decrements associated with circadian misalignment and/or sleep restriction/disruption (Goals 1 and 2)													
• Determine the nature of neurobehavioral and physiological changes induced by chronic sleep restriction at different circadian phases													
• Quantify the impact of chronic circadian disruption and/or sleep restriction/disruption on recovery sleep, circadian adjustment and neurobehavioral performance in different strains of mice (x2) entrained to different light levels (low, medium and high intensity) (Goals 1 and 2)													
Phase 1: Focused Mechanistic Research													
• Investigate the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function (Goals 1 and 2) • Determine how desynchronized organisms respond to infections (Goals 1 and 2) • Determine the performance levels of desynchronized animals (Goals 1 and 2)													
• Investigate the relationship between the degree of sleep and/or circadian disruption and the resulting impairment to neurobehavioral performance in mice (Goals 1 and 2)													
Phase 2: Preliminary Countermeasure Development Research													
• Test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases (Goals 1 and 2)													
• Test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2) • Test if access to a wheel during rest periods (exercise) reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2) • Determine what duration of exercise optimally reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2)													

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
• Test pharmacological countermeasures (melatonin) to reduce the risk of internal desynchronization (Goals 1 and 2)					■	■	■	■					
• Test pharmacological wake-promoting countermeasures (caffeine, modafinil) to reduce the risk of neurobehavioral performance failure due to sleep loss					■	■	■	■					
• Integrate into biomathematical model the impact of wake- and sleep-promoting therapeutics (pharmacological or behavioral) on neurobehavioral performance in the presence of circadian misalignment and/or sleep restriction/disruption (Goals 1 and 2)									■	■	■		
Phase 3: Mature Countermeasure Development Research													
• Develop and test candidate sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Goals 1, 2 and 3)							■	■	■	■			
• Ground test efficacy of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep in humans (Goals 1 and 2) • Ground test efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption in humans (Goals 1 and 2)								■	■	■	■		
Phase 4: Countermeasure Evaluation & Validation													
• Test optimal sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Goals 1 and 2)								■	■	■	■	■	
• Conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep (Goals 1 and 2) • Conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption (Goals 1 and 2)												■	■
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1, 2 and 3)													■
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1 and 2)													■

National Space Biomedical Research Institute

HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 3c. Achieving Goal 3: Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Identify the effect of an altered circadian environment on the well being of the organisms (Goals 1 and 3) • Characterize the effect of long-term exposure to constant conditions on the circadian system (Goals 1 and 3)													
Phase 1: Focused Mechanistic Research													
• Develop human melatonin fluence-response curves below 440 nm and above 600 nm (Goals 1 and 3)													
• Determine effect of altered gravity on circadian period • Test entrainment to Martian day-length and ambient lighting • Test entrainment to Martian day-length and habitat lighting													
Phase 2: Preliminary Countermeasure Development Research													
• Test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases													
• Determine the functional activation of the vestibular and circadian systems by a non locomotor, non-photic, vestibular activating stimulus													
• Efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars)(Goals 1 and 3)													
• Test commercially available head-mounted light devices for circadian efficacy													
• Develop lighting monitoring system for inside of space shuttle and ISS													
• Test human circadian phase-shifting with selected monochromatic wavelengths • Test human melatonin response to simulated ISS, EVA and lunar light environments													

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 3: Mature Countermeasure Development Research													
• Efficacy of intermittent bright light pulses of different intensities and/or wavelengths on circadian entrainment to non-24-hour work-rest schedules (Goals 1 and 3)													
• Develop and test candidate sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Goals 1, 2 and 3)													
• Develop light sources that optimally stimulate human circadian responses • Develop light sources that specifically do not stimulate human circadian responses • Develop window and visor prototypes for optimal human circadian stimulation • Develop window and visor prototypes that minimize human circadian responses													
Phase 4: Countermeasure Evaluation & Validation													
• Ground test lights that optimally stimulate human circadian responses • Ground test lights that specifically do not stimulate human circadian responses • Ground test window and visor prototypes for optimal human circadian stimulation • Ground test window and visor prototypes that minimize human circadian response													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Integrate current ISS and shuttle lighting with new light sources and window systems (2010-2015) • Ground test integration of ISS lighting with new light sources and window systems (2012-2015) • Flight test integration of ISS lighting with new light sources, window systems													
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1, 2 and 3)													

6.0 IMMUNOLOGY, INFECTION & HEMATOLOGY

Team Leader: William T. Shearer, M.D., Ph.D.
Professor of Pediatrics and Microbiology & Immunology
Baylor College of Medicine
6621 Fannin, MC 1-3291
Houston, TX 77030-2399
832-824-1274
832-825-7131 FAX
wshearer@bcm.tmc.edu

6.1 INTRODUCTION

The environmental, inter- and intrapersonal conditions of space flight pose a potential threat to an astronaut's immune system. These conditions include isolation, containment, weightlessness, increased radiation exposure, and enhanced microbial contamination. In all human and animal subjects flown in space, evidence of immune compromise, reactivation of latent virus infection, and development of a pre-malignant or malignant condition exists. Moreover, in all ground-based space flight model investigations, evidence of immune compromise and reactivation of latent virus infection is also observed. Studies are in progress to determine whether malignancy, too, will be observed in these experimental animals. All of these symptoms are similar to those found in a wealth of human pathological conditions where the human immune system is compromised, such as with stress, immunosuppressive drugs, infection, and radiation, and where reactivated, chronic virus infections and cancer appear as a natural consequence. Two examples where these clinical conditions are readily observed are Epstein-Barr virus (EBV)-driven lymphomas in transplanted patients and Kaposi sarcoma in acquired immunodeficiency syndrome (AIDS) patients. Given these known risks to the immune system, it is highly appropriate, indeed imperative, that NSBRI researchers carefully investigate the effects of space flight conditions on human immunity, infection rate, and cancer rate.

6.2 RISKS

The following risks in the Immunology, Infection and Hematology Discipline Area have been identified in the Critical Path Roadmap (risk number in parentheses):

- Immunodeficiency/Infections (22)
- Carcinogenesis Caused by Immune System Changes (23)
- Altered Hemodynamic and Cardiovascular Dynamics Caused by Altered Blood Components (24)
- Altered Wound Healing (25)
- Altered Host-Microbial Interactions (26)
- Allergies and Hypersensitivity Reactions (27)

We have chosen to redefine the risks in a manner better suited to formulation of the present team's research plans. All of these newly stated risks are contained within the original risks.

Risk 1: Radiation Damage to Stem Cell and Immune System
Risk 2: Microgravity and Stress Effects on Immune System and Resistance to Infection
Risk 3: Reactivated Latent Infections
Risk 4: Malignancy
Risk 5: Altered Microbes

In all of the risks proposed for the Immunology, Infection, and Hematology Team, the principal focus must be the underlying stem cell damage that produces the immunological deficits that create the observed risks (e.g., infections on space flights occur because of underlying immune damage).

6.3 GOALS

The Immunology, Infection and Hematology Team has the following goals for its program:

<u>Risk-Based Goals</u>

Goal 1: *Reduce risk of space flight conditions (isolation, containment, stress, microgravity, and radiation) damaging the human bone marrow stem cell and differentiated immune cells.*
Goal 1 covers Risks 1 and 2.

Goal 2: *Reduce risk of astronauts developing new and reactivated infections, premature immune cell death, and malignancy.*
Goal 2 covers Risks 3 and 4.

Goal 3: *Reduce risk of space flight-induced development of superstrains of microbial organisms.*
Goal 3 covers Risk 5.

<u>Non-Risk-Based Goals</u>

Goal 4: *Develop Earth-based applications of space flight studies to help diagnose and treat humans with secondary immunodeficiencies, reactivated viral infections, and malignancy.*

Goal 5: *Integrate research and analysis.*

6.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The Immunology, Infection, and Hematology Team will seek to reduce the risks defined in Section 6.2 above. The first step in this direction is to firmly establish the molecular and cellular consequences of exposure of the human stem cell and differentiated immune cells (peripheral blood, tissue, mucosa) to the conditions of space flight. Knowing the precise damage to the human immune system will greatly facilitate the development of a countermeasures program. A recent example of the team's progress will illustrate this concept. For 25 years, it has been known that humans in space and in the space-equivalent model of the Antarctic winter display weak, delayed-type hypersensitivity skin reactions to recall antigens. This skin test is a very crude method of assessing immune system deficiencies. Our team has greatly advanced knowledge of the precise molecular events taking place in the human immune system in response to space flight equivalent conditions by determining recently that TH2 $CD4^+$ T-cells reduce the output of the proinflammatory cytokine interleukin-10 (IL-10) in humans in the Antarctic winter. We plan also to define the early cellular changes in reactivated viral infections and the role of the stress (hypothalamic-pituitary-adrenal axis) system in creating secondary immunodeficiency, enhanced infection rates, and development of malignancy. In addition, we will strive to understand the potential for the emergence of superstrains of bacteria, viruses, and fungi in irradiated hosts. With this new information, we will be able to much better plan for an effective countermeasures program involving shielding (structural, chemical) for radiation, stress-reduction programs, nutritional, pharmacologic and immunologic prevention and treatment programs (for example, gene or cell inhibitors, immunizations and antibody, cytokine, or stem cell therapy), and a microbiocidal program for prevention of opportunistic infection.

Following the award of the present three-year cycle of grant support that began in September 2000, the Immunology, Infection, and Hematology Team was reconstituted with six projects that possessed a cohesive critical mass of investigators and projects (see **Table 6.1**). The principal focus of five of the projects is the harm to the human immune system that might result from immunosuppressive factors in long-term space flight. These factors include deep space radiation, microgravity, physical and psychological stress, isolation and containment, microbial contamination, altered microbial virulence, and sleep deprivation. All of these factors have produced alterations in immune responses of humans and animals flown in space or their counterparts using earth-bound space-equivalent models. There is collaboration of investigators within a project and between projects. The leadership of the team (Drs. William T. Shearer, Janet S. Butel, and Gerald Sonnenfeld), for example, participate in certain aspects of many of the projects (see **Table 6.2**). Projects 1-5 deal with uncovering the pathogenic mechanisms of risk factors, whereas Project 6 concerns the detection system for pathologic microbes, currently bacteria, but in the future viruses and fungi that would cause immunosuppression.

6.4.1 In terms of an overall **team selection of priorities** for a cohesive research program for the **risk-based goals**, we have decided to focus on two types of immunosuppresive factors—radiation and microgravity, using: 1) radiation studies and 2) anti-orthostatic model studies, respectively. All of the six projects will support these two team studies.

6.4.1.1. In the **first of these team projects**, the co-investigators will include Drs. Shearer, Butel, Ling, Conner, Reuben, and Rosenblatt, members of the NSBRI Immunology, Infection and Hematology Team from Baylor and Dr. Daila Gridley from Loma Linda University (LLU). Selected strains of mice (e.g., BALB/c, C57 black) will be exposed to proton and gamma ray radiation and subsequently to murine viruses (e.g., gamma 68, polyomavirus), in an attempt to determine the combined effects of space radiation and latent virus infection on the immune function of study animals. This first approach will examine the simultaneous effects of radiation and infection and will then be followed by a sequential approach of infection first and radiation second, the likely scenario for human space travelers to Mars. The dose of radiation that will be utilized initially (3Gy, the estimate of radiation received by astronauts on a Mars Mission) will be that used by Dr. Gridley and her colleagues who have demonstrated rapid and profound alterations in immune cells and immune responses in murine subjects. Replicate and controlled experiments will be performed by both the LLU site and the Baylor site to insure that the same methods are followed at both sites and that the results of the experiments at Baylor confirm those of LLU. If gamma radiation proves to be equivalent to proton radiation in terms of effects upon the immune system (e.g., spleen cell T-cell response to non-specific stimuli and specific antigen stimulation; plasma antibody formation to neoantigen; spleen lymphocyte subset distribution), it may be possible to avoid transfer of mice between institutions, as Baylor has a source of gamma radiation.

In addition to examination of the effects of radiation and latent virus infection on immune cells and immune responses, study animals will be evaluated for the development of tumors and blood malignancies. This will be carried out with the assistance of Dr. Cory Brayton, a veterinary pathologist at Baylor, who has agreed to collaborate on this project.

Also, Dr. Alan Gewirtz at the University of Pennsylvania has begun collaborative NSBRI studies with Dr. Elizabeth Sutherland at the Brookhaven National Laboratory (BNL) with bone marrow-derived human stem cell lines. These cell lines were exposed to heavy metal ion (Fe^{56}) radiation and subsequently tested by standard hematologic assays for ability to form colonies of cells in the myeloid series: granulocytes, erythroid cells, and platelets. In the future, similar experiments will be performed at LLU, where the effects of proton and gamma radiation will be evaluated in these same assays. Because the preparation of human stem cells from donor bone marrow also yields precursor cells in the lymphoid system, it will be possible to simultaneously evaluate the effects of the various types of radiation on the development of T- and B-cells. Similarly, macrophages, monocytes, and stromal cells could be evaluated. The methods of analysis of these various types of immune cells could include measurement of cell growth factors (e.g., IL-3, IL-6, IL-7, TGF-β), apoptosis gene regulation (e.g., gene array assay), and cell repair pathways. These studies would include the collaboration of Drs. Gewirtz, Reuben, Rosenblatt, and Gridley.

Also, peripheral blood human stem cells will be harvested by pheresis in subjects given granulocyte-monocyte colony-stimulating factor (GMCSF) to increase the number of circulating stem cells at the M.D. Anderson Cancer Center. Dr. James Reuben will utilize these cell harvests in similar radiation studies and evaluate dendritic cell (#1 and #2 types) function in the presentation of antigens to lymphocytes.

In both bone marrow and peripheral blood stem cell preparations, evidence of genetic damage will be investigated by examination of progenitor cells for chromosomal breaks. These measurements will yield important information on the possibility that radiation of human stem cells might result in leukemogenesis and tumorigenesis.

Future collaborative studies have been proposed for the Radiation Team, in which the use of surrogate markers could be used to assess the risks of tumor development in irradiated animals. Surrogate markers would greatly reduce the time needed to evaluate tumorigenesis and to observe exposed animals for cancer development. For the current Fe^{56} irradiated rat breast tumor model, one such surrogate marker might be the appearance of epithelial cells in the peripheral blood that herald the development of breast cancer. In addition to the detection of epithelial cells, it might be possible to examine the gene imprints of these cells by gene array assays. Such studies might yield a characteristic dysregulation of normal gene activation that would be predictive of breast cancer in this animal model.

This first team project addresses Goals 1 and 2 (space flight conditions damaging immune cells and development of new or reactivated infections, premature immune cell death and malignancy, respectively), but with the assistance of Project 6 we will also be addressing Goal 3, the detection of genetically altered (possibly supervirulent) strains of environment or host microorganisms with the use of DNA probes (see Section 6.5 and Table 6.1). Originally designed to develop genetic probes of spacecraft bacterial contaminants, Project 6 will adapt the genetic probes to detect contaminating viruses and to detect the emergence of both bacteria and viruses made more virulent by exposure to spaceflight conditions, principally radiation.

6.4.1.2 The **second of the team projects** will involve the anti-orthostatic (AOS) (hind-limb suspension) model and addresses Goals 1 and 2. The subgroup on hind-limb suspension felt that it was important that standardized procedures be used by the group to allow for comparison of results across projects. The exact caging and suspension techniques do not have to be identical, but the parameters used for setting up the suspension should be uniform. In the future, all suspension will be set up with uniform parameters. Suspension will be carried out with a 15 to 20 degree head-down tilt. The tilt will be measured at the body axis of the animal. Controls for all experiments will consist of at least vivarium controls in standard housing and restraint controls with animals in suspension hardware but with all four paws on the ground and bearing weight. Additional controls may be added at the investigator's discretion. Vivarium controls will be in individual cages, not housed with multiple animals per cage. All hind-limb suspension experiments will commence in the morning between 9 and 11 AM. Dr. Sonnenfeld has already had remarkable success with these procedures in demonstrating an at least two-fold increase in death in AOS mice challenged with Klebsiella pneumoniae.

We plan to examine changes in differential gene expression in the immune system using commercially available low-density nylon-based gene array technology. Each blot contains 23 specific and two housekeeping genes. Arrays are available that can detect specific sets of genes that are grouped based on their association with known signal transduction pathways. Once changes in particular pathways are identified, pathway-specific gene arrays are available to elucidate changes in expression of pathway-specific genes. In addition, arrays are available to detect changes in gene expression of mouse cytokines, interleukin receptors, chemokines, chemokine receptors, inflammatory cytokines, T-cell activation markers, and B-cell activation markers. The approach is to catalog global changes in the immune system (cell distributions, cytokine production, gene expression) utilizing the AOS mouse model, and then to determine any additive effects of concomitant virus infection and/or proton irradiation on those patterns. This comprehensive approach will provide new insights into mucosal and systemic host immune functions. Additionally, comparison of the results from the animal model and human studies should provide directions for future studies.

6.4.2 In **planning for the next 5 years of research**, it is expected that the immediate research efforts will be directed toward uncovering the mechanisms behind the changes already observed in immunity due to exposure of subjects to space flight conditions. An example of this process would be the information gained from projects that will examine the effects of protons, gamma rays, and heavy metal ions upon mature lymphocytes in the peripheral blood and the pleuripotent hematopoietic bone marrow stem cells in irradiated mice. By carefully adjusting the timing and dose of irradiation, it will be possible to determine where the lesions due to radiation occur along the primordial stem cell to mature lymphocyte differentiation pathway. There could be multiple hits, indicating that several differentiation steps are affected, or the result could be due primarily to stem cell damage early in the differentiation pathway. Not only would this information be important for understanding the pathogenesis of radiation-induced immunosuppression, but it would also be important for construction of an effective countermeasures program. A lethal hit to the primordial stem cell would mandate the countermeasure of replacement of stem cells, most likely by use of an autologous stem cell transfusion with stem cells harvested prior to space flight and preserved from the same radiation damage. Appropriate repair of immune system damage should restore control of reactivated viruses and microbial infections.

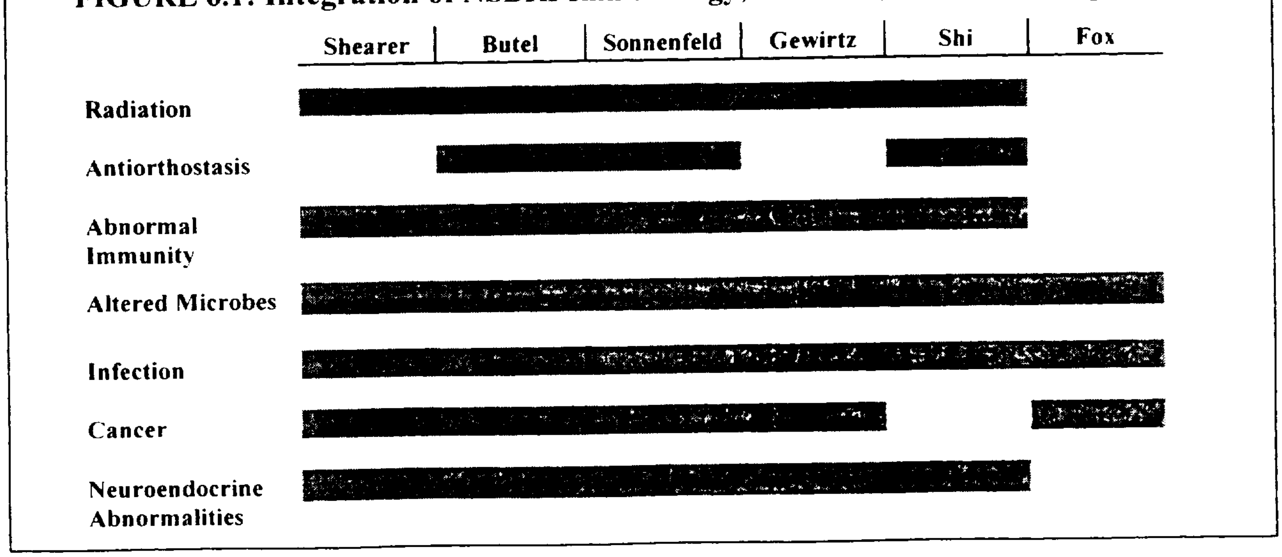
In terms of a 5-10 year plan of research, it is estimated that human evaluation of the countermeasures of the projects will take place in this phase of NSBRI-supported research. It is most likely that the countermeasures will change during the first five years of research, as basic science investigations discover mechanisms unknown at present. Using irradiation of the human bone marrow stem cell development pathway as the example, it will be important to know where radiation effects take place. If the principal radiation damage is to a mature lymphocyte (e.g., $CD4^+$ T-cell), there may not be the need for reconstitution with the primordial stem cell, but rather treatment with cytokines such as IL-7 and IL-12 that produce maturation of early lymphocyte precursors into mature lymphocytes. Thus, the countermeasures proposed for today will yield to the basic scientific discoveries of the first five years of research. Some countermeasures most likely will not change, such as the use of intravenous immunoglobulin (IVIG) in immunocompromised space travelers. IVIG has a half-life of one month and can be used repeatedly in patients until a permanent reconstitution of immunoglobulin by B-cells takes place.

6.4.3 We have initiated plans for the **non-risk goals of our team** as well. For Goal 4, Earth-based applications that help diagnose and treat immunodeficiency, reactivation of viral infection and malignancy, we will begin by examining whether during long distance space travel we can utilize the current AIDS model of the $CD4^+$ T-cell count as a predictor of immunosuppression. For this type of prediction system, constant refinement of standards will be very important as illustrated by the fact that the previous cutoff of 500 $CD4^+$ T-cells/μl of blood that defined the limit of beginning immunosuppression has been lowered to 300 cells/μl. Also, there may be much more suitable surrogate markers that would prove more definitive in alerting space physicians of pending immune compromise. The balance of pro- and anti-inflammatory cytokines (e.g., IFN-γ vs. IL-10), as seen in Antarctic winter dwellers for example, might become a better early warning system. The example given (IFN-γ vs. IL-10 levels in the Antarctic winter model of spaceflight isolation) signaled the simultaneous activation of latent virus shedding. Researchers will now use this cytokine balance to look for early evidence of immunosuppression due to virus infection in children and adults in routine medical practice. Similarly, we will apply whatever we learn for our space-based immunosuppression prediction system for future Earth-based applications.

In further pursuit of Goal 4, the microbial detection system that Dr. Fox is perfecting will enable astronauts to know when water or food sources will give them food poisoning, a condition extremely undesirable in space. It will be important for this microbial detection system to be developed for viruses found in saliva as well so that an early warning system could be activated should latent virus activation occur in astronauts and antiviral therapy need to be initiated. This detection system has many potential Earth-based applications. Another activity towards achieving Goal 4 is to examine whether adaptation of immunoreconstitution therapies to astronauts in space may yield important clues for treatment of humans on Earth, such as the ability to restore a failing immune system before total collapse.

Our team's efforts to achieve the non-risk goal (Goal 5) of integration of research and analysis can be appreciated in **Figure 6.1 and Table 6.2**. At our team retreat in July 2001 and the NSBRI Retreat held in January 2002, we discussed how to interconnect all of the projects by collaborations of investigators and sharing of research specimens and analytical data.

FIGURE 6.1: Integration of NSBRI Immunology, Infection, and Hematology Team



Not only did the team investigators plan for the integration of their own team projects, they also met with investigators of the Radiation Team to plan collaborative projects, particularly the examination of effects of space radiation upon the immune cells, cytokines, and antibodies in animal models that develop malignancies. Also, Dr. Shearer wrote a letter of collaboration to the NSBRI for the new application of Dr. Daila Gridley, LLU, to support her inclusion in the team effort so as to supply the present investigators with a senior radiation biologist/immunologist. Some of the commitments of team collaborators are listed below:

- Drs. Shearer, Butel, Ling, Conner, Reuben, Rosenblatt, and Gridley for studies on radiation, viral infection, and immune responses.
- Drs. Sonnenfeld (also involving Drs. Shearer, Butel, Conner, and Gewirtz as plans develop) and Vazquez (NSBRI Radiation Team) for studies on radiation and immune responses in AOS Mouse Model.
- Drs. Sonnenfeld, Butel, Ling, and Conner for studies of the effects of neuroendocrine hormones on viral growth and replication.
- Drs. Gewirtz, Sutherland, and Reuben for radiation and hematopoietic stem cell research.
- Drs. Sonnenfeld, Fox, and Willson for studies to determine effects of neuroendocrine hormones of gene expression of bacteria by array analysis.
- Drs. Fox, Willson, Butel, and Ling for studies of rapid detection of viruses.
- Drs. Shearer, Rosenblatt, Reuben, Butel, and Ling for Antarctic analog studies. Dr. Desmond Lugg (ANARE) will be a collaborator on these studies, as well.

6.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Presented here are the objectives underlying each goal and the strategy that we plan to use to achieve the goals and objectives of our program.

Goal 1: *Reduce risk of space flight conditions (isolation, containment, stress, microgravity, radiation) damaging the human bone marrow stem cell and differentiated immune cells.*

Goal 2: *Reduce risk of astronauts developing new and reactivated infections, premature immune cell death, and malignancy.*

Since many of the objectives and specific activities for Goals 1 and 2 are similar and interrelated, we have presented them together. They are:

Objective 1A-2A. Assess risk and target level of acceptable risk.

- In human models, develop a system of surrogate markers for the component of the immune system being tested based upon well-established clinical standards (e.g., $CD4^+$ T-cell count and CDC recommendations).
- In animal models, use natural outcomes if the endpoints are reached within days (e.g., death). If the endpoints are to be reached in months (e.g., breast carcinoma), develop surrogate markers of cancer development (e.g., epithelial cells appearing in blood stream).

Objective 1B-2B. Determine mechanisms.

- Complete Antarctic winter-over studies of human pro- and anti-inflammatory cytokine balance in subjects excreting virus.
- Complete study of latent viruses EBV and JCV excretion in Antarctic winter-over human subjects and match data results with those of subjects with altered cytokine balance.

- Match immune and viral study data with psychological profile study of Dr. Joanna Wood on Psychosocial Team.
- Complete study of HPA axis in AOS mice to determine role of catecholamines in lowering immune resistance factors.
- Begin radiation studies of murine model to determine extent of immune compromise and how these animals handle latent virus challenge and whether they develop lymphoreticular malignancy.
- Quantitate immune responses in irradiated and virus-challenged mice and determine effects of radiation on degree of immunosuppression and reactivation of virus.
- Begin in vitro study of proton, gamma, and heavy metal radiation on human pleuripotential bone marrow and peripheral blood stem cells and the myelogenous and lymphocytic differentiation pathways leading to malignancy.
- Determine immune system gene expression profiles in AOS mice before and after virus infection, with and without radiation exposure.
- Begin study of apoptosis in thymocytes of AOS mice to determine effects upon education and selection of lymphocytes.
- Determine TH1 vs. TH2 cytokine profile in AOS mice and effects of immune mediators upon regulation of bone metabolism.
- Increase the specificity of nucleic acid and molecular beacon probes for early detection of microbial contamination of water supply in spaceships.

<u>Objective 1C-2C.</u> Develop countermeasures.

- Form strategic plan for general and specific immunoreconstitution of astronauts based upon the deficits uncovered in exploring the mechanisms of space flight immunodeficiency (see above).
- Based upon current treatments of immunodeficient humans on Earth (i.e., genetically immunodeficient patients, immunosuppressed transplant patients, patients with rheumatoid arthritis, patients with AIDS), plan to adapt therapies involving parenteral immunoglobulin, cytokines, chemokines, monoclonal antibodies, fusion proteins, and autologous stem cells for astronauts who develop secondary states of immunodeficiency in space travel.
- Based upon current and developing treatment regimens for viral infection (e.g., gancyclovir for cytomegalovirus), plan to adapt therapies for astronauts who become infected or re-infected with opportunistic and reactivated viral infections.
- Based upon current and developing experimental treatments of cytokine-mediated (e.g., tumor necrosis factor-alpha) wasting disease, plan to adapt such treatments (e.g., thalidomide) for use in astronauts who develop wasting disease in space due to abnormal TH1 vs. TH2 cytokine balance and apoptosis of lymphocytes.
- Work with Nutrition Team (Dr. Joanne Lupton) to devise nutritional supplements that augment innate and acquired immunity.
- Work with Performance and Psychosocial Teams to provide adequate rest periods for astronauts to restore lymphocyte health.

Goal 3: *Reduce risk of space flight-induced development of superstrains of microbial organisms.*

<u>Objective 3A.</u> Assess risk and target level of acceptable risk.

<u>Objective 3B.</u> Determine mechanisms.

- Isolate and genotype gut flora of irradiated and AOS mice.
- Perform resistance assays of microbes recovered from radiation experiments.

Objective 3C. Develop countermeasures.

- Investigate effects of immunotherapy (e.g. monoclonal antibodies) on drug-resistant microbes.

Goal 4: *Develop Earth-based applications of space flight studies to help diagnose and treat humans with secondary immunodeficiencies, reactivated viral infections, and malignancy.*

Objective 4A. Plan for the future when space flight diagnosis and treatments are being utilized for astronauts with immune compromise, opportunistic infection, and possibly cancer.

- Explore use of T cell count and cytokine balance as indicators of immune compromise.
- Continue efforts to expand microbial detection system to include viruses.

Objective 4B. When such methods of diagnosis and modes of treatment of astronauts in space become a reality, determine whether these methods, dictated by the unique features of space travel (e.g., microgravity, strict regulation of diet, enforced rest periods), might be applied in diagnostic methods and treatment programs on Earth.

Goal 5: *Integrate research and analysis.*

Objective 5A. Integrate research within the Immunology, Infection, and Hematology Team:

- Continue current integration efforts described in **Table 6.2**.

Objective 5B. Integrate research with other teams using modeling, as well as other approaches:

- Enlarge collaboration with Radiation Effects Team. Add Dr. Daila Gridley of LLU to team, if her NSBRI grant application is accepted.
- Continue collaboration with Psychosocial Team (Dr. David Dinges, Dr. Joanna Wood), NASA (Dr. Duane Pierson), and ANARE (Dr. Desmond Lugg) in analyzing: 1) immune factors, 2) virus reactivation, and 3) psychological profiles of Antarctic winter dwellers in a synergy project (submitted to NSBRI for funding [12-13-01]).
- Develop joint projects with Nutrition Team (Dr. Joanne Lupton)
- Develop joint projects with Bone Metabolism Team (Dr. Jay Shapiro)

Objective 5C. Integrate research with investigators not formally associated with the NSBRI.

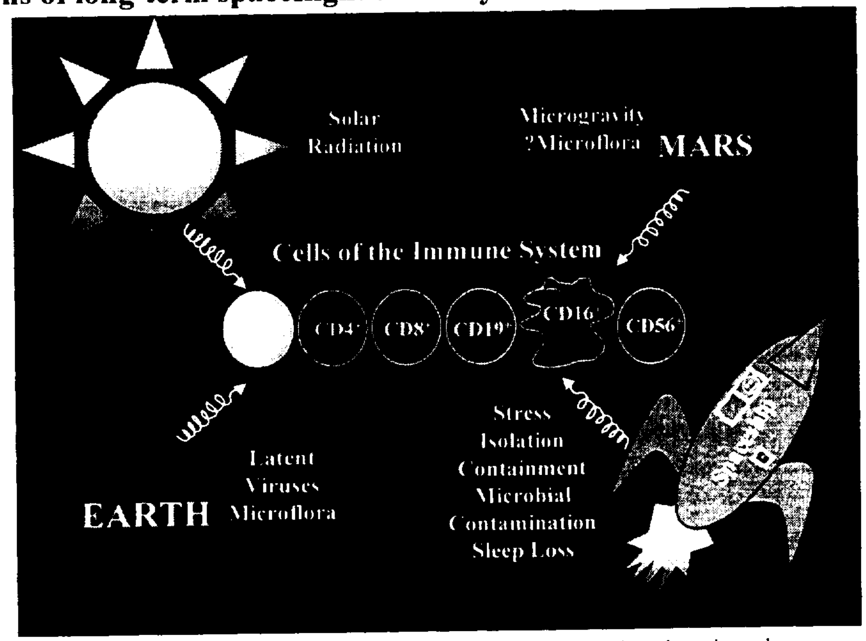
- Continue collaboration of team with Dr. Desmond Lugg (ANARE), Dr. I. Larina (IBMP), Dr. Duane Pierson (NASA), Dr. Marcelo Vazquez (NSBRI radiation team) and Dr. Elizabeth Sutherland (BNL), and Dr. Daila Gridley (LLU).

6.6 SUMMARY

The essence of the challenge facing the investigators of the Immunology, Infection, and Hematology Team is depicted in **Figure 6.2**.

FIGURE 6.2

Conditions of long-term spaceflight that may weaken cells of the immune system.



The voyage to and from the planet Mars is estimated to consume 3 years. During that time, human space travelers will be exposed to stress, microgravity, isolation, containment, sleep disruption, microbial contamination, and solar radiation (up to 3 Gy of proton and gamma radiation). All of these conditions are known or suspected causes of immunosuppression, which is possibly sufficient to lead to reactivation of latent viral infections and malignancy. The immune cells that may be susceptible to these causes of immunosuppression include the bone marrow stem cell ($CD34^+$), helper T-cell ($CD4^+$), cytotoxic T-cell ($CD8^+$), B-cell ($CD19^+$), monocyte-macrophage ($CD16^+$) and natural killer cell ($CD56^+$). Because of the inherent difficulties of assessing these risks in space flight, ground-based models that incorporate some of the conditions of long-term space flight offer the best hope of adequately predicting the harm that may occur to the human immune system in interplanetary travel. Taken from Shearer WT, et al. Antibody responses to phiX-174 in human subjects exposed to the Antarctic winter-over model of spaceflight. *J Allergy Clin Immunol* 2001:107:160-164.

All of the risk factors affecting cells of the immune system by themselves are known to represent risks to earthbound inhabitants. Solar radiation, for example, is known to cause melanomas of the skin, a tumor that is controlled by T-cells. As humans age, T-cell immunosurveillance weakens, and these forms of cancer appear. Unpublished studies by NASA have already shown a 3-fold increased incidence of skin melanomas in astronauts as compared to earthbound NASA employees (295 astronauts compared to 909 controls, Longitudinal Study of Astronaut Health, Surveillance Epidemiology, and End Results Program). Another example is that of reactivated latent viruses, leading to unregulated growth of B-cells and non-Hodgkin lymphomas.

The role of the team is to scientifically define and quantitate the potential harmful effects of the conditions of space travel upon human immune responses and health. Foremost in our efforts will be the constant search for countermeasures to the risks that we define and quantitate. We are not content to merely document the probability that space risk factors exist and are likely to create infections and cancer in astronauts. We want to use the immunological reagents and procedures that are already in use for humans with immunodeficiency on Earth for our astronauts whose immune responses are jeopardized by the immunosuppressive conditions of space travel. We have made progress so far in our team research, and a timeline for the strategic activities for each of our Goals is presented in **Table 6.3**. For Goal 1 **(Table 6.3A)**, the team is already well into the Countermeasure Development Phase 1 (Focused Mechanistic Research) and beginning to enter Phase 2 research (Preliminary Countermeasure Development Research). We expect to complete Phase 2 research by 2009, but overlapping with development of Phase 3 research (Mature Countermeasure Development Research) by 2006-2010. We anticipate beginning Phase 4 research (Countermeasure Evaluation and Validation) during 2009-2011 and Phase 5 research (Operational Implementation of Countermeasure Strategy) during 2011-2012. Similarly, with Goal 2 **(Table 6.3B)** and Goal 3 **(Table 6.3C)**, we anticipate a steady and progressive development of team research from the present Phase 1 level to Phase 5 level over the next 10 years.

National Space Biomedical Research Institute
IMMUNOLOGY, INFECTION AND HEMATOLOGY

Table 6.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BUTEL/Viral Infections and Mucosal Immunity	1-5	Pharmacological Agents	AOS; IR; Humans	Detect immune damage; Measure infection	Formulate antiviral reagents	
FOX/Microorganisms in the Spacecraft Environment	3-5	Pharmacological Therapy	Microbes	Develop microbe detection system	Perfect microbe detection system	Flight test detection system
GEWIRTZ/Effect of Deep Space Radiation on Human Hematopoietic Stem Cells	1,3,4	Stem Cell Therapy, Cancer Chemotherapy	In Vitro Stem Cells	Detect damage to stem cells	Formulate autologous stem cell transplant	Test stem cell Transplantation in space
SHEARER/Space Flight Immunodeficiency	1,3,4	Antibody Therapy, Stem Cell Therapy	IR; Humans	Measure apoptosis in thymocytes	Adapt Earth Rx strategies	Perform Rx in space
SHI/Endogenous Opioid-Mediated Fas Expression in Stress-Induced Lymphocyte Apoptosis	1,2,4	Cytokine Therapy	AOS, IR	Measure HPA in AOS, IR	Formulate drug treatment program	
SONNENFELD/Suspension, the HPA Axis and Resistance to Infection	2-5	Pharmacological Therapy	AOS, IR	Determination of role of different stressors on immune response	Formulate anti-stress program	Test program in space

Risks Key: 1) Radiation damage to stem cell and immune system; 2) Microgravity damage to immune system; 3) Reactivation of latent viral infections; 4) Malignancy; 5) Altered microbes

Definitions: AOS, anti-orthostatically suspended murine model; IR, irradiated mice; Humans, humans exposed to Antarctic winter or isolation in capsules; Microbes, microbial detection systems; HPA, hypothalamic pituitary axis; Rx, treatment

National Space Biomedical Research Institute
IMMUNOLOGY, INFECTION AND HEMATOLOGY PROGRAM

Table 6.2. Integration Activities

	BUTEL	FOX	GEWIRTZ	SHEARER	SHI	SONNENFELD
Internal Communication (E-mail, telecons, retreats, scientific meetings for all projects)	• Shearer • Sonnenfeld • Fox • Gridley (LLU) • Lugg (ANARE) • Pierson (NASA) • Larina (IBMP)	• Butel • Sonnenfeld	• Shearer • Shi • Sutherland (BNL)	• Butel • Gewirtz • Fox • Shi • Sonnenfeld • Gridley • Lugg • Pierson • Dinges (Psych)	• Sonnenfeld • Butel	• Shearer • Butel • Vazquez (Rad)
Integrated Experiment Development	Model Radiation and AOS Studies • Shearer • Gridley • Reuben • Sonnenfeld • Pierson • Larina • Lugg • Fox	Collaborative Gene Probe Studies • Butel • Sonnenfeld	Model Radiation Studies • Reuben • Shearer	Model Radiation and Human Exposure Studies • Butel • Reuben • Lugg • Gridley	Model AOS Studies • Gewirtz	Collaborative Gene Probe Studies • Butel • Fox
Sample Sharing	Blood, Urine • Shearer • Reuben • Larina	Microbes • Butel • Sonnenfeld	Stem Cells • Reuben • Shearer	Blood • Butel • Reuben • Dinges	Blood • Sonnenfeld • Butel	Blood • Vazquez
Synergistic Studies of Opportunity	Antarctic Winter • Shearer • Lugg • Pierson	Radiation, AOS • Butel • Sonnenfeld	Radiation • Reuben • Shearer • Kennedy (Rad. Team)	Antarctic Winter, Sleep Deprivation • Butel • Dinges • Lugg	Radiation • Sutherland • Kennedy	Radiation, AOS • Butel
Development of Computer Model of Integrated Human Function						

Definitions: ANARE, Australian National Antarctic Research Expedition; NASA, National Aeronautics and Space Administration; IBMP, Institute for Biomedical Problems, Moscow; LLU, Loma Linda University; Psych, Psychosocial Team; Rad, Radiation Effects Team; BNL, Brookhaven National Laboratory; AOS, Antiorthostatic Suspension

National Space Biomedical Research Institute

IMMUNOLOGY, INFECTION AND HEMATOLOGY TEAM PROGRAM

Table 6.3A. Achieving Goal 1: Reduce Risk of Space Flight Conditions (Isolation, Containment, Stress, Microgravity, Radiation) Damaging the Human Bone Marrow Stem Cell and Differentiated Immune Cells

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research	■												
Phase 1: Focused Mechanistic Research		■	■	■	■	■	■						
• Define radiation damage to immune system in animals • Define microgravity damage to immune system in animals • Define latent virus damage to immune system in animals • Measure virus excretion in Antarctic-bound humans • Develop surrogate markers of immunity for space													
Phase 2: Preliminary Countermeasure Development Research			■	■	■	■	■	■	■	■			
• Adapt antibody therapy to space travel • Adapt cytokine therapy to space travel • Develop space immunization strategies • Develop radiation shielding methods • Plan stem cell therapy in space													
Phase 3: Mature Countermeasure Development Research							■	■	■	■			
• Perfect and test ready-to-use antibody auto injectors • Perfect and test cytokine auto injector system • Safety study of space vaccines • Safety study of autochthonous (self) stem cell transplants													
Phase 4: Countermeasure Evaluation & Validation										■	■	■	
• Efficacy study of Phase 3 countermeasures (above)													
Phase 5: Operational Implementation of Countermeasure Strategy												■	■
• Spacecraft trial of countermeasures													

National Space Biomedical Research Institute
IMMUNOLOGY, INFECTION AND HEMATOLOGY TEAM PROGRAM

Table 6.3B. Achieving Goal 2: Reduce Risk of Astronauts Developing New and Reactivated Infections, Premature Immune Cell Death, and Malignancy

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research	■												
Phase 1: Focused Mechanistic Research		■	■	■									
• Measure virus excretion in Antarctic-bound humans • Measure tumorigenesis in irradiated/virus-infected animals • Study malignant transformation in irradiated human stem cells • Study additive effect of malnutrition on tumorigenesis • Develop surrogate markers for premalignancy													
Phase 2: Preliminary Countermeasure Development Research				■	■	■	■	■	■	■			
• Develop radiation shielding methods (chemical, physical) • Develop oncogene array assays for gene targeting • Adapt cytotoxic T-cell rescue of EBV tumors for space • Develop cancer virus vaccine for space													
Phase 3: Mature Countermeasure Development Research								■	■	■	■	■	
• Safety study of radiation blockers (animals) • Safety study of cancer gene promotor inhibitors (animals) • Safety study of anti-EBV tumor T-cells (humans) • Safety study of cancer virus vaccine (humans)													
Phase 4: Countermeasure Evaluation & Validation										■	■	■	
• Efficacy studies of Phase 3 countermeasures (above)													
Phase 5: Operational Implementation of Countermeasure Strategy												■	■
• Spacecraft trial of countermeasures													

National Space Biomedical Research Institute
IMMUNOLOGY, INFECTION AND HEMATOLOGY TEAM PROGRAM

Table 6.3C. Achieving Goal 3: Reduce Risk of Space-Flight-Induced Development of Superstrains of Microbial Organisms

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research	■												
Phase 1: Focused Mechanistic Research		■	■	■									
• Genotype gut flora of irradiated mice • Perform resistance assays of organisms of irradiated mice • Combination of microgravity and radiation to determine microbe virulence assays • Adapt Fox gene probes to viral organisms													
Phase 2: Preliminary Countermeasure Development Research					■	■	■						
• Develop monoclonal antibodies to resident organisms • Develop cytokine therapies to augment cytotoxic T-cells • Develop fusion proteins specific for receptors on cancer cells • Develop toxin-antibody conjugate molecules for cancer													
Phase 3: Mature Countermeasure Development Research								■	■	■			
• Safety study of monoclonal antibodies • Safety study of cytokine activation of T-cells • Safety study of fusion proteins for cancer • Safety study of toxin-antibody conjugates													
Phase 4: Countermeasure Evaluation & Validation										■	■	■	
• Efficacy study of Phase 3 countermeasures (above)													
Phase 5: Operational Implementation of Countermeasure Strategy												■	■
• Spacecraft trial of countermeasures													

7.0 MUSCLE ALTERATIONS & ATROPHY

Team Leader: Kenneth M. Baldwin, Ph.D.
Professor
Department of Physiology and Biophysics
University of California, Irvine
Medical Sciences I, Rm. D340
Irvine, CA 92697-4560
949-824-7192
949-824-8540 FAX
kmbaldwi@uci.edu

7.1 INTRODUCTION

Previous research involving both humans and animals clearly indicates that unloading the skeletal muscle system through prolonged space flight or bed rest causes a cascade of negative events within the body. Muscle mass is reduced and although the mechanism for this response is not known for certain, the atrophy is thought to be due to an imbalance between protein synthesis and protein degradation within the targeted fibers. Muscle strength is also reduced, leading to a decrease in physical performance and high power output capacity. However, the reduction in strength often exceeds the loss in muscle mass, suggesting that other, more complex mechanisms may be responsible for the reduced performance. A slow-to-fast shift in the contractile protein phenotype is observed, including shifts to faster myosin heavy chain (MHC) and calcium cycling proteins. These alterations induce the muscle fibers to become less economical in sustaining force output, resulting in an increased fatigability. This decreased resistance to fatigue is important because it could cause functional impairment that would affect the performance of extravehicular activity in space and emergency egress activity following landing. It is reasonable to suspect that the above changes will also make muscle more prone to injury than would otherwise be the case and that weaker muscles would result in an increased susceptibility to accidents that could cause damage to other systems, such as bone or connective tissue. Deleterious alterations in muscle properties may also be closely linked to changes in the ability of the nervous system to accurately control movements. All these effects could alter astronaut safety when performing any type of work in space.

7.2 RISKS

The following risks in the Muscle Alterations and Atrophy Discipline Area have been identified in the Critical Path Roadmap (risk number in parentheses):

- Loss of Skeletal Muscle Mass, Strength, and/or Endurance (28)
- Inability to Adequately Perform Tasks Due to Motor Performance, Muscle Endurance, and Disruption in Structural and Functional Properties of Soft and Hard Connective Tissues of the Axial Skeleton (29)
- Inability to Sustain Muscle Performance Levels to Meet Demands of Performing Activities of Varying Intensities (30)
- Propensity to Develop Muscle Injury, Connective Tissue Dysfunction, and Bone Fractures Due to Deficiencies in Motor Skill, Muscle Strength and Muscular Fatigue (31)
- Impact of Deficits in Skeletal Muscle Structure and Function on Other Systems (32)

Since several of these risks are operationally defined and interdependent, it is difficult to organize and develop a focused research program based on this set. Therefore, we have chosen to redefine the risks in this research area as follows:

- Loss of muscle mass, strength and endurance;
- Loss of motor control/movement performance due to changes in neural control;
- Proneness to muscle injury; and
- Impact of degeneration of muscle or increased injury of muscle on other systems such as bone and connective tissue.

This set of four risks underlies the risks listed in the Critical Path Roadmap and is less interdependent.

7.3 GOALS

The Muscle Alterations and Atrophy Team has the following goals for its program:

Risk-Based Goals

Goal 1: *Reduce risk of loss of muscle mass, strength and endurance*

Goal 2: *Reduce risk of loss of motor control/movement performance due to changes in neural control*

Goal 3: *Reduce risk of proneness to muscle injury*

Non Risk-Based Goals

Goal 4: *Develop monitoring methods using biochemical/molecular markers to predict potential anabolic and catabolic states in muscle*

Goal 5: *Develop rehabilitation methods (nutritional, pharmacological, and exercise-specific agents) that are effective in treating loss of muscle mass, strength and endurance*

Goal 6: *Develop Earth-based applications of exercise training paradigms to ameliorate problems of frailty, injury, morbidity, and mortality that are associated with the aging process, degenerative muscle disorders, and inactivity-related disorders*

Goal 7: *Integrate research and analysis*

7.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The Muscle Adaptation and Alterations team (Muscle Team) will seek to reduce most but not all of the identified risks defined in section 7.2 above. In particular, we are not addressing the fourth of the risks listed in that section, dealing with the impact of muscle degeneration or injury on other systems. While it is apparent that there is important synergy between the properties of skeletal muscle and bone, the bone and connective tissue properties can be studied more effectively by the experts in the bone discipline field by exploiting models that affect both skeletal muscle and bone. The Muscle Team views Goal 1, Reduce risk of loss of muscle mass, strength and endurance, as its primary goal. This goal underlies the Team's research program to prevent or minimize the deleterious adaptations of the structure and function of skeletal muscle in response to the prolonged states of unloading occurring in space flight. Importantly, the amelioration of these deficits will have an inherent beneficial effect in reducing the other, secondary, risk-based goals (Goals 2 and 3) that concern the motor control of muscle function and/or movement performance and the reduction of the proneness of weakened skeletal muscle to injury. Due to budgetary constraints that limit the current size of the investigative team, these two goals, though important, will not be a major focus at the present time. Future research efforts in addressing these secondary goals will evolve as the program is expanded. Additional non risk-based goals include those associated with the assessment of health and application of medical care, transfer of information to Earth-based applications, and facilitation of integration of research and analysis.

In 2001, the Muscle Team's research program was totally restructured. The current team is comprised of ten principal investigators, seven of whom are new NSBRI investigators. The restructuring involved a significant refocus and a shift in the team's research objectives. Table 7.1, entitled "Current Project Research Activities," summarizes for each current Muscle Alterations and Atrophy Team project those risks that are currently being addressed, the experimental system, the countermeasure target and whether a project is part of the strategic steps of Phase 1, 2 or 3 Activities.

All projects directly or indirectly address the critical problem of muscle atrophy and the corresponding loss in muscle strength and human performance. The Baldwin, Goldberg, and Antin projects seek a better understanding of the mechanisms associated with the imbalance in protein synthesis and protein degradation. The Goldberg and Antin projects, while addressing mechanisms of degradation, focus on different, but complementary processes that impact protein loss. The Antin project examines calpain and its role in the regulation of the rate of muscle protein accumulation and the potential use of inhibitors of calpain mechanisms as countermeasures in animal and cellular models. The Goldberg project, alternatively, uses animal and human models to seek to clarify the basis of activation of the ubiquination pathway in unloaded muscles and whether inhibitors of this pathway may be a countermeasure to muscle atrophy. The Baldwin project uses an animal model to directly examine the switch in muscle protein phenotypes that is associated with muscle unloading and to develop a resistance exercise program that ameliorates muscle atrophy and prevents phenotype switch in response to space flight. In addition, Baldwin's group is interacting with scientists outside the NSBRI, such as Dr. Suzanne Schneider at the University of New Mexico and Dr. Per Tesch at the Karolinska Institute, who are directing research projects that seek resistance training countermeasures to prevent muscle atrophy in human subjects in response to ground based models of unloading.

The Kandarian (rodent) and Hamilton (human) projects are determining which key genes are involved in both atrophy and hypertrophy processes using functional genomics and global transcriptional profiling. By examining the expression of ~8,000 genes simultaneously over a time course of unloading, the Kandarian project will uncover patterns of gene expression underlying muscle atrophy. By using a variety of clustering approaches and by comparing the gene expression data set to that in the literature from hypertrophied, aging, and cachextic muscle (Goldberg lab), clusters of gene expression unique to muscle unloading will be revealed. These data will also be compared to the human dataset produced by the Hamilton project. The genes and gene clusters that are uniquely altered by disuse will be studied in further detail (by various investigators) to determine their role during disuse/unloading atrophy. Work recently published from this lab showed that unloading activated an NF-kB pathway, so the effect of NF-kB inhibitors (e.g., asprin, curcumin) will be tested for their ability to ameliorate atrophy and reverse the affected gene clusters.

Focusing mainly on Ca^{2+}-sensitive processes, the Wiseman project will provide insight into cell signaling and regulatory factors that control the protein phenotype and the metabolic capacity of isolated muscle cells. Direct manipulation of cytosolic Ca^{2+} levels may stave off changes in muscle upon unloading. The Reid project will dissect the role of both ionizing radiation and reactive oxygen species on mechanisms of muscle fatigue, as well as muscle atrophy processes in animals and cultured cells. Antioxidants will be tested as potential countermeasures to these effects in human subjects. The Sinha/Edgerton project will use humans to dissect the effects of unloading on stress/strain function in skeletal muscle and determine how muscles may become prone to injury in the face of atrophy and loss of strength. It will also examine its MRI technology for potential use for evaluation of exercise countermeasures using the human lower limb suspension model. Additional interactions are evolving among the Goldberg, Sinha/Edgerton and Baldwin projects, as well as between the Hamilton and Sinha projects. These groups aim to establish "ground zero baselines" that define the mechanisms of muscle atrophy by using the spinal isolation model where animals have complete inhibition of neuromuscular activity.

Complementing the above projects are two additional projects that were originally part of the Integrated Human Function Team. However, due to restructuring within NSBRI program objectives, two projects were reallocated to the Muscle Team, since they were clearly congruent to the goals of the Muscle Team as outlined above.

The Kushmerick project uses a combination of non-invasive ^{31}P and ^{1}H NMR spectroscopies, MR and ultrasound functional images, biomechanical analyses and multi-level modeling in order to conduct analyses leading to an integration of the metabolic and mechanical mechanisms of human muscle. Analysis of limb function is crucial to plan training and to select personnel for optimal efficiency and economy with minimal risk and fatigue. The basic science of this proposal evaluates the mechanisms responsible for transient and steady state performance of limb muscle, which is critical for astronaut performance. This analysis requires the specification of: 1.) the mechanical power output by specific muscles during limb functions; 2.) the analysis of the properties of different muscles in the same individual and of the same muscles in different individuals; 3.) the partition of energy demand into mechanical output and ion transport costs; 4.) the division of metabolism quantitatively between glycolytic and oxidative processes and analysis of their inter-related controls; and 5.) the relationship between these intracellular and mechanical properties and muscle blood flow and perfusion. These experimental approaches and information are crucial to develop a model-based approach to the study of *in vivo* muscle energy balance in humans because the relevant data is not available and more importantly, and because the conceptual basis for integrating the component cellular mechanisms can only be evolved from these new observations.

The Chase project, while originally targeted to the Integrated Human Function Team also provides an excellent fit with the existing Muscle Team. The overall goal of this project is to produce a muscle cell model (digital cell) that will: explain biomechanical adaptations that occur with alterations in muscle protein isoforms due to changes in activity level; predict bioenergetic changes associated with changes in activity level; and be integrated into computational models of human limb and heart. The essential molecular and subcellular components of the model will be identified and algorithms constructed based on experimental data obtained in a controlled environment. The cell model will be tested against published biomechanical and bioenergetic data obtained under a broad spectrum of environmental conditions. The muscle cell model will be one of the main building blocks for constructing a model of integrated human function because the cell is the basic unit of physiological organization and because the musculoskeletal system is ~80% of body mass, thus a major determinant of energy consumption, and is responsible for movement and cardiovascular function. This particular project will closely interface with both the Kushmeric projects and the Wiseman projects as described above.

We anticipate that as the ground-based research matures, over time, three fundamental counter-measure strategies will be applied to ameliorate skeletal muscle dysfunctions. These include:

1) Different forms of preflight and inflight physical exercise with activity-unique prescriptions:
   - *A resistance training prescription to maintain muscle mass and strength.* Studies conducted to date on both animals and humans clearly suggest that exercise paradigms of the high resistance type are only partially effective in reducing muscle atrophy. Future research needs to: a) Utilize human experiments to define the success of resistance paradigms using ground-based models that induce atrophy (bed rest, limb suspension). This effort should be carried out by interactions both within and outside the muscle team. b) Understand the mechanism(s) behind the partial effectiveness of resistance training. c) Define a better exercise prescription that is more effective in reducing muscle atrophy, as well as, more economical in terms of the time devoted to performing such a countermeasure on a daily basis.
   - *An aerobic exercise paradigm that would improve both cardiovascular fitness and skeletal muscle endurance.* Aerobic exercise is an important countermeasure for both skeletal muscle and cardiovascular endurance. While it is recognized that activities such as running and cycling are effective in enhancing endurance in normal weight bearing modes, it remains to be determined whether these paradigms are effective when used with individuals experiencing chronic states of unloading even when performed in conjunction with resistance training paradigms. Activities carried out with both human (Hamilton) and animal models (Baldwin) will be developed in the next few years to provide insight into this issue.
   - *An activity paradigm that would specifically target the sensory-motor pathways to maintain posture, balance and locomotor skills.* This type of activity is an important part of a total exercise prescription, and future research projects need to be sought to address this issue using new funding initiatives.
   - *An impact-loading paradigm that could conceivably affect both the skeletal muscle system and the skeletal systems to stimulate/maintain bone homeostasis.* While it has been recognized that stress/strain reaction forces impact both muscle and bone, research addressing whether there are synergistic/interactive effects of bone stress on muscle and vice versa is still in the infant stages. A visionary goal of the muscle team is to address this problem in future research projects. This research could be facilitated by interactions with both the Bone and Nutritional Teams.

2) Human-powered artificial gravity (gravity-equivalent exercise).
   Funding augmentation should be sought to begin studies using artificial gravity (human-powered centrifuge) as an alternative countermeasure strategy. These activities need to be a high priority for flight testing, because this activity paradigm has the potential to encapsulate all four of the above mentioned exercise-type prescriptions and positively add to the bone, cardiovascular, vestibular, and

nutritional/fitness countermeasure strategies. It is envisioned that the Muscle Team will take a lead role and undertake a multifaceted, integrative research project involving the Neurovestibular, Cardiovascular, Bone, and Nutrition/Physical Fitness research Teams to address these fundamental overarching physiological problems using artificial human-generated gravity equivalent exercise as the centerpiece in the countermeasure program.

3) Novel nutritional, pharmacological and hormonal/growth factor approaches
These activities are being explored in the current funding period. In particular, the gene chip analyses currently underway will contribute significantly to the collective research effort.

In the future, as more resources become available, we would like to seek funding for projects which address the relationship of muscle tissue changes with actual movement performance and that strive to differentiate between problems associated with neural control versus muscle tissue effects (Goal 2). Additional projects examining the proneness of weakened muscle to injury should also be sought (Goal 3). These projects will build off of the fundamental knowledge generated by the combined Sinha, Kushmeric and Chase projects.

Some progress has already been made in achieving the first of the non risk-based goals, e.g., Goal 4, "Develop monitoring methods using biochemical/molecular markers to predict potential anabolic and catabolic states in muscle". In the current funding period, several genes and their encoded proteins have been identified that could play key roles in muscle homeostasis and that could be used as markers. For example, Goldberg's team has identified a novel gene, termed atrogin 1, that may play a pivotal role in regulating muscle-wasting disorders. The Kandarian team has revealed 16 different genes encoding proteasome subunits and 5 ubiquitination genes (including atrogin-1) that are upregulated with unloading, but the ubiquitination genes are upregulated earlier and to a greater magnitude than the proteasome genes. This effect is a distinctly different catabolic response to that seen with aging, for instance. This example is one of many examples of differentially expressed gene clusters revealed by the Kandarian project. Also, the Baldwin group has shown that atrophying skeletal muscles of rodents and humans initially undergo marked losses in ribosomal RNA that serve as the machinery for translating the protein necessary for maintaining muscle mass. Additionally, growth factors (IGF-1 and mechano growth factor) have been identified that appear to be essential in turning on anabolic processes and inhibiting catabolic states in muscle undergoing an altered loading state. Thus, it is anticipated that a cadre of molecular markers will be identified that can be used to assess the state of the muscle in astronauts. By controlling the expression of the genes for these important proteins, we may also be able to maintain the muscle from one functional state to another. In the future, the monitoring methods that we develop for use with the astronauts will also have direct applicability for addressing a variety of Earth-based problems associated with muscle disorders due to inactivity, disease, and sports injury.

Two other non risk-based goals (Goals 5 and 6) are important aims of the Muscle Team's research mission. The future vision of the program will involve expanding the knowledge of muscle cell structure and function and the operational activity regimens so that we can best design rehabilitation methods that overcome the muscle deficits that occur in astronauts in response to prolonged space flight (Goal 5) and the well-known effects of aging on skeletal muscle that closely mimic these effects (Goal 6). Regimens similar to the successful preflight training paradigms may likewise be used as preventative measures for the effects of aging on muscle. Similar preventative and rehabilitative methods may also aid a variety of muscle degenerative disorders and inactivity-related diseases (e.g. type II diabetes) that severely impact large populations of individuals. Thus, Earth-based applications addressing problems of frailty, injury, morbidity, and mortality that are associated with Earth-based disorders represent an important outcome of the Muscle Program. To these efforts, the expertise currently on board the muscle Team (Sinha, Kushmerick, Hamilton, and Chase Projects), should play a significant role in advancing Goals 5 and 6.

Another important non risk-based goal of the Muscle Team (Goal 7) will be to enhance the interaction of individual Muscle Team investigators a) among the current team's research infrastructure, b) among investigators within other teams (Bone, Nutrition and Fitness, Neurovestibular, Cardiovascular), and c) with investigators not formally associated with the NSBRI. This strategy should provide an effective means to leverage a greater scientific return relative to the resources invested by the NSBRI. Table 7.2 summarizes our current efforts at integration. A few examples of integration of the Muscle Team with other teams or researchers outside of the NSBRI are as follows: Dr. Baldwin currently serves as a co-investigator on Dr. Shapiro's Bone Team research project that investigates the effects of bisphophonates on the integrity of bone and skeletal muscle. He is currently interacting with Dr. Ann Kennedy of the radiation team in testing a novel protease inhibitor for its properties in preventing muscle wasting in conjunction with resistance exercise using rodents as the model system. Also, Dr. Baldwin is collaborating extensively with investigators external to the NSBRI program in seeking countermeasures to muscle atrophy in human models of atrophy (both bed rest and limb suspension models). These interactions are with Dr. Suzanne Schneider at the University of New Mexico and with Dr. Per Tesch at the Karolinska Institute in Stockholm, and these projects are using novel resistance training devices and innovative training programs that are aimed at preventing muscle atrophy. As another example of integration from the Muscle Team, the modeling work of Dr. Kushmerick and Dr. Chase will serve to integrate the team with the other NSBRI teams as part of the Core Integrated Human Function effort.

7.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Presented here are the objectives underlying each goal and the strategic activities that we plan to use to achieve the goals and objectives of our program. Table 7.3 summarizes the timeline of the Muscle Team's strategic activities for Goal 1. The other goals are still being developed and will not be summarized in a similar table.

Goal 1: *Reduce risk of loss of muscle mass, strength and endurance*

Objective 1A. Assess risk and target level of acceptable risk

- Complete activities to achieve this objective which are currently a part of the projects in which Dr. Baldwin's group is interacting with outside investigators using resistance training with bed rest studies (in collaboration with Dr. Schneider) as well as using human models of limb suspension in combination with concentric/eccentric resistance exercise (in collaboration with Dr. Tesch).

Objective 1B. Determine mechanisms

- Complete projects defining the underlying processes that cause the catabolic muscle state and develop a better understanding of the processes regulating muscle protein degradation (Antin, Goldberg, Kandarian, Hamilton, and Baldwin projects).
- Complete projects defining the mechanism of the slow-to-fast shift in contractile protein phenotype (e.g., shifts to faster myosin heavy chain and calcium cycling proteins) upon muscle unloading (Wiseman and Chase projects).

- Complete project that seeks insight into the role that reactive oxygen species play in causing muscle atrophy processes (Reid project).
- Complete projects defining muscle loading-sensitive genes using both animal and human subjects with the intent to ultimately determine new approaches to regulating protein balance in skeletal muscle (Hamilton and Kandarian projects).
- Complete projects that address the stress- strain relationship in skeletal muscle of subjects with tendon injuries and muscle weakness due to atrophy processes; and assess the metabolic states of muscle in performing different types of activity (Sinha/Edgerton and Kushmerick projects).
- Initiate a project that determines effects of artificial gravity (such as human-powered centrifuge) on muscle. (This possibility depends on resources coming available by NASA, NSBRI, and NIH.)
- Initiate more projects in humans exploring the reduction of muscle atrophy by resistive exercise.

Objective 1C. Develop countermeasures

- Complete current animal and human projects with collaborators outside of NSBRI (Baldwin Project) and initiate new projects in humans defining and testing potential preflight and inflight activity paradigms (such as different types of resistive exercise training) that create an anabolic state in muscle, ameliorating atrophy processes. Expand to involve the bed rest model and include nutritional interventions (antioxidants and amino acid supplements, etc.) in collaboration with the Nutrition and Fitness Team (see below under Integration Goal).
- Complete current projects that seek pharmacological interventions that can blunt the processes of muscle protein degradation or other effects of muscle unloading (Antin, Kandarian, and Goldberg projects.) Expand to involve co-examination of exercise and pharmacological agents as joint countermeasures.
- Complete current study on the role of antioxidants as a nutritional countermeasure strategy to muscle atrophy (Reid project). This project could evolve to include projects in which amino acid supplements and antioxidants are used in combination with resistance exercise studies involving the animal model of Baldwin's group.
- Initiate studies to determine whether artificial gravity can be a good alternative countermeasure strategy for muscle degeneration.

Goal 2: *Reduce risk of loss of motor control/movement performance due to changes in neural control*

Objective 2A. Assess risk and target level of acceptable risk

Objective 2B. Determine mechanisms

- Seek new funding initiatives and initiate studies that determine the relationship of muscle tissue changes with actual movement performance and differentiate mechanisms associated with neural control from muscle tissue effects that could change the ability of the nervous system to accurately control movements and regulate the properties of muscle strength.

Objective 2C. Develop countermeasures

Goal 3: *Reduce risk of proneness to muscle injury*

Objective 3A. Assess risk and target level of acceptable risk

Objective 3B. Determine mechanisms

- Complete study to determine unloading sensitive genes in animals and humans that target inflammatory processes and signaling pathway molecules (Kandarian and Hamilton projects).

- Complete study examining stress-strain in muscle during atrophy and recovery (Sinha/Edgerton and Kushmerick project) and initiate new studies to amplify how resistance loading and unloading affects stress-strain reactions in human subjects.
- Seek new funding opportunities and initiate studies addressing the mechanism underlying muscle weakness, fatigue, and the proneness of weakened muscle to injury (Kushmerick, Chase, Wiseman, Reid, and Sinha/Edgerton /projects).

Objective 3C. Develop countermeasures

Note: As discussed elsewhere in this document, while Goals 2 and 3 are important objectives of the Muscle Team, they are currently not a high priority due to insufficient resources available to cover these topics. As resources evolve, these goals will receive a greater priority.

Goal 4: *Develop monitoring methods using biochemical/molecular markers to predict potential anabolic and catabolic states in muscle*

Objective 4A. Identify key proteins

- Complete experiments to identify key molecular markers and cellular processes that regulate protein balance in skeletal muscle via protein transcriptional/translational and degradative pathways (Baldwin, Goldberg, Kandarian, Antin projects).

Objective 4B. Develop methods to observe key proteins

Goal 5: *Develop rehabilitation methods (nutritional, pharmacological, and exercise- specific) that are effective in treating loss of muscle mass, strength and endurance*

Objective 5A. Identify effective rehabilitation methods

- Complete research on both animal models and humans using novel resistance loading paradigms and prescriptions that utilize different contraction modes (isometric, concentric, eccentric).
- Seek funding to initiate acute studies that characterize ground based adaptive responses to intermittent bouts of hypergravity-induced stimuli via use of a human-powered centrifuge facility at University of California Irvine.

Objective 5B. Develop and test specific rehabilitation prescriptions

Goal 6: *Develop Earth-based applications of exercise training paradigms to ameliorate problems of frailty, injury, morbidity, and mortality that are associated with the aging process, degenerative muscle disorders and inactivity-related disorders.*

Objective 6A. Identify partners for Earth-based applications

- Seek funding with other agencies that conduct research into medical concerns that parallel the muscle deficits that occur in astronauts in response to prolonged exposure to microgravity.

Objective 6B. Work with partners to make exercise paradigms available to needy Earth-based populations

Goal 7: *Integrate research and analysis*

Objective 7A. Integrate research within the Muscle Alterations and Atrophy Team.

- Continue current integration efforts among the Muscle Team investigators as summarized in Table 7.2.

Objective 7B. Integrate research with other teams, using modeling as well as other approaches.

- Initiate in-depth studies, in conjunction with other NSBRI teams, of the effects of artificial gravity on skeletal muscle structure and function and other affected systems in microgravity. These studies will also make use of the unilateral limb suspension model.

- Explore interactions with the Nutrition and Fitness Team concerning how the separate and combined effects of nutritional modification and physical exercise impact muscle homeostasis and protein balance in bed rest subjects.
- Work with NSBRI Bone Team to begin co-examination of effect of muscle degeneration on other systems. Continue interactions with the Bone Team on countermeasures to both bone and muscle wasting using bisphosphonates, nutrition, and loading paradigms on spinally injured patients. Interact with the Bone Team on using spinally injured subjects as models to study the restoration of wasted muscle through electrical stimulation of muscles and the possible co-maintenance of bone mass. These studies could also explore the combined interventions of bisphosponates and mechanical stress on muscle and bone homeostasis.
- Continue modeling work towards the Core Integrated Human Function effort (Chase, Kushmerick)

Objective 7C. Integrate research with investigators not formally associated with the NSBRI

- Continue interaction of Baldwin's group with scientists outside the NSBRI, such as Dr. Suzanne Schneider at the University of New Mexico and Dr. Per Tesch at the Karolinska Institute, who are directing research projects that seek resistance training countermeasures to prevent muscle atrophy in human subjects in response to ground based models of unloading

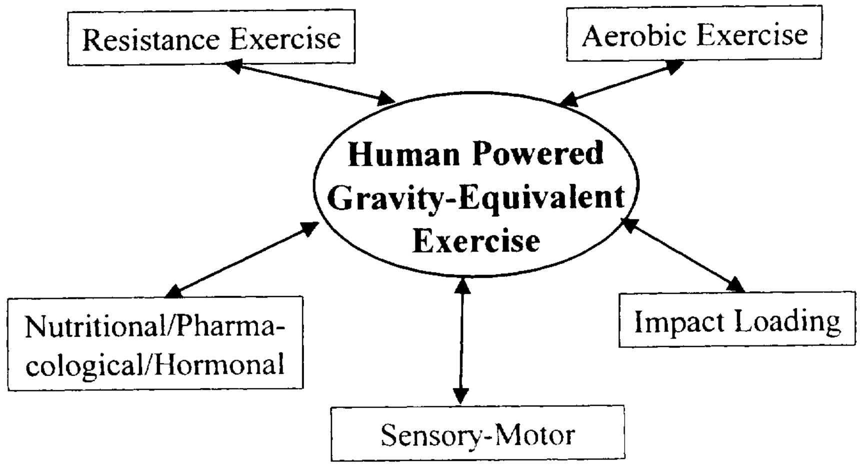
7.6 SUMMARY

In the next 3-5 year time span, the Muscle Team should be able to successfully implement both its fundamental (mechanistic) and applied research programs that address the identified Risks outlined in this Research Plan. As discussed in the plan, the primary goal initially will be to focus on "reducing the risk of loss of muscle mass, strength and endurance". New insights will be derived concerning the cellular and molecular mechanisms of the muscle atrophy process, as well as, proposals of exercise paradigms that are mechanistic in terms of maintaining positive protein balance in skeletal muscle. In addition, the team will evolve a strategy of identifying and validating the ability of different exercise paradigms used in conjunction with nutritional and pharmacological interventions to ameliorate the loss of muscle function (mass, strength and endurance) that occurs in response to chronic states of unloading. Furthermore, Earth-based benefits will be generated both in the prevention of and treatment of a variety of inactivity- and aging-related disorders that are associated with muscle dysfunction, as well as, other disorders (e.g., type II diabetes) that are related to disuse and loss of skeletal muscle integrity.

We also envision, through the development and testing of a human-powered gravity equivalent countermeasure device, an overarching countermeasure paradigm that has the potential, when used in combination with other countermeasures strategies, such as nutritional and pharmacological therapies, to not only ameliorate muscle dysfunction, but to significantly maintain the homeostasis of the skeletal (bone), vestibular, and cardiovascular systems. The integrity of each of these other systems is also compromised by prolonged exposure to unloading states. These strategic cross cutting interactions both within the Muscle Team and with other investigative teams are illustrated in Figure 7.1 below and in the tables presented at the end of the Muscle Team Plan.

Fig. 7.1: The Figure below illustrates the vision of the Muscle Team as to how the human-powered centrifuge could serve an overarching training device. When used in combination with other countermeasure strategies, this device could, in addition to ameliorating the identified risks

of the skeletal muscle system, reduce deleterious alterations that impact the functional integrity of vestibular, cardiovascular, and skeletal systems.



National Space Biomedical Research Institute
MUSCLE ALTERATIONS AND ATROPHY PROGRAM

Table 7.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
ANTIN/Calpains in Simulated Microgravity-Induced Atrophy	Loss of mass, strength and endurance	Not Applicable	• Hindlimb-unweighted transgenic mice • Cultured L8 muscle cells	Understand muscle protein degeneration	Test protective effects of calpastatin in transgenic mice.	
BALDWIN/Role Muscle Loading on Mechanisms of Protein Translation and Impact on Unloading-Induced	• Loss of mass, strength and endurance • Muscle injury	Resistance exercise training	Hindlimb-unweighted rat	• Understand muscle protein degeneration • Determine slow-to-fast phenotype shift	Test activity paradigms that create anabolic state and reduce atrophy	Interact with external researchers on countermeasures with human bed rest studies
Chase/Cell and Molecular Biomechanics: Cardiac and Skeletal Muscle	Loss of mass, strength and endurance	Integrative Modeling (Integrated Human Function Core, "Digital Human")	• High vs. low-activity rats; computational models; • Hindlimb suspension	• Focused mechanistic research: phenotype biomechanics of cells; model bio-mechanics of cells	Adapt phase I model of animal cells to human muscle cells	Integrate cell biomechanics model into "digital human"; incorporate muscle adaptation mechanisms
GOLDBERG/Activation of Protein Breakdown in Muscle Upon Unloading and Possible Countermeasures	Loss of mass, strength and endurance	Pharmacological and activity factors in altering protein degradative processes	Different models of muscle wasting	Understand the role of atrogin-1 in muscle wasting	Pharmacologic interventions in muscle wasting	Determine role of inhibitors of muscle wasting on atrophy processes in response to unloading states
HAMILTON/Genomics of Human Skeletal Muscle During Bed Rest and Exercise	• Loss of mass, strength and endurance • Muscle injury	Resistance and endurance exercise training	Bedrest and limb unloading	Identify the loading responsive genes; validate results using bioinformatics and comparative models	• Test activity paradigms to prevent metabolic and atrophic changes. • Use genomics to select "nonresponders" to unloading	• Screen subjects for genetic selection of resistance to unloading. • Integrate exercise, nutritional and pharmacological measures.

National Space Biomedical Research Institute
MUSCLE ALTERATIONS AND ATROPHY PROGRAM

Table 7.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
KANDARIAN/Gene Expression Profiling of Unloaded Skeletal Muscle	Loss of mass, strength, and endurance	Pharmacological NF-kB pathway e.g. aspirin, curcumin	Hindlimb unloaded rats and mice	Transcriptional markers of catabolic state –(i.e., unloading atrophy)	Test if aspirin alleviates atrophy (by inhibition of NF-kB pathway)	Examine gene expression profiling on tissue (other investigators) on which countermeasure was done
KUSHMERICK/ Integrating human muscle energetics and mechanics	• Loss of muscle mass, strength and endurance • Muscle injury	• Exercise • Monitoring and diagnostic procedure • Integrative Modeling (Core)	Human leg and hand muscle	• Define normal limits of energy balance • Determine acceptable level of metabolic and energetic risk	• Individualize physiologic and energetic parameters • Test efficacy of exercise protocols	
REID/Redox Modulation of Muscle Function in Microgravity	Loss of mass, strength and endurance	Antioxidants, nutritional supplements	• Cultured myocytes, • Excised muscle, • Hindlimb-unloaded mice • Humans	Evaluate signaling pathways that regulate catabolism	Test countermeasures for muscle wasting, weakness in unloaded mice	Test countermeasure for handgrip fatigue in humans
SINHA/In-Vivo Stress-Strain Dynamics in Human Muscle	• Loss of mass, strength and endurance • Muscle injury and atrophy	Exercise (rehabilitative)	MRI and muscle function	Understanding stress/strain properties of muscle so can reduce injury and improve muscle strength	Examine atrophy processes on stress/strain properties	Better techniques to evaluate muscle proneness to injury and rehabilitative processes
WISEMAN/Ca++ Homeostasis and Muscle Phenotype: Role of Cellular Energetics	Loss of mass, strength and endurance	• Pharmacological • Nutrition/Diet	• Isolated muscles • Intact hindlimb	• Understand role of energetics and altered activity on calcium handling in mitochondria and sarcoplasmic reticulum • Understand fast-slow transition phenotype switching	• Test therapeutics on calcium handling • Use model to test phenotype switch	

National Space Biomedical Research Institute
MUSCLE ALTERATIONS AND ATROPHY PROGRAM

Table 7.2. Integration Activities

	ANTIN	BALDWIN	CHASE	GOLDBERG	HAMILTON	KANDARIAN	KUSHMERICK	REID	SINHA	WISEMAN
Internal Communication	• Reid • Wiseman • Hamilton • Kandarian	• Goldberg and Sinha • Shapiro (Bone) • Lupton (Nutrition &Fitness)	• Kandarian, • Wiseman, • Kushmerick, • Bers, Coolihan, McCulloch (Cardio) • Cabrera (Nutrition)	• Baldwin, • Sinha/ Edgerton • Kandarian	• Antin • Sinha • Baldwin • Kandarian	• Hamilton • Goldberg • Antin • Reid	• Sinha • Chase • Cabrera in Nutrition • Bers, Coolahan McCulloch (Cardio)	• Antin • Wiseman • Goldberg • Jones (JSC) • Butel, Conner (Immune)	• Baldwin, • Hamilton, • Goldberg	• Antin • Reid • Chase • Kushmerick
Integrated Experiment Development	• Transgenic animals/ Reid	• Spinal injury (Bone) • Resistance exercise protocols (Nutrition)	Cellular energetics (Wiseman)	• Baldwin/ Sinha/ Edgerton; • Hamilton/ Kandarian			Exercise protocols	• Hindlimb unloading • Transgenic mice • Handgrip fatigue	TBD	• Chronically stimulated hindlimb • Hindlimb suspended animals
Sample Sharing	• Transgenic animals for physiological studies/ Wiseman, Reid	• Muscle biopsies/ Shapiro (Bone) • Muscle samples / Goldberg, Kandarian, Hamilton	• Model Component (Kushmerick) • Hindlimb suspension projects (Baldwin)	• Baldwin; • Sinha/ Edgerton	• Muscle biopsies/ Sinha • Muscle samples/ Baldwin • Other ongoing human studies	Samples from Baldwin and other PIs performing atrophy counter-measures	none	• Probes for transgene develop./ Antin • Muscles from irradiated mice/ Butel, Conner, Gridley	• Hamilton • Baldwin	• Reid • Antin (Potentially Kandarian)

National Space Biomedical Research Institute
MUSCLE ALTERATIONS AND ATROPHY PROGRAM

Table 7.2. Integration Activities (continued)

	ANTIN	BALDWIN	CHASE	GOLDBERG	HAMILTON	KANDARIAN	KUSHMERICK	REID	SINHA	WISEMAN
Synergistic Studies of Opportunity		• Planning of human-powered centrifuge (Bone, Fitness, Cardio, Neurovestib) • Resistance exercise training with humans /Schneider and Tesh (external) • Bisphosphonates/ Shapiro (Bone) • Pprotease inhibitors &muscle atrophy responses (Radiation) • Lupton (Nutrition)	N/A	Combined studies on muscle wasting via hindlimb suspension and pharmacologic interventions	• Model of the entire human genome during unloading • Genomic screens as a test to identify novel gene targets for CMs • Compare CMs on muscle metabolism and gene expression • CM model: Compare rat and human responses to similar CMs & unloading		• Compare generality of human and animal training results • Test "energy phenotype" with adapative responses to exercise • Integrate blood flow, mechanics and energetics with training	• Muscle response to gamma irradiation/ Butel, Conner, Gridley • Muscle-specific, inducible transgenic mice/ Antin, Wiseman • Unloading effects on calcium regulation and metabolism / Wiseman • Beta testing of NASA device for handgrip evaluation on ISS / Jones (JSC)	• Baldwin, Project • Hamilton project	• NASA funded bone group at MSU developing model of mechanically altered limbs (unloaded and loaded) • Cell signaling group at MSU is collaboration on calcium measurements in muscle
Development of Computer Model of Integrated Human Function		TBD	Muscle Cell and Molecular Biomechanics for Integrated Human Function Core		Input data from the entire human genome for muscle and other tissues		Integration of muscle modeling effort with cardiovascular and nutrition		TBD	

National Space Biomedical Research Institute
MUSCLE ALTERATIONS AND ATROPHY PROGRAM

Table 7.3. Achieving Goal 1: Reduce Risk of Loss of Muscle Mass, Strength and Endurance

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Understand muscle protein degradation • Determine slow-to-fast phenotype shift • Discern role of reactive oxygen species • Define loading-sensitive muscle genes													
• Determine how resistive exercise reduces atrophy of human muscle • Determine effects of artificial gravity on muscle • Identify acceptable target levels of risks in humans													
Phase 2: Preliminary Countermeasure Development Research													
• Test activity paradigms that create anabolic state and reduce atrophy in animals and humans • Test pharmacological interventions for muscle degradation and other muscle unloading effects • Study role of antioxidants as nutritional countermeasure strategy													
• Determine whether artificial gravity is a feasible countermeasure to muscle atrophy in humans													
Phase 3: Mature Countermeasure Development Research													
• Develop integrated exercise, nutritional, and pharmacological countermeasure and test in humans													
• Determine whether artificial gravity, in conjunction with the exercise, nutritional, and pharmacological countermeasure above, further reduces muscle atrophy in humans													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of integrated exercise, nutritional, pharmacological countermeasure with artificial gravity													
Phase 5: Operational Implementation of Countermeasure Strategy													

8.0 NEUROBEHAVIORAL & PSYCHOSOCIAL FACTORS

Team Leader: David F. Dinges, Ph.D.
Professor of Psychology in Psychiatry
Director, Unit for Experimental Psychiatry
Department of Psychiatry
University of Pennsylvania School of Medicine
423 Guardian Drive
1013 Blockley Hall
Philadelphia, PA 19104-6021
215-898-9949
215-573-6410 FAX
dinges@mail.med.upenn.edu

8.1 INTRODUCTION

The success of future International Space Station (ISS) and other low-Earth-orbit missions will depend on prevention, identification and mitigation of neurobehavioral and psychosocial risks to crew health, safety and productivity. Astronauts aboard ISS will continue to endure behavioral challenges for longer periods of time than have been experienced thus far in microgravity. Stressors and risk factors include confinement with a small group of people for up to 8 months; isolation from family and friends; complex communications with Earth including two mission control centers; lack of privacy due to habitability constraints; and cognitive and emotional challenges associated with workload, timeline demands, emergencies, and sustained high level performance. There are also risks to group and individual functioning posed by changes in the structure, organization, and nature of such missions if 30-day shuttle missions are used to augment the science capabilities on ISS. Physical illness, interpersonal strife, equipment failure, and the behavioral challenges posed by maintaining countermeasures for other risks (e.g., daily exercise routines) will at times pose risks to group and individual behavioral effectiveness as missions become longer and the ISS structure ages. Differences in language, culture, gender, and work role will also present challenges to crew communication and effectiveness. Without mitigation, these behavioral stressors individually and collectively have the potential to erode cognitive performance; change neuroendocrine, cardiovascular, and immune responses; disrupt appetite, sleep, and other basic regulatory physiology; lead to neuropsychiatric impairment through anxiety and depression; and potentiate serious interpersonal problems among crewmembers and with Earth-based mission support personnel. The Neurobehavioral and Psychosocial Factors area is concerned with the development of novel ways to monitor individual astronaut neurobehavioral functions, as well as group behaviors, and to provide preventive and operational countermeasures to ensure that astronaut behavioral health is maintained during prolonged missions; that the performance of individual astronauts and the flight team are facilitated; and that crew motivation and quality of life are effectively optimized.

8.2 RISKS

The following risks in the Human Behavior and Performance Discipline of the Critical Path Roadmap have been identified (risk number in parentheses):

- Human Performance Failure Because of Poor Psychosocial Adaptation (18)
- Human Performance Failure Because of Neurobehavioral Dysfunction (21)

The Critical Path Roadmap also lists the following two additional risks under Human Behavior and Performance, but neither of these is encompassed by the NSBRI's Neurobehavioral and Psychosocial Factors Team.

- Human Performance Failure Because of Sleep and Circadian Rhythm Problems (19) is subsumed under the Human Performance Factors, Sleep and Chronobiology area of the NSBRI.
- Human Performance Failure Because Of Human System Interface Problems and Ineffective Habitat, Equipment Design, or Inflight Information and Training Systems (20) is not currently represented in the NSBRI areas, but it is a focus of laboratories at NASA Johnson Space Center and NASA Ames Research Center.

8.3 GOALS

The Neurobehavioral and Psychosocial Factors Team has the following goals for its program:

Risk-Based Goals

Goal 1: *Reduce the risk of human performance failure because of poor psychosocial adaptation.*

Goal 2: *Reduce risk of human performance failure because of neurobehavioral dysfunction*

Non Risk-Based Goals

Goal 3: *Develop objective, unobtrusive methods and approaches to monitor stress, neurobehavioral (cognitive, emotional, social) functions and performance capability during missions*

Goal 4: *Develop ways to effectively use communication modalities and contingencies in order to optimally facilitate team performance and problem solving*

Goal 5: *Develop Earth-based applications of technologies for unobtrusively monitoring stress, neurobehavioral functions and performance to help in early objective detection and intervention for cognitive and emotional impairments associated with stressful life events and compromised behavioral health*

Goal 6: *Develop Earth-based applications of communication modalities and contingencies that prevent errors and misunderstandings, and improve group performance and cohesion in demanding environments and safety-sensitive activities.*

Goal 7: *Integrate research and analysis*

8.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The Neurobehavioral and Psychosocial Factors Team was formed in 2000, and funded in 2001, following peer-review of applications for research to mitigate risks to both individual behavioral health (i.e., neurobehavioral functions) and group processes (i.e., psychosocial functions) during space flight. Although each of these areas is relatively broad, they do not encompass all of the risks posed to human behavior and performance. As described above, the Critical Path Roadmap lists two additional risks under Human Behavior and Performance, neither of which is addressed by the Neurobehavioral and Psychosocial Factors Team. These include risks to performance posed by circadian disruption and sleep deprivation on orbit, which are being addressed by the Human Performance Factors, Sleep and Chronobiology Team, and risks to individual and group behavioral functioning posed by limitations due to human-system interface and equipment design, which are not currently being addressed by the NSBRI, but which are a focus at laboratories at NASA JSC and ARC.

As currently configured, the Neurobehavioral and Psychosocial Factors Team is primarily focused on reducing the risks of human performance failure due to poor psychosocial adaptation (Goal 1) or neurobehavioral dysfunction (Goal 2). Specifically, the Team seeks to counter the development of psychosocial risks (Goal 1) manifested through inadequate leadership; interpersonal strife or social alienation (e.g., due to gender, culture or status differences); poor group teamwork; lack of crew coordination in problem solving; ineffective communications within the team or with ground controllers; and loss of crew morale. In a parallel manner, other projects on the Team seek to counter risks to neurobehavioral health (Goal 2) manifested through stress reactions; anxiety; depression; loneliness; anger; and neurocognitive impairments. Unlike some areas of NSBRI research, where there is a single source for the biomedical problem (e.g., microgravity effects on muscle or bone), there are a considerable number of factors in prolonged space flight that could create or contribute to neurobehavioral and psychosocial dysfunctions (e.g., excessively scheduled activities and work requirements, poor physiological adaptation to microgravity; interpersonal strife; perceived risks to health; loneliness for family; inadequate communication with Earth; habitability constraints; radiation). Consequently, the countermeasures being developed through the research by the Neurobehavioral and Psychosocial Factors Team necessarily must cover an array of issues and approaches. The following are the various categories of countermeasures likely to be developed as a result of the research on this team:

(1) Selection criteria for optimal crew cohesion, including culture and gender diversity
(2) Training for group living; training for flight and ground crew optimal relations
(3) Guidelines to optimize communication for crew decisions and problem solving
(4) Technologies for monitoring and early diagnosis of cognitive problems, emotional disturbances, and psychosocial dysfunction
(5) Behavioral treatments for stress; affective disorders; and for resolving team conflicts
(6) Pharmacological treatments for stress; affective disorders and serious neuropsychiatric and neurological reactions
(7) Habitability strategies for privacy; and work strategies for motivation and performance
(8) Support for relaxation and leisure activity for enhancing quality of life
(9) Support for assimilating crews psychosocially and neurobehaviorally after return
(10) Novel countermeasure opportunities identified by NASA and through new scientific efforts
(11) Development of a database on the neurobehavioral and psychosocial effects of countermeasures for other biomedical problems in space flight

Ideally, the risks to individual and group behavioral health created by spaceflight are best dealt with through prevention (e.g., a well-integrated crew with optimal pre-flight training and coordination in effective communication, problem-solving, etc.). Therefore one of the focuses of the projects on the Team is to reduce psychosocial risks (Goal 1) by identifying the psychological and behavioral features of individuals and small groups that result in optimal behavioral effectiveness under ground-based (analog) conditions comparable to space flight. This approach is taken in the Antarctic project directed by JoAnna Wood. Other projects directed by Joe Brady, Judith Orasanu, and James Carter seek to determine ways to prevent or resolve psychosocial miscommunication within teams and between space-bound teams and ground controllers.

While prophylaxis against the development of neurobehavioral and psychosocial dysfunctions is ideal, there is no way to guarantee that preventative strategies alone will suffice. The Team therefore also has a strong focus on early detection and resolution of neurobehavioral problems and psychosocial dysfunction. Especially critical is the need for reliable, objective measures of neurocognitive and emotional states and stress reactions. The projects directed by Phillip Lieberman, David Dinges, and Stephen Kosslyn deal directly with obtaining these measures, thus moving towards achievement of non risk-based Goal 3. The emergence of thought and mood disorders during space flight poses very serious risks not only for the individual's behavioral capability but also for the team's performance. Both neurobehavioral and psychosocial problems have occurred in long-duration space flight—with the latter common enough to have resulted in its rating as among the most serious risks (i.e., Type I) in the Critical Path Roadmap; consequently, there remains an acute need to establish reliable, objective, unobtrusive methods for confirmation of stable cognitive and emotional functioning during prolonged human space flight. Without such information available to an astronaut, it will be difficult to ensure that appropriate neurobehavioral countermeasures (e.g., behavioral and pharmacological) will be deployed in a manner that maintains behavioral health. There must be redundant ways to ensure that neurological, neuropsychiatric, or neurocognitive impairments that develop on orbit (regardless of the cause) are quickly identified and treated before they result in a loss of high level performance capacity in a crew member.

The Team also has another major non risk-based goal of finding optimal ways for crews to use communication modalities and techniques to maintain effective group functioning within a flight crew and between the crew and ground controllers, family, and management (Goal 4). Effective communication can help maintain team performance in the face of adversity, and it is one of the best preventative and operational countermeasures for ensuring strong group psychosocial cohesion and performance. Like the development of novel objective, unobtrusive methods and approaches to monitor stress reactions, cognitive state, mood and performance in individual crew members (Goal 3), the establishment of maximally effective communication techniques for all types of contingencies in space flight (Goal 4) will have significant relevance to a host of Earth-based problems (non-risk Goals 5 and 6, respectively).

The problems addressed in the Neurobehavioral and Psychosocial Factors research area generally focus on developing countermeasures for severe stress reactions, depression, cognitive dysfunction, and conflict resolution during long-duration space travel. The initial strategic research agenda for the Team involves eight ground-based studies and two as yet unfunded flight experiments (in feasibility phase at JSC) that collectively address four thematically interrelated questions: What are the effects of culture, personality, and leadership on performance, stress, and health in isolated groups? What are the major influences on interpersonal actions, communications, and problem solving in small groups? How can affective, neurobehavioral and neurocognitive dysfunction be objectively detected in remote locations? What neurobiological processes of stress and arousal are the optimal targets for behavioral and pharmacological interventions? Six inter-related themes define the range of factors critical for improving crew health and safety and for optimizing performance capability: (1) Biological mechanisms of neurobehavioral dysfunction; (2) Motivation, cognition and performance; (3) Individual factors in selection, training, performance; (4) Pharmacology in space; (5) Team and interpersonal optimization; and (6) Organizational, cultural and management factors.

The current Team projects are briefly described below and Table 8.1 summarizes the risks, countermeasure targets, experimental system, and countermeasure development phases for each project. The projects are equally divided between psychosocial risks (projects directed by Wood, Brady, Orasanu, Carter) and neurobehavioral risks (projects directed by Dinges, Lieberman, Kosslyn, Aston-Jones). The final two projects (Brunner, Kanas) are proposed flight experiments in feasibility assessment at JSC, and as such, they are not yet funded. The Brunner project deals with a neurobehavioral countermeasure question, while the Kanas project deals with a psychosocial countermeasure question.

Wood et al.: Individuals and Cultures in Social Isolation

This psychosocial project seeks to increase understanding of the effects of personality, culture, and group characteristics on both individual and group performance in an extreme environment (Antarctica) that parallels many of the conditions likely to occur in long-duration space missions. Identifying those elements of leadership that maximize crew functioning in extreme environments and increasing our understanding of how individual and group factors affect physical and psychological health under prolonged group isolation in Antarctica can be used in identification and design of optimal flight crew configurations as a preventative countermeasure.

Orasanu et al: Distributed Team Decision Making in Exploration Missions

This psychosocial project examines how team structure and communication medium affect the nature and quality of small team interaction, distributed decision making strategies, and problem solving under a variety of stressful conditions (i.e., time pressure, risk level, information accuracy/completeness). It assesses autonomic nervous system markers and the Specific Affect Coding System technology for detecting when crew interactions and decision-making are degrading. Countermeasure targets include identifying ways to optimize crew problem solving performance during demanding and non-demanding periods.

Brady et al.: Psychosocial Performance Factors in Space Dwelling Groups

This psychosocial project seeks to determine effects of variations in the structure and function of communication channels within and between simulated space-dwelling and Earth-based groups. It addresses the effects on psychosocial performance effectiveness of (1) stressful environmental and behavioral interactions; (2) variations in the appetitive and aversive characteristics of incentive control systems; and (3) selection, training and experience. Countermeasure targets include personality characteristics to optimize crew communication and performance and identifying ways to reinforce the appropriate use of communication strategies for optimal problem solving.

Carter et al.: Designing a Smart Medical System for Psychosocial Support

This project seeks to develop a prototypical smart medical system for neurobehavioral and psychosocial support. The computer-based system will address neurobehavioral issues, including the assessment of affect and suggested interventions, and provide a training module on interpersonal conflict resolution. The system will be developed and evaluated with experienced users and content experts. Countermeasure targets include using the system to help detect (via standardized questions) behavioral dysfunction in individual astronauts and among flight crews and having the computer-based system offer suggestions to crews for remediating problems and conflicts.

Dinges et al.: Optical Computer Recognition of Behavioral Stress

This neurobehavioral project seeks to determine whether a state of the art optical computer recognition algorithm based on facial expression can be developed that will objectively discriminate when subjects are undergoing behavioral stressors and negative affect. It also evaluates the effects of different behavioral stressors on physiological responses, on psychological responses, and on performance responses, and explores the magnitude of stress responses relative to the accuracy of an optically based computer recognition algorithm of the face. Countermeasure targets include using the system to objectively detect significant negative affect and emotional dysfunction in astronauts when verbal and self-report communications are not possible or not reliable in order to recommend behavioral and pharmacological countermeasures for affective disorders.

Kosslyn et al.: Quick Assessment of Basic Cognitive Function
This neurobehavioral project seeks to develop a set of brief performance tasks that will be computerized versions of 11 standard tasks from cognitive psychology, which tap the range of basic cognitive abilities. The performance tasks being developed will be very short versions or variants of tasks that will capture the processing differences indicated by scores on the standard tasks and be designed to be self-administered. Countermeasure targets include using the brief tests to objectively detect cognitive performance deficits in individual astronauts, to alert crewmembers to diminished behavioral capacity and the need for rest or other interventions.

Lieberman et al.: Speech Monitoring, Cognitive and Personality Alterations
This neurobehavioral project seeks to develop a system that will detect cognitive deficits, changes in personality and emotional disturbances by means of acoustic measures of speech. The project utilizes data from studies of speech and behavior of individuals in a space analog (Mt. Everest climbers) as well as patients suffering neurodegenerative diseases (Parkinson's) to develop and verify techniques for analysis of conversational speech for detection of cognitive changes. Countermeasure targets include using the system to objectively detect significant personality changes and emotional dysfunction in astronauts when optical recognition and self-report communications are not possible or not reliable in order to recommend behavioral and pharmacological countermeasures for the personality disturbances.

Aston-Jones et al.: Stress, Performance and Locus Coeruleus
This neurobehavioral project seeks to analyze rodent locus coeruleus (LC) activity during a continuous performance task, to determine the effects of acute and repeated stress on changes in LC function and performance, and to identify pharmacological countermeasures to mitigate stress effects on LC activity and attentional function.

Proposed Flight Experiment—Brunner et al.: Effect of Spaceflight on Pharmacokinetics of Psychotherapeutic Agents. This neurobehavioral project seeks to determine the effects of space flight on the pharmacokinetics, pharmacodynamics and the underlying physiologic processes (gastric motility and drug absorption) of the anti-anxiety drug, lorazepam (Ativan®), and the anti-depressant drug, venlafaxine (Effexor®). Countermeasure targets include studying both oral and intravenous use of both drugs to determine ways to maximize their effectiveness for affective disorders and stress reactions that may develop in prolonged space flight, while minimizing their toxicity.

Proposed Flight Experiment—Kanas et al.: Psychosocial Education (PSE) Training for ISS Missions. This psychosocial project seeks to evaluate the effectiveness in five International Space Station (ISS) crews and their support personnel of a 5-hour, pre-launch Psychosocial Education (PSE) training program designed to reduce tension and displacement of dysphoria to outside personnel and to increase cohesion, leader support, expressiveness and personal growth. Countermeasure targets include determining whether the PSE training program can reduce hostility among astronauts and between astronauts and mission ground support personnel while increasing group satisfaction and behavioral effectiveness.

It has been approximately 18 months since the formation and funding of the Neurobehavioral and Psychosocial Factors Team. The 1-2 hour monthly telecons involving all 10 project Principal Investigators, some co-investigators, and Dr. Al Holland (Chief Psychologist from JSC) have already resulted in excellent integration across the broad scope of the projects and a number of planned collaborations. Table 8.2 shows progress at integration efforts for the team to date (Goal 7).

The research goals of the team have excellent relevance to Earth-based applications (Goals 5 and 6). Neurobehavioral and psychosocial dysfunctions characterize a wide range of human conditions, from mood disorders to neurological conditions, to cultural biases and hostilities. Progress in developing techniques and methods for improving objective detection of stress reactions in space flight should be of value in the many contexts on Earth in which there is a need to know how much distress a person is experiencing in order to know when to intervene and with what modality (e.g., evaluation of victims, emergency workers, military personnel, etc.; Goal 5). Similarly, finding ways to enhance effective communication and group problem solving could help in a wide range of contexts in which high level performance and problem solving are essential (e.g., emergency management, power plants, transportation systems, etc.; Goal 6). Finding ways to reduce neurobehavioral and psychosocial risks could also be of value to those treating patients who have cognitive and emotional impairments associated with neuropsychiatric and neurological disorders.

Although the Neurobehavioral and Psychosocial Factors Team does address a range of Critical Path questions that must be answered in order to maintain astronaut behavioral health and group effectiveness in long-duration flights, significant gaps in the program do remain due to current funding limitations. The External Advisory Council (EAC) of the NSBRI rated the current research program of the Neurobehavioral and Psychosocial Team as "very good" in its initial evaluation in September 2000 but expressed concerns regarding the potential limitations of some of the empirical approaches and recommended additional funding be set aside to solicit proposals in those areas identified as gaps in the current team. These views were expressed again in the February 2001 review by the EAC, in which it concluded that although the Team has "great potential," it was also "very diverse," and that "there exists a level of complexity that could easily require orders of magnitude additional funding to accomplish their goals." At that time the EAC went on to state—consistent with the Critical Path Roadmap ranking of risk severity—"the problems addressed by this team are among the most important for long term space travel—attempting to develop countermeasures for severe stress reactions, depression, cognitive dysfunction, and conflict resolution," and that the team could "benefit from support for new methodologies and technologies (e.g., functional magnetic resonance imaging [fMRI], mass resonance spectroscopy [MRS], novel tests of cognitive function, and virtual reality)." Accordingly, if the team gaps are to be closed, in addition to continuing to support the current research projects, the NSBRI needs to support research that addresses the following four questions in the next five years.

> What behaviors, experiences, intellectual capacities, performance capabilities, personality traits, demographic, interpersonal and leadership styles of crewmembers, as well as

gender, age and ethnicity combinations, can be identified during the selection process and be used to select and assemble the best teams for long duration missions?

1. How can novel neuroscience technologies (e.g., neuroimaging via fMRI, MRS, positron emission tomography [PET], near-infrared [NIR] optical imaging; and transcranial magnetic stimulation [TMS]) be used to develop countermeasures for the psychosocial and neurobehavioral effects of prolonged space flight?

2. How can novel behavioral methodologies (e.g., virtual reality; prolonged behavioral monitoring and experimental manipulation of small group microsocieties in isolation and in tandem) be used to develop countermeasures for the psychosocial and neurobehavioral effects of prolonged space flight?

3. What are the effects on neurobehavioral health and psychosocial functioning of the countermeasures devised for other vital physiological systems (e.g., diet, exercise, light exposure for circadian entrainment, and pharmacotherapies used as countermeasures for the effects of radiation, cardiovascular, neurovestibular, bone loss, etc.)?

Tables 8.3a and 8.3b provide projected timelines for achieving Risk Goals 1 and 2, and Non-Risk Goals 3 and 4. They also presume that in the near future, new projects that address the four critical gap questions described in the preceding paragraph will be supported. Table 8.3a deals with countermeasure development to reduce the serious risks posed by poor psychosocial adaptation in space flight, and Table 8.3b deals with countermeasure development to reduce the risks posed by neurobehavioral dysfunction in prolonged space flight.

8.5 OBJECTIVES AND STRATEGIC ACTIVITIES

The objectives underlying each goal are presented below, along with strategic activities that will be used to achieve the goals and objectives.

Goal 1: *Reduce the risk of human performance failure because of poor psychosocial adaptation.*

Objective 1A. Assess risk and target level of acceptable risk

- Determining the full range of psychosocial stressors in space flight continues to be a priority in order to mitigate these stressors. Various team members (Wood, Brady, Kanas, Carter, Buckey, Dinges) have been acquiring information from published reports, JSC personnel, and former and current astronauts on the sources of psychosocial stress.

Objective 1B. Determine mechanisms

- Complete projects that seek to identify predictors of vulnerability to poor psychosocial adaptation environments (Wood, Brady, Orasanu, and Carter projects).
- Complete projects that seek to determine the effects of contingencies on use of communication channels (Brady and Orasanu projects).
- Complete work on establishing astronaut-guided content for a prototypical computerized self-diagnostic system for conflict management (Carter and Buckey project).
- Complete project that seeks to identify interrelationships among social context, cultures, and health in an analog environment (Wood project in Antarctica).

- Complete projects that seek to identify selection criteria for optimizing effective leadership and group cohesion (Wood project).

Objective 1C. Develop countermeasures

- Complete projects that establish effects of training, incentives and experience on communication (Brady and Orasanu projects).Complete project on prototypical computerized self-help system for psychosocial support (e.g., simulated encounters with "virtual crew members") and assessment (adaptation of an existing self-guided psychiatric assessment) (Carter and Buckey project).Complete projects on effects of stressors, gender and cultural differences on problem solving (Orasanu, Wood, and Brady projects).
- Complete projects seeking to develop training to prevent poor psychosocial adaptation (Brady, and Orasanu projects).
- Complete projects seeking to develop a hierarchy of ways to maximize group communication, decision making and problem solving (Orasanu and Brady projects).
- Complete projects that seek to develop insights into factors relevant to training for living well in confinement, away from family (Wood and Kanas projects).
- Complete the development of technologies for early detection of psychosocial dysfunction (Wood, Orasanu, and Brady project).Complete projects that seek to identify optimal interventions for preventing and resolving interpersonal conflicts (Carter and Kanas projects).
- Complete projects that seek to identify techniques to maintain effective flight and ground crew relations (Brady, Orasanu and Kanas projects).
- Continue and expand projects that measure behaviors, experiences, intellectual capacities, performance capabilities, personality traits, demographic, interpersonal and leadership styles of crewmembers, as well as gender, age and ethnicity combinations, that could be used in identification during the selection process to select and assemble the best teams for long duration missions.
- Initiate studies of novel behavioral methodologies (e.g., virtual reality; prolonged behavioral monitoring and experimental manipulation of small group microsocieties in isolation and in tandem) to develop new countermeasures for the psychosocial effects of prolonged space flight.
- Initiate projects that seek to develop strategies for privacy, relaxation, novelty, leisure, and re-acclimation.
- Initiate projects that seek to identify effects on psychosocial functions of novel countermeasures for other risks (e.g., muscle, bone, radiation, neurovestibular, sleep and chronobiology). (This initiative will depend upon the rate at which new and effective countermeasures come on line from other areas. The goal here is to ensure they do not have adverse effects on communication and other interpersonal functions.)

Goal 2: *Reduce risk of human performance failure because of neurobehavioral dysfunction*

Objective 2A. Assess risk and target level of acceptable risk

- Determining the full range of neurobehavioral stressors in space flight continues to be a priority in order to mitigate these stressors. Various team members (Wood, Brady, Kanas, Carter, Buckey, Dinges) have been acquiring information from published reports, JSC personnel, and former and current astronauts on the sources of neurobehavioral stress.

Objective 2B. Determine mechanisms

- Complete the project that seeks to determine the effects of stress and attentional performance demands on the locus coeruleus to identify novel pharmacological approaches to maintaining performance in the face of high stress (Aston-Jones project).
- Complete projects that seek to identify predictors of vulnerability to cognitive and/or affective dysfunction under stress in analog environments (Wood and Lieberman projects).
- Complete the project on prototypical computerized self-help system for assessment of depression (adaptation of an existing self-guided psychiatric assessment) (Carter and Buckey project).
- Complete the project that seeks to determine if facial expressions reveal physiological stress under performance demands (Dinges project).
- Complete the project that seeks to determine the validity of brief versions of cognitive tests (Kosslyn project).
- Complete the project that seeks to determine if voice-onset time measures cognitive functions (Lieberman project).
- Complete projects that seek to develop technologies that objectively and reliably monitor affective responses (Dinges, Carter, Lieberman and Orasanu projects).
- Complete projects that seek to develop technologies that objectively and reliably monitor neurocognitive responses (Lieberman, Kosslyn, and Dinges projects).
- Initiate and complete the project that seeks to determine pharmacokinetics in space flight (Brunner project).
- Complete projects that seek to identify promising pharmacological countermeasures for stress and mood reactions in space flight (Aston-Jones and Brunner projects).

Objective 2C. Develop countermeasures

- Complete project on prototypical computerized self-help system for assessment of depression and recommended intervention (adaptation of an existing self-guided psychiatric assessment) (Carter and Buckey project).Complete project on development and test of accuracy of optical computer recognition of facial expression of stress (Dinges project).Complete project on establishment of norms and sensitivity of brief cognitive tasks to neurocognitive abilities (Kosslyn project).Complete project on determining whether analysis of common speech can detect cognitive and personality changes in hypoxia climbers on Everest (Lieberman project).
- Initiate project on pharmacological approaches to adverse neurobehavioral reactions (mood, cognition) in space flight.
- Initiate project on behavioral approaches to adverse neurobehavioral reactions (mood, cognition) in space flight.
- Initiate projects to identify adverse CNS / ANS effects from radiation and countermeasures from other areas. (This initiative will depend upon the rate at which new and effective countermeasures come on line from other areas. The goal here is to ensure they do not have adverse effects on cognitive and affective functions. An animal project is underway on the Radiation team (Vasquez project) to evaluate the neurobiological and neurobehavioral effects of simulated space radiation. Ultimately, sensitive neurobehavioral tests will be needed on astronauts if adverse effects are found in rodent models.)
- Initiate projects using novel neuroscience technologies (e.g., neuroimaging via fMRI, MRS, PET, NIR; transcranial magnetic stimulation) to develop countermeasures for the neurobehavioral effects of prolonged space flight.

Goal 3: *Develop objective, unobtrusive methods and approaches to monitor stress, neurobehavioral (cognitive, emotional, social) functions and performance capability during missions.*

Objective 3A. Develop monitoring methods

- Complete projects that seek to determine if objective, unobtrusive measures of facial expressions and speech analysis can detect cognitive, dysfunction and physiological distress during work demands (Dinges and Lieberman projects).
- Complete projects that seek to determine the validity of brief versions of cognitive tests to detect changes in performance capability (Kosslyn project).
- Complete projects that seek to determine whether technologies can be developed for objective detection of psychosocial dysfunction (Wood, Orasanu, and Brady projects).

Objective 3B. Establish best approaches to interpret monitored data

- Initiate projects that study how to best use reliable objective measures of cognitive, affective and psychosocial function/dysfunction to deliver maximally effective countermeasures.

Goal 4: *Develop ways to effectively use communication modalities and contingencies in order to optimally facilitate team performance and problem solving.*

Objective 4A. Enhance effective use of communication systems

- Complete projects that seek to determine the effects of contingencies, stress, modality options and time pressure on effectiveness of communications in problem solving and group performance (Brady and Orasanu projects).

Objective 4B. Establish best approaches to use of communication systems

- Initiate projects that study how to best use communication systems to deal with different levels of performance stressors.

Goal 5: *Develop Earth-based applications of technologies for unobtrusively monitoring stress, neurobehavioral functions and performance to help in early objective detection and intervention for cognitive and emotional impairments associated with stressful life events and compromised behavioral health.*

Objective 5A. Encourage transition of technologies to Earth-based needs.

- Identify applications for monitoring behavioral states in space flight to Earth-based needs. Because neurobehavioral and psychosocial problems are common on Earth (unlike microgravity, which only occurs off planet), the Earth-based applications of technologies for unobtrusively monitoring stress, neurobehavioral functions and performance have considerable potential to help in early objective detection and intervention for cognitive and emotional impairments associated with stressful life events and compromised behavioral health.
- Identification of partners for Earth-based applications of objective technology for cognitive and emotional functions will be undertaken by seeking funding through other interested Federal (e.g., NIH) and private agencies that sponsor research on neuropsychiatric and neurological disorders.

Goal 6: *Develop Earth-based applications of communication modalities and contingencies that prevent errors and misunderstandings and improve group performance and cohesion in demanding environments and safety-sensitive activities.*

Objective 6A. Encourage transition of communication systems to Earth-based needs.

- Finding ways to enhance effective communication and group problem solving could help in a wide range of Earth-based contexts in which high level performance and problem solving are essential (e.g., emergency management, power plants, transportation systems, large scale construction, etc.).
- Identification of partners for Earth-based applications of communication technology and systems for effective team performance will be undertaken by seeking funding through other interested Federal (e.g., DOD) and private agencies that sponsor research on ways to maintaining group functioning in a complex and stressful environment.

Goal 7: *Integrate research and analysis*

Objective 7A. Integrate research within the Neurobehavioral and Psychosocial Factors Team.

- Continue current integration efforts among team PIs, co-investigators and key personnel at JSC as summarized in Table 8.2.

Objective 7B. Integrate research with other teams.

- Continue to build collaborative between the Team projects and projects on other teams, especially other teams with a focus on central nervous system (CNS) functions (e.g., Neurovestibular Team; Radiation Team)
- Coordinate with Human Performance Factors, Sleep and Chronobiology (HPFSC) Team regarding the effects of sleep loss, circadian displacement, and countermeasures for these factors on cognition, mood and social interaction.
- Coordinate with the Neurovestibular Adaptation Team regarding the effects of space motion sickness and countermeasures for it on cognition, mood and social interaction.
- Coordinate with the Nutrition and Rehabilitation Team regarding the potential for nutrition to enhance cognitive, affective and psychosocial functioning as well as the need for neurobehavioral and psychosocial rehabilitation following flight.
- Coordinate with the Smart Medical Systems Team regarding the potential for neuroimaging to enhance objective detection of neurocognitive and neuroaffective dysfunctions in space flight.
- Coordinate with the Immune Team regarding the role of psychosocial and neurobehavioral distress in endocrine and immune responses and the potential of using immune markers as indices of the chronic stress being experienced.
- Coordinate with the Radiation Team regarding the effects of space radiation on neurobehavioral functions in animals as a prelude to assessing effects in humans.

Objective 7C. Integrate research with investigators not formally associated with the NSBRI.

- Although most of the projects on the Neurobehavioral and Psychosocial Factors Team involve collaborations among leading investigators from different schools, universities, companies, and Federal agencies (e.g., projects by Wood, Brady, Orasanu, Dinges, and Carter), Team PIs continue to seek out expertise from scientists not formally part of the NSBRI who are experts in many of the areas under study. In this regard, Dr. Wood has recently begun collaboration with Dr. John Cacioppo, the foremost investigator of social biology, and Dr. Norbert Kraft (National Space Agency of Japan and Commander of a long-duration isolation study) has joined Dr. Orasanu's project.

8.6 SUMMARY

The relatively recent development of the Neurobehavioral and Psychosocial Factors Team reflects the recent categorization of these factors as Type I (severe) risks during prolonged human space flight and the need for novel, evidenced-based approaches to mitigate these risks to ensure the safety and well being of the flight crew and the success of the mission. The Team's current configuration serves well the breadth of the neurobehavioral and psychosocial areas with four ground-based projects in each area, and two as yet unfunded flight projects (one in each area, and both undergoing feasibility review). While the breadth of the research underway is appropriate for the Team's mandate, the current limited number of funded projects restricts experimental depth in any one area. That is, the answers to most of the Critical Path questions for this Team rely on single experiments. Therefore, care in experimental execution and replication of results will be vital to ensure their generalizability to space flight.

Within the next 2-3 years the projects should have sufficient data to determine the viability of some of the basic information and technologies being investigated and begin producing viable countermeasure strategies. Unfortunately this achievement on its own will likely not diminish the controversy that at times surrounds this area-- perhaps more so than other areas of space biomedicine, the neurobehavioral and psychosocial area tends to engender pro-con debate about any one countermeasure approach over another when seeking to mitigate the vulnerability of individuals and groups to the psychological, behavioral, and social effects of prolonged space flight. Examples of the contrasting options for countermeasures include: 1) Whether to seek to identify factors relevant to select-in versus select-out criteria; 2) Whether to investigate subjective versus objective techniques for assessing mood, stress, cognitive capability, and psychosocial adaptation; and 3) Whether to study behavioral versus pharmacological countermeasures.

In order to minimize the impact of these traditionally controversial issues, the Team approach has been and will continue to be to obtain the best possible data sets and reliable information and report these findings. We believe that some of the novel perspectives and approaches being attempted in the current team projects will yield new opportunities for countermeasure development. Within 5 years we should be able to have at least one and likely two objective techniques that will be ready for mature countermeasure development (Tables 3a and 3b) in the areas of objective monitoring of neurobehavioral and psychosocial functioning. Similarly, we should be well along in developing priorities for optimal communication techniques under both low and high performance demands. Finally, we should have a clearer idea of the individual characteristics and group dynamic factors that make up optimal behavioral capability under adverse circumstances.

The figure below (Figure 8.1) illustrates the major research themes and anticipated countermeasure types of the current projects and our view that they form critical complementary components to the maintenance of behavioral and psychosocial health and capability during long duration missions. We appreciate the opportunity to work on such challenging scientific questions.

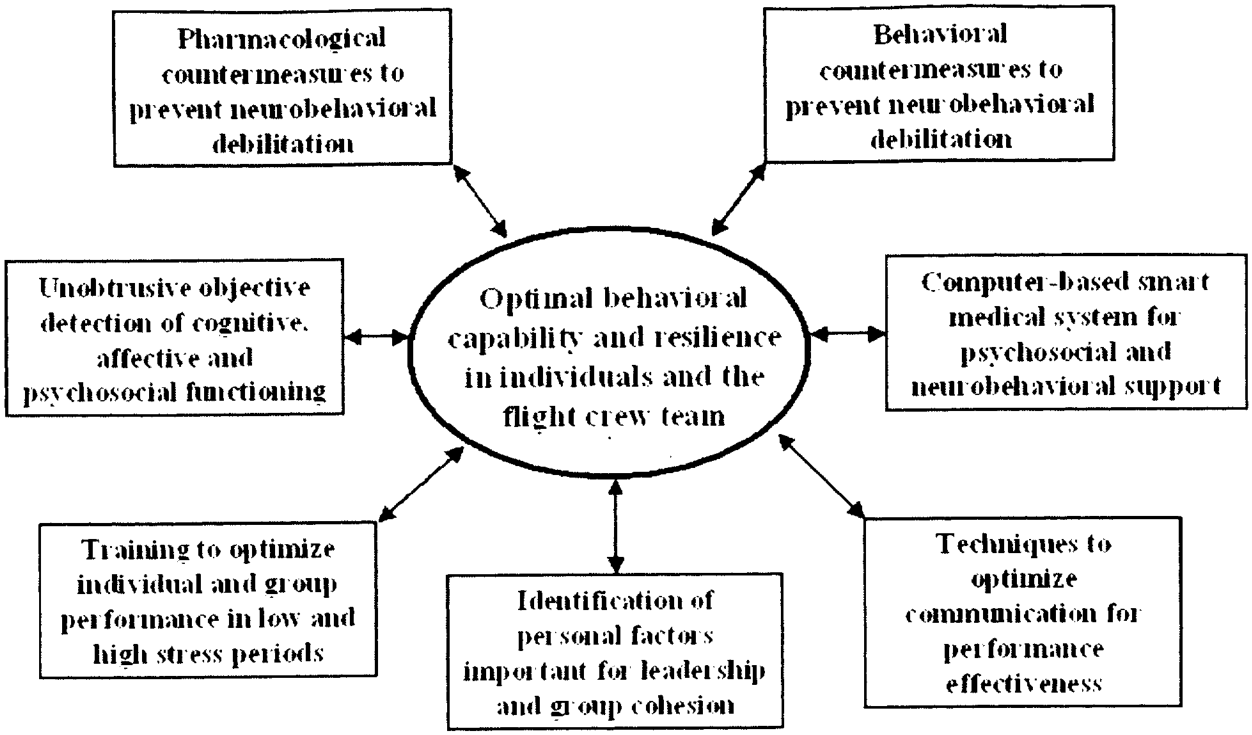


Figure 8.1. Major Research Themes and Currently Anticipated Countermeasure Types.

National Space Biomedical Research Institute
NEUROBEHAVIORAL AND PSYCHOSOCIAL FACTORS PROGRAM

Table 8.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
ASTON-JONES/ Stress, Performance and Locus Coeruleus	Neurobehavioral dysfunction	Pharmacological agents	Stress and drug effects on LC and performance in rats	Understand stress effects on locus coeruleus		
BRADY/Psychosocial Performance Factors in Space Dwelling Groups	Poor psychosocial adaptation	Training, Environmental manipulation	Humans performing computerized simulation of mission	Determine effects of varying functions of communication channels	Test effects of training, incentives & experience on communication	
CARTER/Designing a Smart Medical System for Psychosocial Support	Psychosocial and neurobehavioral dysfunction	Monitoring & diagnosis procedures; Other (suggestions for treating problem)	Humans developing content from expert & astronaut input	Establish content for prototypical computerized self-diagnostic system	Develop computerized self-help system for psychosocial support	
DINGES/Optical Computer Recognition of Behavioral Stress	Neurobehavioral dysfunction	Monitoring and diagnosis procedures	Humans undergoing high- and low-stress performance	Determine if facial expressions reveal physiological stress	Develop & test optical computer recognition of stress expressions	
KOSSLYN/Quick Assessment of Basic Cognitive Function	Neurobehavioral dysfunction	Monitoring and Diagnosis Procedures	Humans performing on communication simulation	Determine validity of brief versions of cognitive tests	Establish norms & sensitivity of brief to relevant stressors	
LIEBERMAN/Speech Monitoring, Cognitive & Personality Alterations	Neurobehavioral dysfunction	Monitoring and Diagnosis Procedures	Speech evaluations in humans on Everest & Parkinson's patients	Determine if voice-onset time measures cognitive functions	Test voice analysis to detect cognitive and personality changes	
ORASANU/Distributed Team Decision Making in Exploration Missions	Poor psychosocial adaptation	Training, Other (crew selection)	Humans performing computerized simulation of tasks	Develop technology to monitor affective responses	Establish effects of stressors & gender on problem solving	
WOOD/Individuals and Cultures in Social Isolation	Poor psychosocial adaptation and neurobehavioral dysfunction	Training, Other (crew selection)	Humans wintering over in Antarctica	Identify inter-relationships among social context, cultures, and health		
***BRUNNER**/Effect of Spaceflight on Pharmacokinetics of Psychotherapeutic Agents	Neurobehavioral dysfunction	Pharmacological agents	Humans in space flight	Determine pharmacokinetics of drugs in space flight		
***KANAS**/Psychosocial Education (PSE) Training for ISS Missions	Poor psychosocial adaptation .	Training	Humans in space flight		Develop training to prevent poor psychosocial adaptation	Test effectiveness of psychosocial education training in space flight

***Not yet funded; in feasibility phase evaluation at JSC.**

National Space Biomedical Research Institute
NEUROBEHAVIORAL AND PSYCHOSOCIAL PROGRAM

Table 8.2. Integration Activities*

	ASTON-JONES Stress and locus coeruleus	BRADY Psychosocial performance	CARTER Computerized psychosocial support	DINGES Optical computer recognition	KOSSLYN Quick assessment of cog. functioins	LIEBERMAN Speech monitoring	ORASANU Distributed team decision making	WOOD Social isolation / Antarctic
Internal Communication	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Annual team meeting; NSBRI Retreat; Biannual NASA meeting; National scientific meetings
Integrated Experiment Development		Complements communication variables in ORASANU project		Assess potential of optical computer recognition for detection of fatigue (with HPFSC Team)			Complements communication variables in BRADY project	
Sample Sharing		Using same psychosocial scales (e.g., alexithymia scale)		Using same psychosocial scales (e.g., alexithymia scale)	Using same psychosocial scales (e.g., alexithymia scale)		Using same psychosocial scales (e.g., alexithymia scale)	
Synergistic Studies of Opportunity				Acquiring speech data in project for LIEBERMAN to analyze		Analyzing speech data from low and high stressor conditions in DINGES		Developing collaboration with Immune project by SHEARER
Development of Computer Model of Integrated Human Function								To be determined--under discussion with BALDWIN

***Although not yet funded, space flight experiments proposed by Brunner (Pharmacokinetics in space flight) and Kanas (PSE training for space flight) are included in monthly Team telecons and annual meetings.**

National Space Biomedical Research Institute

NEUROBEHAVIORAL AND PSYCHOLSOCIAL PROGRAM

Table 8.3a. Achieving Goals 1 and 4: Reduce Risk of Human Performance Failure Because of Poor Psychosocial Adaptation

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Identify psychosocial stressors that occur during prolonged space flight													
Phase 1: Focused Mechanistic Research													
• Identify predictors of vulnerability to poor psychosocial adaptation • Determine effects of contingencies on use of communication channels • Establish content for prototypical computerized self-diagnostic system • Identify interrelationships among social context, cultures, and health													
• Identify selection criteria for optimizing group cohesion													
Phase 2: Preliminary Countermeasure Development Research													
• Establish effects of training, incentives and experience on communication • Develop prototypical computerized self-help system for psychosocial support • Establish effects of stressors, gender and cultural differences on problem solving													
• Develop training to prevent poor psychosocial adaptation • Develop hierarchy of ways to maximize group communication, decision making and problem solving • Develop training for living well in confinement, away from family • Develop technologies for early detection of psychosocial dysfunction • Identify optimal interventions for preventing and resolving interpersonal conflicts • Identify techniques to maintain effective flight and ground crew relations • Develop strategies for privacy, relaxation, novelty, leisure, and re-acclimation • Identify effects on psychosocial functions of novel countermeasures for other risks (e.g., muscle, bone, radiation, neurovestibular, sleep & chronobiology)													
Phase 3: Mature Countermeasure Development Research													
• Develop best select-in criteria for optimizing group cohesion (culture, gender) • Develop best training techniques for crews to optimize group cohesion • Develop optimal communication protocols • Develop full computerized self-help system for psychosocial support													

Table 8.3a (continued). Achieving Goals 1 and 4: Reduce Risk of Human Performance Failure Because of Poor Psychosocial Adaptation

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 4: Countermeasure Evaluation & Validation													
• Test best select-in criteria for optimizing group cohesion (culture, gender) • Test best training techniques for crews to optimize group cohesion while living in confinement • Test optimal communication protocols • Test techniques to maintain effective flight and ground crew relations • Test full computerized self-help system for psychosocial support and problem solving • Test techniques for early detection of psychosocial dysfunction • Test strategies for optimizing privacy, relaxation, novelty, leisure, and re-acclimation													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 8.3b. Achieving Goals 2 and 3: Reduce Risk of Human Performance Failure Because of Neurobehavioral Dysfunction

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Identify neurobehavioral stressors that occur during prolonged space flight													
Phase 1: Focused Mechanistic Research													
• Understand stress effects on locus coeruleus and attention • Identify predictors of vulnerability to cognitive and/or affective dysfunction under stress in analog environments • Establish content for prototypical computerized self-diagnostic system • Determine if facial expressions reveal physiological stress • Determine validity of brief versions of cognitive tests • Determine if voice-onset time measures cognitive functions • Develop technology to monitor affective responses													
• Understand pharmacokinetics in space flight • Identify promising pharmacological countermeasures for stress and mood reactions in space flight													
Phase 2: Preliminary Countermeasure Development Research													
• Develop prototypical computerized self-help system for neurobehavioral diagnosis and supportDevelop and test optical computer recognition of facial expression of stressEstablish norms and sensitivity of brief cognitive tasksTest voice analysis to detect cognitive and personality changes													
• Establish and test pharmacological approaches to adverse neurobehavioral reactions (mood, cognition) in space flight • Establish and test behavioral approaches to adverse neurobehavioral reactions (mood, cognition) in space flight • Identify adverse CNS / ANS effects from radiation and countermeasures from other areas													

Table 8.3b (continued). Achieving Goals 2 and 3: Reduce Risk of Human Performance Failure Because of Neurobehavioral Dysfunction

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 3: Mature Countermeasure Development Research													
• Develop full computerized self-help system for neurobehavioral diagnosis and support • Develop best pharmacological approaches to adverse neurobehavioral reactions (mood, cognition) in space flight • Develop best behavioral approaches to adverse neurobehavioral reactions (mood, cognition) in space flight													
• Develop best predictors of vulnerability to cognitive and/or affective dysfunction • Develop best objective (minimally obtrusive, maximally reliable) technique for remote detection of cognitive dysfunction • Develop best objective (minimally obtrusive) technique for remote detection of affective dysfunction													
Phase 4: Countermeasure Evaluation & Validation													
• Test full computerized self-help system for neurobehavioral diagnosis and support • Test best pharmacological approaches to adverse neurobehavioral reactions (mood, cognition) in space flight • Test best behavioral approaches to adverse neurobehavioral reactions (mood, cognition) in space flight • Test best predictors of vulnerability to cognitive and/or affective dysfunction • Test best objective (minimally obtrusive, maximally reliable) technique for remote detection of cognitive dysfunctionTest best objective (minimally obtrusive) technique for remote detection of affective dysfunction													
Phase 5: Operational Implementation of Countermeasure Strategy													

9.0 NEUROVESTIBULAR ADAPTATION

Team Leader: Charles M. Oman, Ph.D.
Senior Research Engineer
Department of Aeronautics and Astronautics
Director, Man-Vehicle Laboratory
Center for Space Research
Massachusetts Institute of Technology
77 Massachusetts Avenue, Rm. 37-219
Cambridge, MA 02139-4301
617-253-7508
617-258-8111 FAX
cmo@space.mit.edu

9.1 INTRODUCTION

The most overt change affecting an astronaut in space flight is the immediate response of the neurovestibular system to changes in gravity. NSBRI's neurovestibular adaptation research program supports research aimed at developing scientifically-based countermeasures against the vestibular problems associated with space flight: spatial disorientation, space motion sickness, oculomotor deficits, postflight postural instability and gait ataxia. Problems typically arise first when astronauts transition from 1-G to 0-G, unfortunately at a time when their physical and cognitive performance is often critical for mission success and safety. Postflight problems have generally been more severe after 3-5 month Mir and ISS flights than on 1-2 week Shuttle missions, showing that some components of vestibular adaptation to 0-G take place over time scales of months, rather than weeks. Operationally significant vestibular problems are also anticipated when astronauts make the transition from 0-G to partial G, or from 0-G to an artificial gravity environment. During the Shuttle/Spacelab era (1980s and 90s), many of NASA's major ground and flight neurovestibular experiments addressed basic issues related to the effects of 0-G vestibular reflexes. NSBRI research is designed to develop countermeasures for a broader set of risks identified by the NASA Critical Path project. In 1997, five principal neurovestibular risk areas were identified (criticalpath.jsc.nasa.gov/main.asp). Since that time, additional information has become available from long duration Shuttle, Mir and ISS flights. Because of NASA's shift in emphasis from exploration (e.g. Mars) missions to long duration ISS long duration flights, the NSBRI neurovestibular team reexamined its critical path risks. In collaboration with colleagues from the JSC Neurophysiology lab, and the JSC Medical Operations branch, the risks were updated and regrouped into seven areas which also define the spaceflight related long term goals of the program. In priority order, these are:

9.2 RISKS

1. Vertigo on reentry and landing, triggered by sudden vehicle accelerations or head movements in a now-unfamiliar gravitational environment, can cause involuntary eye movements (nystagmus), difficulty reading instruments and orientation illusions. Together, these can cause misperception of the attitude, velocity, and acceleration of the vehicle. In critical situations, such as during landing they can lead to involuntary control movements and control errors, resulting in faster and harder landings and potentially in the loss of the vehicle and crew.

2. Acute space motion sickness on insertion into microgravity can produce nausea, vomiting, loss of concentration and inability to follow procedures. The sickness, which can sometimes last for several days, could cause catastrophic failure of EVA suit life support systems and render space suits unreusable, were sickness to occur during EVA. Consideration of this has caused deferment of non-emergency EVAs and Shuttle rendezvous and docking to the fourth day of flight, which has an important impact on Shuttle procedures and crew productivity.

3. Postlanding imbalance, instability, vertigo and orthostatic hypotension have made some crewmembers unable to stand up or walk unassisted after medium and long-duration flights. Associated with this, there is decreased tone in postural muscles, impaired locomotor coordination, instability of vision, difficulty turning corners or negotiating stairs. Any or all of these compromises the ability of crewmembers to egress from the Shuttle rapidly. Potentially, this could lead to injury or death of crewmembers in the event of an emergency or failed landing.

4. Inflight spatial disorientation and frame of reference problems, triggered by 3D body movements as well as inversion and visual reorientation illusions, causing reaching errors and spatial memory problems, difficulty locating emergency egress routes, EVA height vertigo, and operational difficulties during docking and remote manipulation of payloads that could cause dangerous collisions.

5. Chronic space motion symptoms resulting in decreased crew work capacity. Symptoms include fatigue, "space stupids", decreased vigilance, loss of motivation, irritability, gastrointestinal stasis, anorexia, dehydration, weight loss, side effects of anti-motion sickness drugs and changes in sleep-wake cycle.

6. Artificial Gravity related disorientation, nausea, vomiting, and loss of coordination. Symptoms occur in short and medium radius artificial gravity environments due to Coriolis effects on the vestibular semicircular canals, and biomechanical Coriolis forces which disturb normal limb movements. Symptoms necessitate movement restrictions which will compromise crew productivity.

7. Peripheral and central vestibular function changes due to exposure to microgravity, that may contribute to orthostatic intolerance on landing. It is also conceivable that changes in otolith or hair cell function occur after very long duration exposure to weightlessness, or exposure to radiation and environmental ototoxins (e.g. CO) that could cause permanent impairment of balance function. If so, these changes could cause loss of crew productivity when landing on a distant planet or crew injury or death during emergency egress.

9.3 GOALS

The ultimate goal of NSBRI's neurovestibular research program is to develop countermeasures that ultimately will to allow crewmembers to: avoid disorientation, meet the physical requirements of emergencies, treat motion sickness without side effects, and safely control vehicles and systems.

Risk #1 (Vertigo on Rentry and Landing) is believed to represent a serious ("Class I") risk on long duration missions. Though Shuttle pilots are aware of the problem, and voluntarily limit head movements, vehicle accelerations cannot be avoided. Vertigo and nystagmus cause well known difficulties reading flight instruments. Reentry vertigo has been recognized since the earliest days of the Shuttle program, but its operational significance has probably been masked by the traditional "can do" attitude of military-trained pilots who believe they can concentrate on their instruments and "fly through" episodes of vertigo. Flight surgeons report that vestibular disturbances are more severe after long flights. Although the landing vertigo problem has been manageable on 1-2 week flights, it is likely to become a significant problem if shuttle mission duration is extended to 3-4 weeks. McClusky, Clark, Stepaniak 2001 (NASA JSC SD2) found shuttle landing flight technical error (height over threshold, and distance, vertical velocity, and airspeed speed errors at touchdown on 9 missions) correlated with intensity of postlfight neurologic symptoms (9 missions, 8 subjects). Vertigo on short final, flare, or touchdown could cause loss of vehicle control. Vestibular and related somatosensory factors may have contributed to pilot induced oscillations on some Shuttle landings. Additional quantitative data on head movements, vehicle accelerations, and flight technical error are needed. The Shuttle does not have full autoland capability at all likely landing sites. Countermeasures to pre-adapt crewmembers or display/flight control changes and training procedures which reduce disorientation and flight technical error will be required. Providing Shuttle autoland capability does not completely resolve the problem, since pilots must still have sufficient visual acuity to monitor displays used in landing.

Risk #2 (Acute space motion sickness) also represents a Class I risk during EVA, since the Shuttle space suit ("EMU") has no containment bag. In 1980s, Hamilton Standard (P. Heimlich) noted vomitus in the LiOH canister creates exothermic reaction, and shuts down EMU primary vent loop. Frozen vomitus in secondary vent nozzle could shut down the secondary vent loop, leaving only a few minutes of residual in suit O2 remaining. Vomitus is biologically active, so if there is an episode, the suit cannot be reused unless completely refurbished on the ground. Vomitus volume could be somewhat reduced by eating/drinking less frequently, but this is often inappropriate. Modifying the suit to include a vomitus containment receptacle has been considered, but is expensive and may be impractical. Risk is serious if emergency EVA is required. Risk exposure currently is currently reduced by prohibition of non-emergency EVAs before flight day 3. One in-suit vomiting episode has occurred, but before actual EVA began. Acute vomiting episodes – even during IVA – are momentarily disabling. Drug or behavioral countermeasures which reliably and quickly reduce probability of vomiting are needed. Feasibility of EMU modifications to reduce susceptibility or provide containment should be reinvestigated. Opening the early-mission window for EVA by 1-2 days will add useful flexibility in mission planning, and improve overall STS-ISS productivity.

Risk #3 (Postlanding imbalance, instablility, vertigo) remain a concern for all Shuttle crewmembers in the event an emergency requires rapid egress from the vehicle. Although recent cardiovascular and neuromuscular countermeasures have been successful on ISS, neurovestibular balance problems remain a problem for some individuals. Many crew tested cannot run 1000 ft on a treadmill. Countermeasures are needed to pre-adapt returning crewmembers, to mitigate the risk of injury resulting from an accidental fall. It is also important to understand whether there is a vestibular contribution to postflight orthostatic hypotension.

Risk #4 (Inflight spatial disorientation and frame of reference problems) are more significant inside space stations (Mir, ISS) than on Shuttle, due to the complex 3D interior architecture (Richards, et al, 2001), which provides multiple visual frames of reference, and causes visual reorientation illusions. Mental rotation and frame of reference problems have been noted in debriefs of some crewmembers doing ISS robotic ops. Such problems complicated the Mir crew's response to the collison with the Progress spacecraft in 1997. Shuttle crewmembers visiting Mir easily became lost. Mir and ISS crewmembers occasionally report height vertigo when the Earth is in their lower visual field, and for some the experience has been momentarily disabling. The lack of visual references cues during the dark half of each orbit has caused disorientation and concern among some ISS EVA crew. Potential countermeasures include preflight visual orientation training – perhaps using appropriate virtual reality techniques or ground simulators – and improved physiologically based human factors standards for spacecraft architecture and éscape path signage.

Risk #5 Chronic space motion sickness symptoms affect 75% of crewmembers to some degree during the first 3-5 days in space, and impair the average physical and mental efficiency of crewmembers, and cause profound somnolence, nausea related inability to follow procedures, and loss of initiative. The impact on operational capability of the crewmember equals or exceeds the somnolence produced by other aberrant circadian cues associated with spaceflight. Though acute space sickness problems are generally confined to the first week, several cases lasting weeks have been described by Russian colleagues, and there is reason to believe chronic low grade symptoms ("sopite syndrome") may persist in some crewmembers for weeks. Existing drugs were developed to prevent and treat acute space motion sickness, and have significant side effects. They may not be the best agents for treating chronic space motion sickness symptoms. Countermeasures include both techniques which accelerate adaptation to weightlessness, and improved anti-motion sickness drugs and other therapies which can be used to block or treat symptoms and signs without unacceptable cognitive or circadian side effects.

Risk #6 Artificial Gravity related disorientation, nausea, vomiting and loss of coordination. Artificial gravity (AG) remains a potentially important multi-system countermeasure for neuromuscular, bone, cardiovascular and neurovestibular dysfunction in 0-G. Large radius AG spacecraft systems are likely at least a decade away, but short radius (2-3 m) systems could be developed now which fit inside Shuttle or an ISS module. As a neurovestibular countermeasure, AG is a double-edged sword: it probably can be used to pre-adapt crewmembers for return to planetary gravity, but if crewmembers move their heads out of the plane of rotation, the resulting vestibular Coriolis stimulus potentially produces complex disorientation and motion sickness. In a rotating artificial gravity environment, with the body's principal oriented perpendicular to the axis of rotation, the direction and magnitude of the vestibular Coriolis effects depend on which way the crewmember happens to be facing. The extent to which a person can adapt in a context specific way to this kind of stimulus is unclear, and requires further research. Establishing the values of AG system radius and RPM, and the duration/repetition rate of AG sessions which are effective for neuromuscular, bone, cardiovascular and neurovestibular therapies remain a NSBRI wide priority.

Risk #7 Peripheral and central vestibular changes due to prolonged 0-G, radiation, or environmental toxins. There is no conclusive evidence that prolonged (months to years) exposure to 0-G produces irreversible vestibular changes, but only half a dozen individuals have yet flown beyond 6-8 months. Anatomical changes have been seen in vestibular sensory epithelia in animals on flights of several weeks and longer, but the functional significance of these changes is unclear. The effects of radiation exposure on the vestibular end organs and central vestibular system (e.g. brain stem, cerebellum, thalamus, hippocampus)has not been established. The effects of gravity on the formation of otolith crystals is not well understood. Loose otoconia will presumably float benignly in 0-G, but returning crewmembers may be more susceptible to disorienting effects (e.g. cupulolithiasis) during landing and postflight. The lack of validated, sensitive instrumentation and methods for early detection of impairment of vestibular reflexes, particularly those associated with response to gravity and linear acceleration is a continuing problem.

In 1999, the NSBRI neurovestibular team held a workshop in Houston to solicit the advice of a panel of outside experts. This group mapped the neurovestibular risks of spaceflight into eight interrelated thematic research areas, and defined a set of critical questions associated with each. These themes and questions formed the basis for the solicitation for the current research program:

1. Sensory-Motor Adaptation

- Can an individual's ability to adapt to multiple gravitational environments be enhanced so astronauts can rapidly transition between 1-G and 0-G, 0-G and partial G, or 0-G and artificial G with minimal performance impairment or motion sickness ? What are the sensory-motor responses that must change in a functionally adaptive manner during prolonged space flight? Does such adaptation take place? How can it be reliably measured?
- Can preflight or inflight training accelerate adaptation ? Can these adaptive responses be trained to be context-specific? What context cues are effective ? Must they be associated with active movement ? How long does context-specific pre-adaptation last ? Does adaptation of eye movements transfer to e.g. arm movement ?
- What is the evidence for and the physiological bases of oscillopsia, disorientation, ataxia, impaired gaze holding, and reduced dynamic visual acuity reported by crewmembers, particularly while making head movements during re-entry and immediately postflight?
- Can long-term exposure to space flight impair sensorimotor plasticity?
- What is the mechanism responsible for postflight sensory flashbacks occasionally reported by some crewmembers ?
- How do countermeasures (e.g., artificial gravity, inflight exercise or preflight training) affect adaptation rates and levels? How do rates and levels associated with physiological (sensorimotor, autonomic, emetic) adaptation to microgravity and 3/8 G on Mars correlate with operational performance changes ?

- What are the appropriate space flight analog environments that can be used as test beds for evaluating neurological adaptation, adverse operational implications, countermeasures and impacts of adaptation on other anatomical and physiological systems?

2. Artificial Gravity

- What are the effects of AG on human eye, head and limb movements ? What are the pros and cons of artificial gravity (AG) as a countermeasure against the effects of 0-G on neurovestibular function ? What are the advantages and disadvantages of large radius continuous AG vs. short radius intermittent AG, and how are these influenced by mission duration and post-landing environment (Mars vs. Earth)?
- Can humans successfully adapt to working perpendicular to the angular velocity vector?
- How can transitions between AG levels be eased?
- What is the maximum tolerable rotation rate for a given G level? What is the best habituation schedule?

3. Visual (Multisensory) Orientation, Spatial Memory, and Navigation

- How do visual and nonvisual cues interact to influence human orientation perception and motor behavior?
- How do visual, vestibular and haptic cues and biases contribute to inversion illusions, visual reorientation illusions, extravehicular-activity acrophobia, disorientation and poor 3-D spatial memory in 0-G?
- What is the neural basis of inversion illusions, visual reorientation illusions, EVA acrophobia, disorientation and 3-D spatial memory problems in 0-G? Does neural coding of place and direction three dimensional, or is it principally two dimensional due to our terrestrial evolutionary heritage ? Does the coding change after adaptation to 0-G?
- Does 1-G training in simulated environments (e.g. using virtual reality or neutral buoyancy techniques) reduce disorientation, and improve 3-D spatial memory and performance in orientation and navigation tasks such as emergency escape ? Can the architecture and layout of spacecraft interiors be improved to minimize disorientation ?
- How can 0-G immersive teleoperation displays be designed to reduce disorientation and/or motion sickness?

4. Vestibular/Autonomic/Emetic Physiology and Countermeasures

- What is the physiological basis for the "sensory conflict" theory for motion sickness ? What is the locus and function of the putative "conflict" signal ? What is the neural or chemical linkage between balance and emetic centers ? What mechanisms establish the threshold for nausea and emesis ? What neurotransmitter and receptor systems are involved ? Is the physiology of space motion sickness fundamentally different from other forms of motion sickness ?
- How do anti-motion sickness drugs affect sensory-motor adaptation and eye movements ?
- Can more effective anti-motion sickness drugs be developed which target emetic centers or the vestibular-emetic linkage ? Drugs must be effective, easily and safely used over days to weeks with minimal side effects and must not impair neurovestibular adaptation.

- Can improved anti-motion delivery systems and dose and side effect monitoring systems be developed? What are the best ground-based techniques for evaluating 0-G pharmacokinetics and for assessing the effectiveness and side effects of drug countermeasures ?
- How does chronic space motion sickness (including sopite syndrome) affect mood, initiative and interpersonal relationships?
- Does the neurovestibular response to weightlessness impair postlanding cardiovascular regulation and contribute to orthostatic intolerance ? How is it mediated ? What is the effective frequency range of compensation ? Can an effective countermeasure (e.g., AG) be developed to exploit this knowledge?

5. Postflight Locomotion and Gaze Assessment

- What causes the profound impairments of posture, gaze and locomotion stability in many returning astronauts (and in vestibular patients), and how can these be quantified?
- What causes the large differences in level of impairment observed among different crewmembers ?
- How do these differences correlate with physiological and operational performance changes?
- How are the multiple, mutually dependent sensorimotor systems responsible for locomotion altered by exposure to space flight? For example, what is the role of the vestibulo-ocular, vestibulo-collic and vestibulo-spinal reflexes in 3-D control of locomotion and gaze while walking, turning or ascending stairs?
- How are target acquisition, smooth pursuit and saccadic mechanisms programmed during locomotion? How do oculomotor and gait control systems interact during locomotion and head turning? How is this interplay affected by space flight?
- What roles do visual cues play in postflight locomotor control?
- In an altered sensory environment, does motor control require increased cognitive resources?
- Does this multi-tasking impair performance? Can a dual-task paradigm be used to monitor adaptation?
- What is the linkage between space flight-induced changes in sensory-motor control and astronaut functional performance?
- What measures represent composite and global indicators of locomotor and/or gaze dysfunction after space flight? What measures are the most efficient and sensitive indicators of changes in locomotion and/or gaze? What is their correlation with functional performance after space flight.

6. Neurovestibular Rehabilitation

- What are the relative contributions of neurovestibular adaptation, neuromuscular deconditioning and orthostatic intolerance to postflight neuromuscular coordination, ataxia and locomotion difficulties?
- Why do certain astronauts recover balance and locomotion function more rapidly than others postflight ?
- What is the effect of cardiovascular, muscle and skeletal rehabilitation therapies on neurovestibular recovery, and the converse ?

- Can preflight or inflight training, balance exercises, sensory aids, prostheses and assessment techniques improve postlanding postural and locomotor control and functional task performance ?
- How should somatosensory information be used to accelerate neurovestibular redaptation?
- Can crewmembers "learn how to learn" by adapting to surrogate sensory-motor rearrangements ?
- How does attention to a new sensory-motor task affect performance of a secondary task?

7. Effects of Stress, Isolation, Immobilization and Diet on Vestibular Function

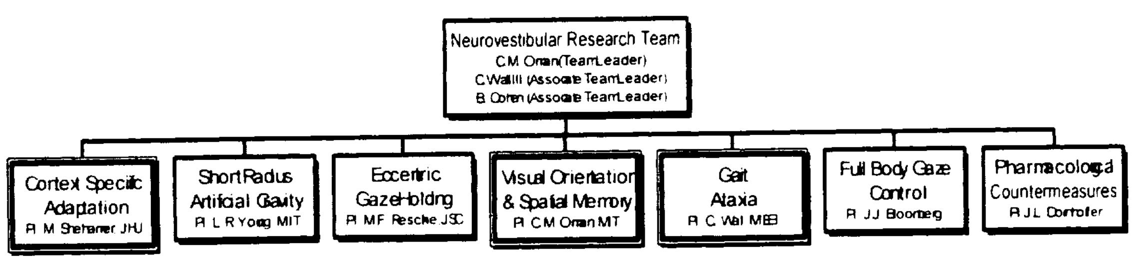
- What are the effect of psychological stress, isolation, immobilization, and diet on vestibular function ? How can they be distinguished from the effects of weightlessness and "normal" physiological variability?
- If there are important effects, what countermeasures can be developed?

8. Potential Mechanisms For and Diagnosis of Irreversible Neurovestibular Changes

- How might very long duration exposure to 0-G or partial G, radiation or environmental toxins such as carbon monoxide or ethylene glycol cause irreversible (pathophysiological) changes in central or peripheral vestibular function or development, or cause acceleration of the normal aging process? What is the likelihood of this ? Would some individuals be more susceptible than others? What is the potential time course? How could such changes be reliably detected at an early stage? What is the best way to non-invasively assess the function of the human otolith end-organs ? How does serum calcium homeostasis impact otoconial turnover?

8.4 DESCRIPTION AND EVALUATION OF THE CURRENT PROGRAM:

NSBRI's neurovestibular research program is led by Dr. Charles Oman (MIT) assisted by Drs. Bernard Cohen (Mt. Sinai School of Medicine) and Conrad Wall (Harvard Medical School/Mass Eye and Ear Infirmary). The current research portfolio of seven projects was selected based on a February, 2000 solicitation (NSBRI 00-01) and independent peer review. Six of the seven are three year projects. Three of the projects (double boxed in the figure below) were initiated in 1997, and competitively renewed in 2000.



The investigators, their institutions, the critical path risks addressed, thematic areas, experimental model, specific aims, countermeasure types and countermeasure development strategy of each of the seven projects are summarized below:

<u>Context-Specificity and Other Approaches to Neurovestibular Adaptation.</u>
PI: Mark J. Shelhamer,
CoIs: Minor, Zee, Angelaki, Zhou, Wu.
Institutions: Johns Hopkins U. School of Medicine, Washington U., U. Mississippi Med Ctr.
Critical path risks addressed: 1. Vertigo on rentry and landing., 3. Postlanding imbalance and vertigo.
Thematic area: Sensory Motor Adaptation
Experimental models: Human and animal (primate)
Countermeasure Types: assessment, prediction, training.
Current readiness level: 2
Specific Aims:

- Is torsional eye position a context cue for saccade adaptation ?
  - Does a rest interval between stimuli promote adaptive consolidation ?
  - Can cyclovergence adaptation provide a countermeasure to ocular torsion changes in parabolic flight ?
  - How do pursuit and LVOR deficits correlate in cerebellar lesioned monkeys ?
  - How do pursuit and LVOR adaptation transfer across frequencies in humans and monkeys
  - Can LVOR adaptation be trained with pursuit stimuli, and how do cerebellar lesions influence adaptation.
  - Does head tilt adaptation of saccades and VOR transfer to arm movements in monkeys ?
  - What is the best way to induce context specific LVOR adaptation in humans ?
  - Does the naso-occipial LVOR also show context specific adaptation ?

<u>Neuro-Vestibular Aspects of Artificial Gravity Created by Short-Radius Centrifugation</u>
PI: Laurence R. Young.
CoIs: Hecht, Oman, Mast, DiZio, Lackner, Paloski, B. Cohen,
Dai, M. Cohen, Welch, Stone.
Institutions: MIT, Brandeis, NASA-JSC, Mt. Sinai Hospital, NASA-Ames.
Critical Path Risks: 6. Artificial Gravity, 2. Acute space motion sickness, 5. Chronic space motion sickness
Thematic areas: Artificial G, Drug countermeasures
Experimental model: Human
Countermeasure Types: assessment, training, environmental manipulation, drugs.
Current readiness Level: 4
Specific Aims: Using short and medium radius centrifuges and rotating chairs, to determine:

- How context cues influence VOR, perception and motion sickness adaptation.
- What is the role of sensory-motor (non-vestibular) adaptation to AG ?
- What types of sensory conflict drive adaptation ?
- What are the optimal duty cycles and inter-session intervals ?

- Does body orientation re gravity provide a context cue ?
- In what way does adaptation generalize to different rotating environments?
- How does intermittent training influence the accuracy of head movements ?
- How does promethazine affect adaptation and eye movements in humans and monkeys ?

Modification of Eccentric Gaze-Holding.
PI: Millard F. Reschke
CoIs: Paloski, Kornilova, Wood, Leigh
Institutions: NASA-JSC, IBMP/Moscow, BCM, University Hospitals of Cleveland
Critical Path Risk: 1 Vertigo on reentry and landing, 3. postlanding vertigo, 7. peripheral or central vestibular changes.
Thematic areas: Sensory-motor adaptation, Irreversible changes).
Experimental model: Human
Countermeasure types: assessment, prediction, training.
Countermeasure Readiness Level: 2
Specific Aims:

- Effect of tilt and proprioception on centripetal drift time constant
- How rebound nystagmus provides adaptive compensation.
- How centrifugation influences gaze holding.
- Why adaptation fails in cerebellar patients.
- Whether gaze-holding is impaired immediately following spaceflight.

Visual Orientation and Spatial Memory.
PI: Charles M. Oman.
CoIs: Howard, Shebilske, Taube, Hecht, Harris, Jenkin, Liu, Stuerzlinger. Institutions MIT, York University, Dartmouth Medical School, Wright State University.
Critical path risk: 4. Inflight spatial disorientation and frame of reference problems, 2. Acute space motion sickness etiology.
Thematic area: Orientation and Spatial Memory.
Experimental models: Human and animal (rat)
Countermeasure types: assessment, prediction, training, environmental manipulation. .
Countermeasure Readiness Level: **5**
Specific aims:

- Human visual orientation. Effects of visual frame, polarity, brightness, motion, and gravireceptor cues on the subjective vertical, eye movements, and limb movements.
- Three dimensional spatial memory and spatial frameworks. Generic and environment specific preflight and onboard virtual reality training methods, interior architectural standards, and escape path countermeasure design and evaluation.
- Neural coding of spatial orientation. How do visual, vestibular, gravireceptive, proprioceptive, and motor pathways drive limbic head direction cells in the rat, as a model for visual reorientation illusions in astronauts.

Advanced Techniques to Assess and Counter Gait Ataxia

PI: Conrad Wall III

Co-Is:Bloomberg, Oddson, Raphan, Solomon.

Institutions: Mass Eye and Ear Infirmary, NASA-JSC, Boston University, Mt. Sinai Hospital, U. Penn.

Critical Path Risks: 3. Postlanding imbalance, instability, vertigo.

Thematic area: Locomotion and gaze.

Experimental model: Human

Countermeasure types: assessment, prediction, training, prosthesis.

Countermeasure Readiness Level: 5

Specific Aims:

- Quantify body, head, & eye coordination during perturbed straight walking. And also:
- during straight and circular walking on a circular treadmill.
- while ascending/descending stairs.
- while wearing a tactile prosthetic countermeasure.
- assess effect of dynamic balance exercises.

Understanding Full-Body Gaze Control During Locomotion

PI: Jacob J. Bloomberg, Jacob

Co-I:H. Cohen.

Institutions: NASA-JSC, Baylor College of Medicine

Critical Path Risks: 3. Postlanding imbalance, instability, vertigo, and hyptension.

Thematic area: Locomotion.

Experimental model: Human

Countermeasure types: assessment, prediction, training.

Countermeasure Readiness Level: 5

Specific Aims: How are eye, head, trunk, and lower limb movements coordinated. Specifically:

- How do eye, head, trunk, and legs absorb heel strike while treadmill walking? How do subjects adapt to magnifying and minifying lenses?
- To reduced degrees of freedom, for example wearing a neck brace ?
- To wearing knee braces ?

Pharmacological Countermeasures for Space Motion Sickness.

PI: John L. Dornhoffer

CoIs: Garcia-Rill, Paule, Van De Heyning.

Institutions: U. Arkansas for Medical Sciences, National Center for Toxicological Res., U. Hospital, Antwerp.

Critical Path Risks: 2. Acute space motion sickness, 5 Chronic space motion sickness.

Thematic area: Autonomic/drug

Experimental model: Human

Countermeasure types: assessment, prediction, pharmacological.

Countermeasure Readiness Level: 5

Specific Aims: (2 year project)

- What are the effects of lorazepam, meclizine, promethazine, and scopolamine on coriolis induced motion sickness symptoms ?
- How do these drugs affect reticular sensory gating (P50 double click auditory evoked potential), time perception, short term memory, and learning ?

Each of the current projects resembles a small NIH Program Project Grant in that (Boomberg's project exceptedall involve multiple experiments conducted concurrently at several institutions, and significant collaborations between investigators. In addition, there are significant inter-project collaborations and coordinations. For example, Drs. Wall, Oddson and Bloomberg are coordinating their locomotion research, and developing a portable locomotion testing platform. Dr. Minor (Shelhamer project) is assisting Dr. Taube in developing a semicircular canal blocked animal preparation. Drs. Shelhamer, Solomon, and B. Cohen and are working with JSC clinical colleagues on development of a postflight neurological assessment battery.

The neurovestibular team has maintained a strong record of scientific productivity. As of the spring of 2002, we had 23 manuscripts published or submitted. Between 1997 and 2000, the initial 3 projects published 14 journal articles, along with 3 reports, 6 graduate theses, 23 abstracts, with 15 manuscripts accepted or in review. Eleven graduate students and 10 postdoctoral trainees participated. Two students interned at NASA JSC, and one is now employed there. In addition, progress is reported annually in written and oral presentations to the NSBRI External Advisory Council. There is a strong interaction with NASA JSC. Drs Wall and Oddson are constructing a portable locomotion test platform for the Neurophysiology lab at JSC. Dr. Shelhamer serves on the JSC Medical Branch Neurophysiology Integrated Project Team. Dr. B. Cohen serves on the Critical Path Project Review Board. Dr. Oman, Mr. J. Richards, Dr. J. Clark (JSC) and Dr. Marshburn (JSC & Smart Med. Team) prepared a retrospective summary of Mir neurovestibular episodes, which was initially distributed to neurovestibular specialists and crewmembers for comment and has since been submitted for publication. The team developed a web site to provide project science details. Drs. Wall and Oman worked with members of the NSBRI Education and Outreach Team at Harvard Medical School to prepare a vestibular case study for use in high schools ("Cecilia's Story"), and Dr. B. Cohen participated in the summer high school outreach teaching program at Mt. Sinai. The team has held panels at the Aerospace Medical Association and Neural Control of Movement meetings. The team is preparing a special issue of the Journal of Vestibular Research in 2002, and are major participants a 6th Symposium on the Role of the Vestibular Organs in Space Exploration in Portland, Oct. 1-3, 2002. This symposium will be a satellite to the concurrent Barany Society meeting in Seattle, and continues the series initiated at Pensacola in the 1960s and 70s. We also informally advise several neurovestibular-related projects underway on other teams: Ray Vestibular Autonomic project /Cardiovascular Team; Morin Vestibular effects on circadian/Chronobiology; Putcha Intranasal motion sickness drug adminstration/Smart Medicine.

The current project portfolio collectively addresses some aspects of six of the seven critical path risks and five of the eight potential thematic areas. Most of the projects have countermeasures concepts defined and in development, though two currently have not yet reached that stage. Recent retroactive cuts to the NSBRI budget during FY 2002 have impacted progress on several projects. Also, there are significant strategic gaps in the current program, partly due to funding limitations and also to the particular thematic distribution of proposals solicited by the most recent NSBRI research announcement (NSBRI 00-001).

These strategic gap areas include:

- Vertigo on rentry and landing.
- Vestibular/autonomic/emetic physiology
- Postflight neurovestibular rehabilitation
- Mechanisms of long term spaceflight effects on otolith end organ function and reflexes.

With respect to rentry and landing vertigo, the Shelhamer, Reschke, and Bloomberg projects address the question of context specific preadaptation for return, and how visual acuity is affected during walking. However none of our current projects focus specifically on rentry disorientation, acuity loss due to vehicle and/or head movement, or and resulting inappropriate control flight path error. Some flight surgeons suspect that landing vertigo may become the most significant factor contributing to mission risk if Shuttle visits are extended to 3-4 weeks, and manual landings continue to be made. Pilots can practice landing procedures on orbit using laptop flight simulators, but cannot experience the vehicle accelerations or make head movements in a gravitational environment until the actual re-entry is flown. As noted earlier, a correlation between landing parameters and the strength of neurovestibular symptoms has recently been noted. Research is needed to document the head movements and vehicle accelerations pilots experience, and to better understand the types of G-excess and otolith-tilt-translation-reinterpretation and other somato-gravic illusions they produce. Controlled tests on recently returned crewmembers in motion simulators and the Shuttle Training Aircraft will probably be needed so that its then possible to develop an appropriate 1-G experimental simulation, and design improved procedures, controls and displays.

The Young and Dornhoffer projects are studying motion sickness produced by Coriolis stimulation, and evaluating promethazine and several other agents as potential countermeasures, but a broader attack on the motion sickness problem is needed. The vestibular/autonomic/emetic area is challenging because of its interdisciplinary aspects. The physiological basis of the sensory conflict theory and the linkage to emetic centers remains unknown. Existing anti-motion sickness drugs have been empirically discovered. A breakthrough in vestibular/autonomic/emetic physiology could have important implications for development of targeted pharmacologic countermeasures. Recent research on vestibulo-autonomic reflexes should remain a priority. The vestibular system thought to play a role in cardiovascular, respiratory, and circadian regulation, but relatively little is yet known about mechanism or functional significance. NASA and NIH have not provided major funding for vestibular-emetic research since the early eighties, so the number of active researchers is very small at the moment. However new research avenues in this area have been potentially opened in the intervening years the development of modern molecular neuroscience and functional imaging techniques. A coordinated NASA/NIH research initiative in this basic research area could yield dramatically important results. Given the almost universal human susceptibility to motion sickness, validated concepts for targeted pharmacologic approaches to motion sickness could potentially be of interest to some NSBRI Industry Forum partners, once the fundamental physiologic breakthrough identification of the emetic linkage mechanism has been made. In addition to new agents, improved methods of rapid drug treatment which are less painful than the present method of intramuscular injection, and which could be used for treatment during EVA are highly desirable.

Neurovestibular rehabilitation is a challenging area because most of the clinical techniques used today are empirical, guided by qualitative theories about the relative advantages of adaptation vs. sensory substitution. Hypothesis-driven research techniques and quantitative assessment techniques are only slowly entering the field. Astronauts differ physiologically from vestibular patients in several important ways. There is no widely accepted 1-G research analog for the space environment which can be used for neurovestibular rehabilitation studies in a manner analogous to the way bed rest or leg suspension in neuromuscular rehabilitation studies. Further, it is not clear from clinical experience how to optimize the readaptation and functional recovery of returning flight crews, or how neurovestibular, neuromuscular, bone, and cardiovascular rehabilitation techniques may interact.

Although all of the neurovestibular effects of spaceflight encountered to date are apparently reversible, it is now clear that in general the longer a person is in 0-G, the longer lasting the postflight aftereffects, and only a very few people (all of them cosmonauts) have experienced weightlessness for more than seven months. We cannot confidently predict the potential long term effects of weightlessness (including systemic changes in body calcium for example) on the vestibular end organs, on the otolith-ocular and otolith-spinal reflexes, and know if they are reversible. We do not yet have a reliable, sensitive method for assessing the function of the human otolith organs, analogous to clinical audiometric testing.

8.5 OBJECTIVES AND STRATEGIC ACTIVITIES

NSBRI research teams normally particpate in steps 2-5 of the countermeasures development process. After the neurovestibular problems are initially discovered and phenomenologically described (phase one), our NSBRI research team hypothesizes the physiological mechanisms and/or cognitive processes responsible for neurovestibular risks; performs the necessary focused mechanistic research to validate these hypotheses (phase two); formulates potential countermeasures, and then does the ground and/or parabolic flight experiments to establish their efficacy (phase three). Most research will initially be done in ground laboratories or in parabolic flight. We then work with JSC to evaluate whether the countermeasures are practical in an operational environment, sometimes via simulation(phase four), and an independent, non-advocate group reviews the case for using the countermeasure. The countermeasure is evaluated on the ground using surrogate subjects, and then ultimately in flight.

The long term goals of NSBRI's neurovestibular research program correspond to each of the seven space flight risk areas. An eighth programmatic goal – to develop improved methods for diagnosis and treatment of vestibular disorders on Earth is also identified. Tables 8.1-8.8 below outline the progression of research required to develop countermeasures for each risk area in an ideal program. Though the 7 existing projects fit well within this framework, the the overall scope of a broad based neurovestibular program significantly exceeds the resources now available. For the seven projects in the current portfolio, the countermeasures development status and type is shown schematically in Table 8.9.

National Space Biomedical Research Institute
NEURVESTIBULAR ADAPTATION PROGRAM

Table 8.1 Achieving Goal 1: Minimizing risk of vertigo on rentry and landing

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Review existing data on effect of vertigo on shuttle flight technical error, postflight visual acuity, and gaze stability.													
Phase 1: Focused Mechanistic Research													
• Monitor and quantify shuttle pilot head movements, vehicle accelerations. • Quantify incidence and magnitude of nystagmus, disorientation loss of visual acuity, gaze stability, and linear VOR components in returning crews. • Quantify effect on simulated landing performance parameters. • Define pilot tasks and head movements in manual, autoland, and emergency landings. • Develop mathematical models for nystagmus, perception, manual control errors; vehicle loss scenarios. • Quantify manual control and visual acuity loss under analogous disorientation conditions induced in simulators.													
Phase 2: Preliminary Countermeasure Development Research													
• Conduct simulations to define how changes in pilot role (supervisory vs. manual) or head up/head down display format could reduce impact.													

• Develop preflight training techniques to preadapt subjects to otolith-tilt-translation-reinterpretation and G-excess illusions. • Use models and data to define potential procedural changes to reduce disorientation. • Define and valuate potential in flight preadaptation techniques or in flight landing rehearsal countermeasures.													
Phase 3: Mature Countermeasure Development Research													
• Develop integrated landing vertigo countermeasure, and verify feasibility.													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of integrated countermeasure procedure													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 8.2 Achieving Goal 2: Minimizing risk of acute space motion sickness

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Determine side effects of existing anti-motion sickness drugs (e.g. effects on sensory-motor adaptation, eye movements, alertness). • Determine effects of 0-G on drug bioavailability and effectiveness. • Determine role of head movements, visual and haptic cues in triggering space motion sickness.													
• Evaluate potential non-pharmacologic countermeasures (e.g. parabolic flight preadaptation, movement restriction, haptic cues, biofeedback, etc.) • Define options for minimizing impact of vomiting episode in space suit. • Define physiological basis of sensory conflict and emetic linkage in animal models • Identify new pharmacologic agents which could specifically block the emetic linkage or increase rate of sensory-motor adaptation. • Determine what physiological factors determine individual susceptibility. • Determine role of brainstem and cerebellar mechanisms in adaptation. • Determine effect of acute motion sickness on circadian and cardio regulatory systems.													

Phase 2: Preliminary Countermeasure Development Research													
• Develop anti-motion sickness drugs targeted at sensory conflict, emetic linkage or adaptive mechanisms using animal models. • Evaluate non-pharmacologic motion sickness countermeasures. • Develop improved drug delivery and side effect monitoring techniques.													
• Evaluate techniques for mitigating impact of EVA emesis.													
Phase 3: Mature Countermeasure Development Research													
• Develop behavioral and pharmacological countermeasures and test in humans													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of behavioral and pharmacological countermeasure.													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 8.3 Achieving Goal 3: Minimizing risk of postlanding imbalance, vertigo and orthostatic hypotension

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Postflight neurologic exams, posture platform and treadmill assessments. • Determine incidence of sensory-motor flashbacks.													
Phase 1: Focused Mechanistic Research													
• Develop reliable techniques for quantifying postural, locomotor and gaze control deficits in returning astronauts. • Determine how head and body motor strategies influence visual acuity and ability to stand, walk and run. • Determine whether training (e.g. "learn how to learn") helps normal subjects rapidly adapt to analog stimuli. • Determine whether there is a significant vestibular contribution to orthostatic hypotension and dizziness.													
• Determine physiologic basis for intra-individual differences in magnitude and duration of postflight symptoms and signs.													
Phase 2: Preliminary Countermeasure Development Research													
• Develop normative database for postflight postural, locomotor and gaze assessment techniques, and relate test parameters to functional performance loss. • Define preflight and inflight preadaptation techniques. • Define and develop appropriate sensory aids to assist temporarily disoriented crewmembers.													
• Identify and evaluate potential neurovestibular and neuromotor rehabilitation techniques.													

• Identify potential operational changes which would reduce crew susceptibility to postflight injuries. • Determine whether vestibular-autonomic factors can be manipulated to decrease susceptibility to postflight orthostatic hypotension and dizziness.													
Phase 3: Mature Countermeasure Development Research													
• Develop integrated countermeasures and test in human volunteers													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of integrated countermeasure													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 8.4 Achieving Goal 4: Minimizing risk of inflight spatial disorientation and frame of reference problems.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Postflight crew debriefs, task analyses and workstation evaluations. • Assess ISS remote manipulation controls and displays to better define frame-of-reference issues.													
Phase 1: Focused Mechanistic Research													
• Determine how vestibular and environmental visual cues contribute to spatial disorientation, navigation, height vertigo and frame-of-reference problems. • Determine how gravitational orientation of human subjects influences the relative weighting of sensory cues. • Determine whether/how "place" and "direction" is neurally coded in 3 dimensions, and limits of human abilities to interrelate multiple reference frames.. • Develop techniques for assessment of individual mental rotation and spatial memory skills, and susceptibility to height vertigo.													
• Evaluate use of virtual reality techniques for studies of EVA height vertigo.													
Phase 2: Preliminary Countermeasure Development Research													
• Develop generic (e.g. "learn how to learn") and/or environment specific training techniques (e.g. using virtual reality or neutral buoyancy) which could help normal subjects retain spatial memory while performing 0-G analogous tasks.													

• Develop improved techniques for 3D egress path marking, "you-are-here" maps. • Revise NASA Standard 3000 for spacecraft interior architecture and workstation layout.													
• Identify operational changes which would reduce crew susceptibility to inflight spatial disorientation and EVA height vertigo.													
Phase 3: Mature Countermeasure Development Research													
• Develop countermeasures and test in human volunteers													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of countermeasures													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 8.5 Achieving Goal 5: Minimizing risk of chronic space motion sickness symptoms.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Correlate postflight crew debriefs, neurologic exams, retrospective task analyses, crew performance, diet, sleep, and drug use data.													
Phase 1: Focused Mechanistic Research													
• Identify anti motion sickness drugs and delivery methods suitable for longer duration administration, and which will combat sopite syndrome symptoms. • Develop techniques to quantify attention deficits, somnolence, vigilance and short term memory loss in chronic motion sickness.													
• Develop methods to quantify attention deficits, short term memory loss, ability to multi-task, somnolence, and vigilance.													
Phase 2: Preliminary Countermeasure Development Research													
• Test anti-sopite drugs on normal subjects experiencing chronic motion sickness symptoms (e.g. produced in rotating rooms or by prism wear). Evaluate for both effectiveness and cognitive and circadian side effects. • Identify operational changes which would reduce crew susceptibility to and impact of chronic space motion sickness.													
Phase 3: Mature Countermeasure Development Research													
• Develop countermeasures and test in human volunteers													

Phase 4: Countermeasure Evaluation & Validation													
• Testing of countermeasures													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 8.6 Achieving Goal 6: Minimizing risk of artificial gravity related disorientation, nausea, vomiting and loss of coordination.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research		■	■	■	■	■							
• Determine whether human subjects show context specific oculomotor and sensory-motor adaptation to vestibular Coriolis stimulation. • Determine how radius, RPM, G level, duration, and repetition rate limits for subjects oriented perpendicular to the angular velocity vector. • Determine whether adaptation generalizes to different rotation environments. • Evaluate intermittent artificial gravity as a potential countermeasure for adverse cardiovascular, musculo-skeletal and neurovestibular effects of long duration spaceflight, using analog models.													
Phase 2: Preliminary Countermeasure Development Research		■	■	■	■	■	■	■					
• Evaluate short radius centrifuge designs for use as a multi-system countermeasure on ISS class missions. • Determine optimal adaptation schedule for chosen radius, RPM. • Define medium large radius centrifuge concepts for eventual use on planetary missions.													

Phase 3: Mature Countermeasure Development Research													
• Develop countermeasure protocols and test in human volunteers													
Phase 4: Countermeasure Evaluation & Validation													
• Evaluate prototype short radius centrifuge countermeasure in flight.													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 8.7 Achieving Goal 7: Minimizing risk of permanent vestibular function change .

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Evaluate postflight crew debriefs and neurologic exams of long duration crew for evidence of irreversible vestibular changes, and exposure of crew to significant radiation or environmental toxins. • Retrospective testing of vestibular function using currently available techniques of previously flown long duration crewmembers.													
Phase 1: Focused Mechanistic Research													
• Investigate effects of prolonged 0-G exposure on otolith formation and resorption, vestibular sensory epithelia in animal models, and identify potential mechanisms. • Determine effects of potential environmental toxins (e.g. carbon monoxide, ethylene glycol) on central and peripheral vestibular function. • Determine effects of radiation exposure on central and peripheral vestibular function. • Determine the effect of age, stress, isolation, and immobilization on vestibular function.													
Phase 2: Preliminary Countermeasure Development Research													
• Develop sensitive techniques for early detection of impairment of peripheral and central vestibular function. • Develop appropriate evidence-based countermeasures, based on understanding of physiologic mechanisms.													

Phase 3: Mature Countermeasure Development Research													
• Testing of normals and vestibular patients using new techniques.													
Phase 4: Countermeasure Evaluation & Validation													
• If evidence for long duration changes warrants, continue countermeasure development.													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Retrospective testing of previously flown long duration crewmembers using new techniques.													

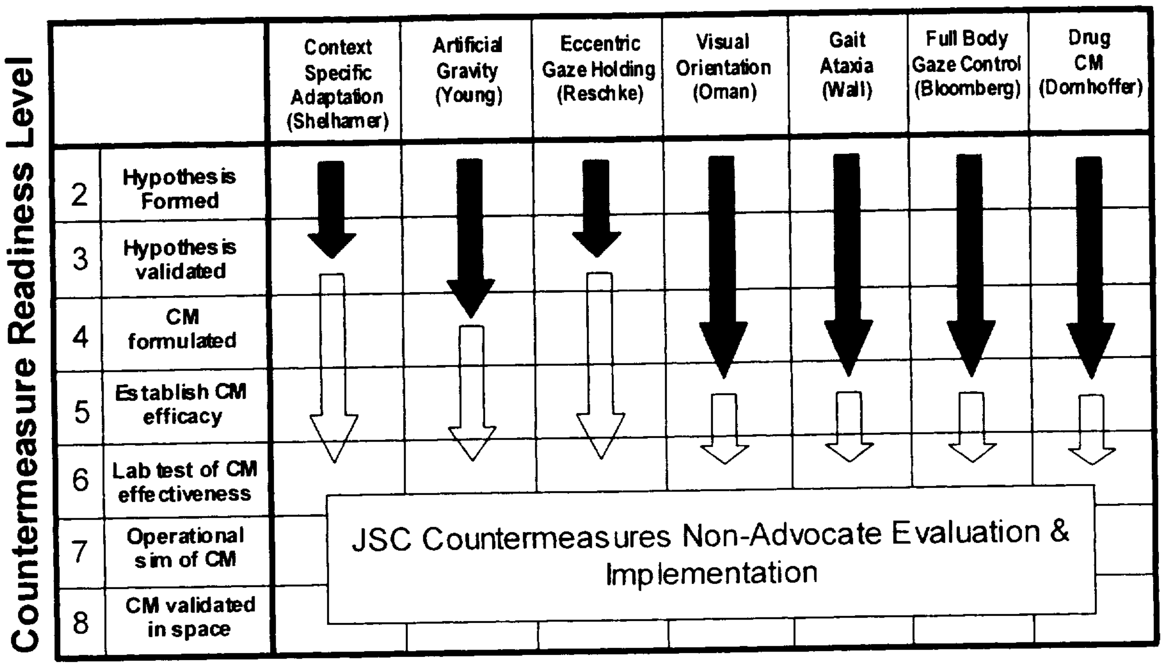
Table 8.8 Achieving Goal 8: Improving methods for diagnosis and treatment of vestibular disorders on Earth.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Define the physiological mechanisms responsible for otolith formation and resorption, and vestibulo-ocular, vestibulo-collic, and vestibulo-spinal reflex adaptation. • Define physiological basis of motion sickness, including sensory conflict and emetic linkage in animal models. Identify pharmacologic agents which could specifically block the emetic linkage or increase rate of sensory-motor adaptation. • Define the role of the vestibular system in cardiovascular regulation. • Determine effects of potential environmental toxins (e.g. carbon monoxide, ethylene glycol) on central and peripheral vestibular function. • Determine effects of radiation exposure on central and peripheral vestibular function. • Determine the effect of age, stress, isolation, and immobilization on vestibular sensory epithelia in animal models, and identify potential mechanisms.													
Phase 2: Preliminary Countermeasure Development Research													
• Develop anti-motion sickness drugs targeted at sensory conflict, emetic linkage or adaptive mechanisms using animal models.													

• Evaluate non-pharmacologic countermeasures for motion sickness. • Identify and develop sensory aids and rehabilitation techniques for use by vestibular patients. • Develop sensitive techniques for early detection of impairment of vestibular function with particular emphasis on diagnosis of otolith related pathologies. • Develop appropriate evidence-based countermeasures, based on understanding of physiologic mechanisms.													
Phase 3: Mature Countermeasure Development Research													
• Testing of normals and vestibular patients using new techniques.													
Phase 4: Countermeasure Evaluation & Validation													
• Continue countermeasure development.													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Deploy countermeasures in a clinical setting.													

Table 8.9 Countermeasures development status of existing program components

Filled arrows show the current (2001) status, and the open arrows show the phases required during the next decade



Countermeasure Type

	Context Specific Adaptation (Shelhamer)	Artificial Gravity (Young)	Eccentric Gaze Holding (Reschke)	Visual Orientation (Oman)	Gait Ataxia (Wall)	Full Body Gaze Control (Bloomberg)	Drug CM (Dornhoffer)
Assessment	▲	▲	▲	▲	▲	▲	▲
Prediction	▲	▲	▲	▲	▲	▲	▲
Training	▲	▲	▲	▲	▲	▲	
Environmental Manipulation		▲		▲			
Pharmacological		▲					▲
Prosthesis					▲		

Some projects are transitioning research products beyond CRL5 this year. For example, the Wall project is finishing a locomotion evaluation platform which will be used by JSC in testing, and the Bloomberg project is using some components developed with NSBRI support in JSC astronaut testing. The Oman project is preparing a proposal for preflight astronaut spatial memory training, and a draft revision of NASA Standard 3000 for work area layout and architecture. The Young project team wrote a preliminary plan last year for potential use of an AG countermeasure on a proposed (but since cancelled) Shuttle/Spacehab mission. There have also been useful negative results. For example, Dornhoffer recently showed that lorazepam 1 mg. p.o. was ineffective against laboratory coriolis induced motion sickness.

Realistically not all of the current countermeasures development efforts will be successful. Those projects which fail to generate countermeasures concepts (Step 3) will be discontinued . When countermeasures concepts prove ineffective (Step 4), the thrust of the project will be redirected. Developing an effective working relationship with our NASA scientific and clinical colleagues is a priority for our team during the next five years. Once countermeasure reliability is established assessment using preflight/postflight testing (e.g. locomotion and dynamic acuity tests) is relatively straightforward. Ground facilities needed for neurovestibular research include a neurovestibular testing laboratory for pre and postflight experiments, equipped with angular, linear, and artificial gravity stimulus devices, 3D eye movement, whole body kinematic, otolith, posture and locomotion testing and immersive VR display equipment. Access to the VMS Shuttle landing simulator and the Shuttle Training Aircraft for studies of landing vertigo and JSC immersive VR facilities for preflight visual orientation training is also forseen.

Other types of countermeasures (e.g. those involving environmental manipulations such as artificial gravity) can ultimately only be validated via spaceflight. Unfortunately NASA budget caps and descoping of planned activities on ISS over the next few years will significantly limit the number of subjects available initially. Experiments must be carefully planned. Hopefully by the end of this decade access to space flight and opportunities for sophisticated experimentation will increase. There are several basic human and animal neurovestibular experiments (associated with the hypothesis testing phase of countermeasures development level 3) that will eventually require access to ISS and Shuttle crewmembers preflight, inflight and postflight for large n longitudinal studies. Orbital research facilities include a short or medium radius human centrifuge for both neurovestibular adaptation research and countermeasure use. Also needed will be second generation eye, head, and body movement research equipment with capabilities beyond those currently aboard the ISS-Human Research Facility.

10.0 NUTRITION, PHYSICAL FITNESS & REHABILITATION

Team Leader: Joanne R. Lupton, Ph.D.
Regents Professor and William W. Allen Endowed Chair in Human Nutrition
Texas A&M University
213 Kleberg Center, MS 2471
College Station, TX 77843-2471
979-845-0850
979-862-1862 FAX
jlupton@tamu.edu

10.1 INTRODUCTION

Optimal human performance during space exploration requires the maintenance of all physiological systems, such as cardiovascular capacity, bone mineral density, and skeletal muscle function. Adequate nutrition and physical fitness affect all physiological functions and are dependent in part on each other. Not only must energy expended on physical activity be balanced by appropriate food intake, but also the timing of exercise with respect to food ingestion must be well planned since it impacts such important physiological effects as uptake of amino acids into muscle. Thus specific nutrients, ingested at the appropriate time, may help to maintain muscle mass. In addition, the appropriate combination of foods may result in release of glucose into the blood over time, and contribute to the maintenance of a high-energy status, which maximizes physical performance. The critical issues for nutrition are: (1) counteracting the observed anorexia of space flight; (2) determining nutrient needs to meet modified requirements due to space flight stressors including microgravity; and (3) developing new strategies including use of functional foods, supplements, and timing of food intake relative to specific activities that will optimize human performance. Equally important is remaining physically fit. Critical issues for physical fitness include: (1) development of appropriate protocols with respect to frequency, duration and intensity of aerobic and resistive exercise; (2) development of appropriate equipment (relevant to space flight) to maintain aerobic capacity and muscle performance (as measured by strength and endurance); and (3) optimizing the appropriate timing of exercise programs with respect to food intake and other activities (e.g. extra vehicular activity; EVA). Since physical activity will, in part, determine nutrient needs, and the optimization of nutrient delivery will in part depend upon blood flow and muscle mass (which are affected by physical activity), these two disciplines need to be considered together.

10.2 RISKS

Relevant risks (numbered in parentheses) that may be ameliorated by nutrition and physical activity interventions are found in many Discipline Areas of the Critical Path Roadmap:

Food and Nutrition:

- Inadequate Nutrition (Malnutrition) (7)
- Human Performance Failure Due to Nutritional Deficiencies (55)
- Difficulty of Rehabilitation Following Landing Due to Nutritional Deficiencies (54)

Muscle Alterations and Atrophy:

- Loss of Skeletal Muscle Mass, Strength, and/or Endurance (28)
- Inability to Perform Tasks Due to Motor Performance, Muscle Endurance, and Disruption in Structural and Functional Properties of Soft and Hard Connective Tissues of the Axial Skeleton (29)
- Inability to Sustain Muscle Performance Levels to Meet Demands of Performing Activities of Varying Intensities (30)
- Propensity to Develop Muscle Injury, Connective Tissue Dysfunction, and Bone Fracture Due to Deficiencies in Motor Skill, Muscle Strength and Muscular Fatigue (31)
- Impact of Deficits in Skeletal Muscle Structure and Function on other Systems (32)

Bone Loss:

- Acceleration of Osteoporosis (9)
- Fracture/Impaired Fracture Healing (10)
- Injury to Soft Connective Tissue (11)
- Renal Stone Formation (12)

Cardiovascular Alterations:

- Occurrence of Cardiac Dysrhythmias (13)
- Impaired Response to Orthostatic Stress (14)
- Diminished Cardiac Function (15)
- Manifestation of Previously Asymptomatic Cardiovascular Disease (16)
- Impaired Cardiovascular Response to Exercise Stress (17)

Human Behavior and Performance:

- Human Performance Failure Because of Poor Psychosocial Adaptation (18)
- Human Performance Failure Because of Sleep and Circadian Problems (19)
- Human Performance Failure Because of Neurobehavioral Dysfunction (21)

Immunology, Infection and Hematology:

- Immunodeficiency/Infections (22)
- Altered Wound Healing (25)
- Altered Host-Microbial Interactions (26)
- Allergies and Hypersensitivity Reactions (27)

Neurovestibular Adaptation:

- Disorientation and Inability to Perform Landing, Egress, or Other Physical Tasks Especially During/After G-Level Changes (33)
- Impaired Neuromuscular Coordination and/or Strength (34)
- Impaired Cognitive and/or Physical Performance Due to Motion Sickness Symptoms or Treatments, Especially During/After G-Level Changes (35)

Radiation Effects:

- Carcinogenesis Caused by Radiation (38)

Clinical Capabilities:

- Altered Pharmacodynamics and Adverse Drug Reactions (45)
- Development and Treatment of Space-Related Decompression Sickness (47)
- Difficulty of Rehabilitation Following Landing (48)

Multisystem Alterations:

- Post-landing Alterations in Various Systems Resulting in Severe Performance Decrements and Injuries (49)

The number of risks impacted by the level of nutrition and physical fitness is enormous, revealing the very interdisciplinary nature of the concerns of the Nutrition and Physical Fitness Team. In order to allow for the creation of a well-managed research program, we have modified the risks into broader "categories" of risk that can then be addressed more readily in our program. They are as follows:

- Suboptimal Nutritional Status due in part to Microgravity and other Stressors
- Suboptimal Level of Physical Fitness Induced by Microgravity and other Stressors
- Diminution of Skeletal Muscle Function
- Reduced Cardiovascular Capacity
- Radiation Enhanced Development of Cancer
- Decreased Cognitive Function
- Alterations in Sleep Patterns
- Poor Psychosocial Adaptation
- Depressed Immune Function
- Loss of Bone Mineral Density

10.2 GOALS

The Nutrition, Physical Fitness and Rehabilitation Team has the following goals for its program.

Risk-Based Goals

Goal 1: *Reduce Risk of Suboptimal Nutritional Status*

Goal 2: *Reduce Risk of Suboptimal Physical Fitness*

Goal 3: *Reduce Risk of Diminution of Skeletal Muscle Function*

Goal 4: *Reduce Risk of Reduced Cardiovascular Capacity*

Goal 5: *Reduce Risk of Radiation Enhanced Development of Cancer*

Goal 6: *Reduce Risk of Decreased Cognitive Function*

Goal 7: *Reduce Risk of Alterations in Sleep Patterns*

Goal 8: *Reduce Risk of Poor Psychosocial Adaptation*

Goal 9: *Reduce Risk of Depressed Immune Function*

Goal 10: *Reduce Risk of Loss of Bone Mineral Density*

Non Risk-Based Goals

Goal 11: *Develop Monitoring methods for assessment of food intake and physical activity.*

Goal 12: *Develop noninvasive techniques for assessing the effectiveness of diet and physical fitness interventions.*

Goal 13: *Develop Earth-based Applications for diet and physical fitness interventions*

Goal 14: *Integrate Research and Analysis*

10.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The Nutrition and Physical Fitness team will develop countermeasures to most but not all of the risks noted in Section 9.2 above. Our primary immediate area of focus is on goals 1-5 and 11-13. Goal 1 (Reduce Risk of Suboptimal Nutritional Status) and Goal 2 (Reduce Risk of Suboptimal Physical Fitness) are our two primary goals. In fact, these two goals underlie all of the others, since if an individual is not physically fit and nutritionally replete, every organ system will be affected. The third goal (Reduce Risk of Diminution of Skeletal Muscle Function) is the focus of four of the five current research projects and has served to integrate nutrition and physical fitness in our current team program. Goal Four (Reduce Risk of Reduced Cardiovascular Capacity) follows from Goal 2, since optimal physical fitness will, by definition, improve cardiovascular capacity. Goal 5 (Reduce Risk of Radiation Enhanced Development of Cancer) is also addressed by the current research program with the Lupton radiation and colon cancer model. Additional non risk-based goals include developing monitoring systems for food intake and exercise which are noninvasive and require as little crew input as possible (Goal 11) and developing noninvasive techniques for assessing the effectiveness of diet and physical fitness interventions (Goal 12). Finally, nutrition and physical fitness countermeasures lend themselves very well to the development of Earth-based applications (Goal 13). For example, a well-designed amino acid supplement could improve protein synthesis not only in space but also on Earth and may be effective for patients with muscle loss due to stress, wasting, burns, etc. As another example, a resistance exercise device that effectively helps maintain muscle mass can also be used for individuals in nursing homes, under bed rest conditions, etc.

Although the potential impact of diet and exercise on reducing the risk of decreased cognitive function (Goal 6); alterations in sleep patterns (Goal 7); and the risk of poor psychosocial adaptation (Goal 8) is very strong, the basic science of how diet and exercise impact these risks is not as fully developed as it is for the other goals. For that reason we will concentrate our initial efforts in those areas where we expect to see the most immediate use of countermeasures based on strong basic science. Similarly, Goal 9 (reduce risk of depressed immune function) and Goal 10 (reduce risk of loss of bone mineral density) will not be a major component of the Nutrition and Physical Fitness Team's research agenda until the team becomes more mature. The specific risks of space flight to immune function are just now being elucidated. When the risks are more clearly defined, the diet and exercise countermeasures will be able to be developed in a more targeted manner. With respect to bone mineral density, NSBRI has a strong bone team, which has a variety of countermeasure approaches to this problem. In addition, NASA has a strong nutrition team with solid expertise in calcium metabolism and bone turnover. For these reasons we have chosen, at this time, to measure indicators of immune function and bone health in projects as appropriate, to cooperate/collaborate with NASA scientists in these areas, but not to have them as primary areas of focus in this initial period.

The Nutrition and Physical Fitness Team is new, and became operational in 2001. It presently consists of three nutrition countermeasure projects (Lupton, Wolfe, and Tobin), an "in flight" physical fitness project (Schneider) which is at the feasibility stage, and a modeling project (Cabrera) which was recently assigned to the team from the former Human Integrated Function Team. Table 10.1, entitled "Current Project Research Activities," summarizes for each current Nutrition and Physical Fitness Team project what risks are addressed, the experimental system, the countermeasure target and whether a project is part of the strategic steps of Phase 1, 2 or 3 Activities.

Specifically, *Nutritional Countermeasures to Radiation Exposure*, JR Lupton, PI, Texas A&M University, is testing the hypothesis that a particular diet intervention (an n-3 lipid and fermentable fiber combination) in rats should protect against radiation-enhanced colon cancer by targeting DNA damaged cells for apoptotic removal. It is directed to Goal 5: Reduce Risk of Radiation Enhanced Development of Cancer and will also contribute to Goal 1. Rats receive one of four diets, are exposed to heavy iron radiation at Brookhaven National Laboratory and are injected (or not) with a colon specific carcinogen. A variety of measurements are taken at three stages of the tumorigenic process (initiation, promotion, and final tumor development). This project also has a noninvasive component of monitoring changes in gene expression over time as a result of radiation and carcinogen exposure using microarray technology. If validated in rats, the diets and techniques can be modified for future studies in humans. This noninvasive technology is also directed at Goal 12: Develop noninvasive techniques for assessing the effectiveness of diet and physical fitness interventions.

Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress, R. R. Wolfe, PI, University of Texas Medical Branch at Galveston, is testing an amino acid supplement designed to ameliorate muscle wasting induced by stress-and microgravity-induced depression of protein synthesis in a bed rest study. The study consists of 12 individuals with or without consumption of the supplement in a 30-day bed rest trial. A unique feature of this study is the use of a cortisol infusion at two times during the intervention period to mimic (in part) the documented elevated cortisol levels during space flight. Although primarily targeted to Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function, we have considered this bed rest study to be our cornerstone project and have added a large number of ancillary grants which use the bed rest model and the nutritional intervention to address issues related to other goals. These "add on" projects will be discussed further in reference to Goal 14: Integrate Research and Analysis. To summarize here, separate projects working off of the Wolfe bed rest study are targeted to: Goal 1: Reduce Risk of Suboptimal Nutritional Status; Goal 2: Reduce Risk of Suboptimal Physical Fitness; Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function; Goal 9: Reduce Risk of Depressed Immune Function; Goal 10: Reduce Risk of Loss of Bone Mineral Density; and Goal 14: Integrate Research and Analysis.

Nutritional Modulation of Pancreatic Endocrine Function in Microgravity, B. W. Tobin, PI, Mercer University School of Medicine, will determine amino acid countermeasure effects on endocrine function of human pancreatic islets of Langerhans with the goal to optimizing insulin synthesis and secretion under microgravity conditions. Dr. Tobin uses human pancreatic islet cells cultured on static plates or in a high aspect ratio vessel (HARV) designed to replicate some of the conditions of microgravity. The goal of this research project is to determine how different physiological conditions, characterized by over or under expression of certain hormones, affect insulin secretion and to develop an amino acid combination that will optimize this secretion. In becoming part of the Nutrition and Physical Fitness Team, Dr. Tobin has added a myocyte culture model to determine the effect of maximizing insulin secretion on muscle cell response. In addition to targeting Goal 1 (as do all nutrition based projects), this project specifically addresses Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function, since uptake of amino acids into muscle is governed by insulin. Optimal insulin synthesis should maximize uptake of amino acids into muscle and thus enhance muscle protein synthesis. The other goal targeted by this research project is Goal 14: Integrate Research and Analysis. This goal will be described more fully later under Goal 14, but briefly stated, Tobin's project is using the amino acid levels found in blood of subjects from Wolfe's bed rest study who have received his amino acid supplement. Thus, there is integration between these two projects.

Treadmill Exercise as a Countermeasure for Microgravity Deconditioning, S. M. Schneider, PI, University of New Mexico, will evaluate, in flight, the effectiveness of two treadmill countermeasures to maintain aerobic capacity and leg strength, prevent increases in bone resorption and help prevent muscle atrophy. The anticipated countermeasure resulting from this research program will be an optimally designed treadmill, with a protocol that maximizes the above outcome measures, and is achieved with the least time expenditure. This research targets Goals 2, 3, 4, and 10.

Metabolic Adaptations of Skeletal Muscle to Training/Detraining. A Systems Model, M. E. Cabrera, PI, Case Western Reserve University, uses mathematical modeling to perform quantitative predictions of work capacity after periods of training/detraining. These models and predictive equations are based on data from animal and human studies and will provide a framework for quantitative understanding of the skeletal muscle metabolic adaptations to periods of training and detraining. Part of the database used in these predictive equations is nutritional information or metabolic status. Therefore, this research project serves to integrate nutrition and physical fitness and targets goals 1, 2, and 3, as well as, goal 14, integration.

We anticipate that the ground based research summarized above, combined with future projects discussed below, will eventually result in three fundamental countermeasure strategies to provide optimal nutrition and physical fitness, which in turn will ameliorate the risks shown in section 10.2. These general, broad-based strategies are summarized below.

1) *Development of the rationale and mechanistic justification for a combination of traditional and targeted functional foods which are highly palatable and designed to minimize the risks summarized in section 9.2, without negatively impacting either food intake or other risks for which they may not be specifically targeted.* For example, an amino acid supplement designed to enhance protein synthesis should not depress immune response or negatively impact bone health. A coordinated effort at the team level is required to achieve this goal. Some of these foods/supplements will be general to meet the nutrient requirements for all individuals in space. Others may need to be task specific, e.g. time-release energy foods for prolonged activity without additional food intake such as may be experienced during EVA. Although it is not the goal of the nutrition team to develop the foods and supplements, it is a team goal to determine the requirements for what should be in those foods/supplements.

2) *Development of an exercise protocol, and the appropriate equipment to maximize both muscle strength, lean body mass, bone strength, and aerobic capacity.* Studies will be designed to determine the optimal as well as minimal prescription for frequency, duration, and intensity of

the exercise countermeasure to obtain the most time efficient method to maintain muscle and cardiovascular capacity. Traditionally, this prescription is considered to involve two types of exercise protocols (resistance training and aerobic exercise), but where possible, their integration should be a priority. For example the Schneider project involves optimizing protocols for treadmill exercise. This form of exercise is typically considered an aerobic exercise, but properly structured with appropriate force and heel strike requirements; it may also contribute to leg muscle strength and potentially have a positive effect on bone strength (outcomes which are being tested with the proposed protocol). The overall intention of the physical fitness program is to produce the most physically fit individual (from both a strength and aerobic viewpoint) in the least amount of time. Since exercise takes time from other tasks and also requires energy input, which means greater food intake, accomplishing this task will have many benefits. In addition, the Nutrition and Physical Fitness Team is aware that different forms of preflight and in-flight physical exercise are a major countermeasure thrust for the Muscle Team and will work with the Muscle Team to coordinate and maximize the effectiveness of our collective programs to address shared goals.

3) *Development of a strategy of timing of food intake with respect to physical activity.* This countermeasure plan will be key to the overall health of individuals in space. Often overlooked, when one eats with respect to when one exercises has important consequences for overall utilization of nutrients and for human performance. The current recommendations for food intake timing with respect to exercise as practiced in flight are not based on strong scientific studies. A scientific basis for the timing of food intake and exercise prescriptions is needed. For example, R. Wolfe has shown in human studies, that providing amino acids prior to rather than after an exercise bout will enhance protein synthesis by up to three fold. Also, the appropriate combination of foods or new functional foods with time release components could provide a certain level of blood glucose over extended periods of time so that exercise or other tasks such as EVA could be performed without stopping to eat.

Keeping these three overarching countermeasure strategies in mind, the following is a discussion of the current status and future plans of the program with respect to the ten risk-based and four non-risk based goals defined in section 10.3. As noted above, goals 1 and 2 are considered central to all of the other goals. They are (1) Reduce Risk of Suboptimal Nutritional Status and (2) Reduce Risk of Suboptimal Physical Fitness. With respect to Goal 1, designing optimal diets for individuals in space is not just taking the recommended dietary reference intake values (DRIs) developed for Americans and Canadians and modifying them for microgravity conditions. Optimal nutritional status for maximal performance both in space and for optimal health after space flight has to be more than meeting minimal RDI requirements. One needs to ask the question, "Optimal for what?", and in this case it is for maintaining muscle strength, bone mass, immune function, etc. This fact means that all of the nutrition projects (Lupton, Wolfe and Tobin) are addressing various aspects of what would represent optimal nutrition – Lupton from a view towards protecting against radiation-enhanced cancer; Wolfe and Tobin from the viewpoint of maintaining muscle mass through amino acid uptake into muscle and appropriate insulin response. However, this view also means that many aspects of "optimal nutrition" are not currently being addressed. The most critical gap in meeting this goal is the absence of a program that deals with the anorexia of space flight. If one does not consume sufficient food, no matter how well designed the food is, the individual will not be nutritionally replete. Although clearly a multifactorial problem involving such diverse factors as psychosocial interactions, scheduling tasks, food palatability and ease of access and preparation, nausea and gastrointestinal disturbances, there appears to be a less clear, additional, causative factor induced by microgravity which is independent of other factors and results in diminished food intake. Alleviating this anorexia of space flight is a high priority for the Nutrition and Physical Fitness Team and was the basis for a listed priority item in the recent request for proposals in the last combined NASA/NSBRI funding announcement. The Team has benefited greatly from the combined expertise of Helen Lane and Scott Smith from NASA/JSC who know what has been tried in the past, what works and what does not work with respect to nutrition. These two individuals are on our team, are an integral part of our meetings and conference calls, and will assist in resolving this issue.

With respect to Goal 2 (Reduce Risk of Suboptimal Physical Fitness), again, development of successful countermeasures to meet this goal underlies all of the other goals. In many ways, there are already potential countermeasures at a high stage of development (exercise equipment and protocols) and with further relatively simple studies we could have countermeasures in place within a rapid time frame. The Schneider protocol is an example of such a study, which really tests the duration and intensity of treadmill exercise required to meet several "success" criteria. Studies such as this one will provide the scientific basis for exercise prescriptions. The Nutrition and Physical Fitness Team sees Goal 2 as being very practically oriented, rather than at the level of basic science. Protocols to be tested need to be ones that can be used in space and should aim towards the maximum benefits in the shortest amount of time. If funding for this team were increased, our next two subgoals within this goal would be: first, to have an exercise intervention which involves both aerobic and resistive training and second, to initiate a study designed to integrate exercise with diet (such as a study that would use the same protocol as the Wolfe bed rest study). This suggestion was also part of the request for proposals that went out in response to the combined NASA/NSBRI grants program in late 2001.

Goal 3 (Reduce Risk of Diminution of Skeletal Muscle Function) is the primary research focus of the current program, and four out of the five projects address this goal (Wolfe, Tobin, Schneider, Cabrera). The problem addressed is that muscular inactivity leads to decreased protein synthesis. This problem is compounded by the fact that stress (mediated by moderate hypercortisolemia) leads to increased protein breakdown. The combined effect of decreased synthesis and increased breakdown results in loss of skeletal muscle mass, which leads to loss of muscle strength. This compromises crew capabilities, including EVA or potential emergency egress. Countermeasures to these risks include an amino acid supplement designed to enhance protein synthesis (*Wolfe bedrest study)* which should also enhance insulin secretion and thus amino acid uptake into muscle and muscle synthesis (*Tobin, insulin secretion*). This dietary countermeasure, combined with an appropriate treadmill exercise should help maintain leg strength and aerobic capacity (*Schneider, treadmill)*, positively affecting both muscle strength and uptake of amino acids into muscle for protein synthesis. Finally, the newest addition to the team (*Cabrera, modeling adaptations of skeletal muscle*), will take data from the Wolfe, Tobin and Schneider programs and combine it with existing data from previously conducted research, to develop equations that will predict work capacity after periods of training/detraining. Progress towards achieving this goal is advancing, and the goal is adequately addressed by current research projects. In addition, as we more fully integrate with the Muscle Team (See Goal #14), our combined strengths in this area position us to advance rapidly through phases of countermeasure development.

Goal 4 (Reduce Risk of Reduced Cardiovascular Capacity) is partially addressed by the Schneider treadmill project. Additional aerobic exercise based protocols proposed by this team or others could serve to reduce further the risk of diminished cardiovascular capacity. The NSBRI cardiovascular team is also tackling various aspects of this problem directly. Given limited resources, therefore, our Team does not recommend a new project specifically targeted to cardiovascular capacity that is independent of enhancing aerobic capacity.

Goal 5 (Reduce Risk of Radiation Enhanced Development of Cancer) is currently being addressed by the Lupton project. Risks to personnel in space from radiation exposure are considered to be a tier one problem by NASA. A primary risk of radiation exposure is later cancer development. Of all the cancers, colon cancer is the second leading cause of death from cancer in the United States today. It strikes men and women equally. On the positive side, it is the cancer most amenable to diet intervention. Thus, studying mechanisms by which we can protect against the development of this cancer with respect to previous radiation exposure is important. To maximize our effectiveness in addressing this goal, future plans involve adding on projects to work off of the Lupton rat study, since rats irradiated at Brookhaven and kept through until tumor formation are a valuable resource that should be shared wherever possible. In addition, we plan to collaborate more closely with the Radiation Team in the future, in particular with Dr. Ann Kennedy, who also has a diet/radiation project using antioxidants.

Goal 6: Reduce Risk of Decreased Cognitive Function; Goal 7: Reduce Risk of Alterations in Sleep Patterns; Goal 8: Reduce Risk of Poor Psychosocial Adaptation are not part of the current program and are not anticipated to be part of the program in the near future. However, these are important risks, which are amenable to diet and/or exercise interventions. Nutrition and Physical Fitness are both interventions that affect all body systems and almost every risk. The challenge is to concentrate on those risks that have the best science base already established so that the NSBRI program can more rapidly achieve production of countermeasures. Goals 6,7 and 8 are at an early stage of scientific knowledge and therefore will be part of the program in the future rather than at this time.

Goal 9: Reduce Risk of Depressed Immune Function will not be addressed at this time. As mentioned above, the key risks of space flight to compromised immune function are being defined at this time. Therefore, the science is somewhat less mature than that for how muscle behaves during flight. For that reason, this goal will not be a primary area of research focus at this time. However, we currently have two projects related to this goal which are working off the Wolfe bedrest study: *(1) Effects of bed-rest on immune and inflammatory reaction and it's modulation by corticosteroids*. P. Uchakin, PI, Mercer University. Uchakin's hypothesis is that stress during inactivity alters the balance between cell-mediated and humoral immunity. *(2) Effects of prolonged bedrest on herpesvirus-specific immunity*. R. Stowe, PI, UTMB. The group's hypothesis is that prolonged bedrest will result in increased reactivation of latent herpes viruses.

Goal 10: Reduce Risk of Loss of Bone Mineral Density is addressed by a collaborative effort with R.Wolfe on the cornerstone bedrest study: *The effect of bed rest and amino acid supplementation on bone markers of calcium metabolism*. S. M. Smith, PI, NASA, JSC. Smith's hypothesis is that amino acid supplementation will reduce calcium excretion from bones via its effects on skeletal muscle.

The non risk-based goals are at various levels of development at this time. Goal 11: Monitoring Methods for Assessment of Food Intake and Physical Activity is being handled well by NASA but could be optimized with back up systems (for measuring exercise specifically). D. Hagan, Leader for exercise/physical fitness at NASA/JSC, is a member of our team, and we will work closely with him in the future to improve this monitoring system. Goal 12: Develop Noninvasive Technologies for Assessing the Effectiveness of Diet and Physical Fitness Interventions is in its infancy. One important aspect of the Lupton project is the use of microarray technology on mRNA from fecal material to see which genes are turned on or off during particular diet interventions, which ones are affected by radiation exposure, and how these gene array patterns predict for a variety of endpoints. This patented technique is well developed in the rat, and the plan is to later apply it to humans. As noted previously, diet and physical fitness interventions lend themselves very well to Earth-based applications (Goal 13). In particular, we envision a protein supplement that will enhance amino acid uptake into muscle and muscle protein synthesis as a result of the Wolfe bed rest study. This supplement will also be useful for individuals on Earth who have muscle wasting due to a variety of causes. We also envision a supplement of omega 3 fatty acids combined with pectin (a fermentable fiber) which may protect against both oxidative and alkylation damage to colonic DNA. With colon cancer the second leading cause of death from cancer in the US today, such a supplement could prove to be very beneficial. Modifications to a treadmill and developing strategies for simultaneously enhancing leg muscle strength along with aerobic capacity would also certainly be welcome for many people in the US who need to get the maximum benefit from exercise in the minimum amount of time.

Goal 14: Integrate Research and Analysis has already been a major part of the Nutrition and Physical Fitness Team. This goal includes efforts to enhance the interaction of individual Nutrition and Physical Fitness Team investigators: a) among the current team's infrastructure, b) among investigators within other teams (eg. Muscle, Radiation Teams), and c) with investigators not formally associated with the NSBRI. The activities will allow us to greatly expand the resources of the NSBRI and the ability to tackle the risks of space travel. Table 10.2 summarizes our current efforts at integration. In addition to strong collaborations within our team, a few examples of integration of the Nutrition and Physical Fitness Team with other teams or researchers outside of the NSBRI are as follows: Lupton is collaborating with Judex (Bone Team) in supplying rat hind limbs from irradiated rats on different diets. The Wolfe bed rest study is a true collaborative effort with the following investigators/projects: P. Uchakin, Mercer University, testing the hypothesis that stress during inactivity alters the balance between cell-mediated and humoral immunity; S. M. Smith, NASA, JSC, The effect of bed rest and amino acid supplementation on bone markers of calcium metabolism; R.R. Fitts, Marquette University, The effect of prolonged bed rest and amino acid supplementation on muscle fiber function; and R. Stowe, UTMB, Effects of prolonged bedrest on herpesvirus-specific immunity. Similar measurements to the Stowe bedrest study are also being performed on the Shuttle and ISS crewmembers, and so the Stowe study would serve to complement in-flight work. Additional collaborative projects with the Wolfe study include: T.P. Stein, UMD-NJ, Does bed rest + hypercortisolemia lead to increased oxidative stress during the recovery phase?; H W Lane, NASA, JSC, The effect of bed rest and amino acid supplementation on muscle energy production during exercise. In addition to collaborative projects, several people who were not directly funded with NSBRI grants have become an active part of our team. They include Helen Lane and Scott Smith from NASA/JSC in the area of nutrition and Don Hagan, also NASA/JSC, in physical fitness. These close ties to NASA enable the Nutrition and Physical Fitness Team to be up to date on the most recent countermeasure approaches to addressing nutrition and physical fitness related risks.

10.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Goal 1: *Reduce Risk of Suboptimal Nutritional Status*

Objective 1A. Assess Risk and/or Determine Level of Acceptable Risk

- Initiate a project that determines the metabolic basis of the anorexia of space flight if funds become available from NSBRI/NASA.

- Complete project to determine the combined effect of radiation and a colon carcinogen on the development of colon cancer and the level of risk caused by each type of DNA damage, individually and collectively (Lupton)

Objective 1B. Determine Mechanisms

- Complete project to determine effect of microgravity on insulin secretion and muscle metabolism (Tobin)
- Complete project to determine how and why specific diets protect against radiation and carcinogen induced DNA damage (Lupton)
- Complete project to determine if an amino acid supplement enhances protein synthesis during bed rest and cortisol infusion (Wolfe)

Objective 1C. Develop Countermeasures

- Complete project to develop diet intervention that ameliorates muscle wasting and therefore helps to reduce risk of suboptimal nutritional status (Wolfe)
- Complete project to develop fiber/fat supplement that ameliorates DNA damage (Lupton)
- Complete project that will develop the ideal ratio of amino acids to maximize insulin secretion and myocyte uptake facilitated by insulin which can later be made into a supplement (Tobin)

Goal 2: *Reduce Risk of Suboptimal Physical Fitness*

Objective 2A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 2B. Determine Mechanisms

- Complete project to determine if treadmill exercise, properly configured, can also benefit bone health and muscle strength (Schneider).

Objective 2C. Develop Countermeasures

- Complete project to determine the optimal duration and intensity of treadmill exercise to ameliorate loss of muscle strength and loss of aerobic capacity (Schneider).
- If funding for this team were increased, determine the optimal combination of aerobic and resistance exercise, preferably in combination.
- If funding for this team were increased, integrate exercise with diet to determine the best combination with respect to both type and amount of food and exercise, and timing of one with respect to the other.

Goal 3: *Reduce Risk of Diminution of Skeletal Muscle Function*

Objective 3A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 3B. Determine Mechanisms

- Complete project to determine effect of microgravity on insulin secretion and muscle metabolism and myocyte response (Tobin)

Objective 3C. Develop Countermeasures

- Complete project to develop diet intervention that promotes protein synthesis in muscle and ameliorates muscle wasting (Wolfe)
- Complete project to develop optimal physical fitness protocols for space that will serve to maintain skeletal muscle function (Schneider)
- Develop equations that can be used to predict for work capacity after periods of training/detraining (Cabrero)
- Working with the Muscle Team, integrate the proposed countermeasures between teams

Goal 4: *Reduce Risk of Reduced Cardiovascular Capacity*

Objective 4A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 4B. Determine Mechanisms
Objective 4C. Develop Countermeasures

- Complete project to develop optimal physical fitness protocols for space (Schneider)

Goal 5: *Reduce Risk of Radiation Enhanced Development of Cancer*
Objective 5A. Assess Risk and/or Determine Level of Acceptable Risk

- Complete project to determine the additive or synergistic effect of radiation and a colon specific carcinogen on tumor development (Lupton)

Objective 5B. Determine Mechanisms

- Complete project to determine how radiation and carcinogen result in greater DNA damage than either alone (Lupton).
- Complete project to determine how diet is protective against the development of radiation-enhanced colon carcinogenesis (Lupton)

Objective 5C. Develop Countermeasures

- Complete project to develop diet intervention that protects against radiation-induced cancers (Lupton)

Although the next three goals (6,7,8) represent important risks, which are amenable to diet and/or exercise interventions, a stronger science base is required before we can effectively target countermeasures to these risk areas. For that reason the Nutrition and Physical Fitness Team does not have specific strategic activities in support of these goals at this time.

Goal 6: *Reduce Risk of Decreased Cognitive Function*
Objective 6A. Assess Risk and/or Determine Level of Acceptable Risk
Objective 6B. Determine Mechanisms

- Initiate a project to determine how diet and/or exercise could potentially ameliorate the risk of decreased cognitive function. This would be possible if funding became available

Objective 6C. Develop Countermeasures

Goal 7: *Reduce Risk of Alterations in Sleep Patterns*
Objective 7A. Assess Risk and/or Determine Level of Acceptable Risk
Objective 7B. Determine Mechanisms

- Initiate a project to determine how diet and/or exercise could potentially ameliorate the risk of alterations in sleep patterns. This would be possible if funding became available

Objective 7C. Develop Countermeasures

Goal 8: *Reduce Risk of Poor Psychosocial Adaptation*
Objective 8A. Assess Risk and/or Determine Level of Acceptable Risk
Objective 8B. Determine Mechanisms

- Initiate a project to determine how diet and/or exercise could potentially ameliorate the risk of poor psychosocial adaptation. This would be possible if funding became available

Objective 8C. Develop Countermeasures

Goal 9: *Reduce Risk of Depressed Immune Function*
Objective 9A. Assess Risk and/or Determine Level of Acceptable Risk
Objective 9B. Determine Mechanisms

- Complete project to determine how bed rest and corticosteroids affect immune and inflammatory reactions (Uchakin, collaboration with Wolfe).
- Complete project to determine if prolonged bedrest will result in increased reactivation of latent herpesviruses (R. Stowe, collaboration with Wolfe).

Objective 9C. Develop Countermeasures

Goal 10: *Reduce Risk of Loss of Bone Mineral Density*

Objective 10A. Assess Risk and/or Determine Level Of Acceptable Risk

Objective 10B. Determine Mechanisms

Objective 10C. Develop Countermeasures

- Complete project to develop optimal physical fitness protocols for space (Schneider)
- Complete project to determine if the amino acid supplement in the Wolfe bedrest study also ameliorates loss of bone mineral density (S. M. Smith, collaboration with Wolfe).

Goal 11: *Develop Monitoring Methods for Assessment of Food Intake and Physical Activity*

- Work with NASA/JSC to optimize monitoring methods

Goal 12: *Develop Noninvasive Techniques for Assessing the Effectiveness of Diet and Physical Fitness Interventions*

- Complete project to determine which changes in gene expression predict for later tumor development (Lupton) in rats.
- Using these markers (noted above) optimize protocols for their applications to humans.

Goal 13: *Develop Earth-based Applications for Diet and Physical Fitness Interventions*

Objective 13A. Develop a protein supplement that will enhance amino acid synthesis and can be used in conditions of muscle wasting.

Objective 13B. Develop an omega 3/fiber combination supplement that may be used to protect against colon cancer.

Objective 13C. Develop appropriate modifications and exercise prescriptions for treadmill exercise that may benefit individuals both aerobically and with respect to strength.

Goal 14: *Integrate Research and Analysis*

Objective 14A. Integrate Research Within the Nutrition and Physical Fitness Team.

- Continue current integration efforts among the Nutrition and Physical Fitness Team investigators as summarized in Table 10.2.
- Use Wolfe amino acid supplement in Tobin project and complete both projects
- Complete collaborative project between Wolfe and Uchakin (part of Tobin project) to determine the impact of amino acid supplement and bedrest on immune response.
- Use data from all projects within the team to become part of the mathematical modeling project and complete modeling project (Cabrera)

Objective 14B. Integrate Research With Other Teams. Using Modeling as well as Other Approaches.

- Complete synergy project between Lupton (Nutrition) and Judex (Bone).
- Use of common diet and exercise protocols

Objective 14C. Integrate Research with Scientists Outside of NSBRI

- Complete integrative project between Wolfe bedrest study and S. M. Smith, NASA/JSC, on the effect of amino acid supplementation on bone markers of calcium metabolism.

- Complete collaborative project with R.R. Fitts, Marquette University, and the Wolfe bedrest study on the effect of prolonged bed rest and amino acid supplementation on muscle fiber function.
- Complete collaborative project with R Stowe, UTMB, and the Wolfe bedrest study on the effects of prolonged bedrest on herpesvirus-specific immunity. These measurements are also being performed on the Shuttle and ISS crewmembers and would serve to complement in-flight work
- Complete collaborative project with the Wolfe study and T.P. Stein, UMD-NJ, on whether or not bed rest + hypercortisolemia leads to increased oxidative stress during the recovery phase.
- Complete collaborative project with the Wolfe study and H W Lane, NASA, JSC, on the effect of bed rest and amino acid supplementation on muscle energy production during exercise
- Continue collaborative partnerships with H. W. Lane, S. M. Smith and D. Hagan at NASA/JSC to seek out areas in which we can work together towards common goals.

10.6 SUMMARY

In the next 3-5 years, the Nutrition and Physical Fitness Team should be able to implement both the fundamental and applied research programs that address the identified risks outlined in this Research Plan. As discussed in the plan, the primary unifying goal at the onset is to develop countermeasures to diminution of skeletal muscle function (Goal 3). Four of our five currently funded projects are targeted to this goal. One of these projects will allow us to understand, mechanistically, how bed rest and heightened cortisol levels affect muscle protein synthesis and how an amino acid supplement can ameliorate the risks of muscle atrophy. From the second project, we will understand at a basic level the amino acid requirements for efficient insulin synthesis and secretion, and how insulin secretion can be optimized with an appropriate amino acid supplement. Adding to our applied outcome knowledge base will be information from the third project, which will delineate how often and what intensity treadmill exercise is required to maintain leg muscle strength and aerobic capacity (also achieving Goal 4). Finally, our mathematical modeling project will take data from the three projects mentioned above, plus other NSBRI projects and research in the literature, and develop predictive equations to determine, in advance, how an individual in space will perform (from a metabolic and fitness viewpoint) when following a specific exercise regimen. The integration (Goal 14) of these four projects towards this common goal is shown in Figure 10.1. This focus on muscle function will also serve to help meet our first two goals, which involve optimizing nutritional status and physical fitness. Earth-based benefits will be generated from the projects targeted to maintaining muscle mass and strength (Goal 13). Such benefits include appropriate foods/supplements to enhance protein synthesis in muscle wasting states and to optimize muscle strength using exercise protocols. The timeline for accomplishing the tasks targeted to Goal 3 are shown in Table 10.3.

Another major accomplishment envisioned during this time frame is an understanding of the mechanism by which radiation exposure and exposure to a carcinogen can interact to promote colon cancer development (Goal 5). Further, the nutritional countermeasure to combat DNA damage from radiation will be identified and established with sufficient substantial data to justify a human clinical application.

In addition, one of the most significant accomplishments over the next five years will be the combined findings of the seven ancillary projects that are using the Wolfe bed rest study as their source of material. Figure 10.2 shows the synergistic nature and areas of research that will be completed using the same subjects and intervention protocol of the Wolfe study. Not only will these results provide important data independently, but also the fact that they all use the same subjects and interventions will provide a rich database for comparisons between the outcome variables. At the end of this study, we will know not only how and if an amino acid supplement protects against depressed protein synthesis but also how this intervention affects immune response, muscle fiber type, markers of bone health, oxidative stress and muscle energy production.

The overarching aim of the NSBRI Nutrition and Physical Fitness program is to provide diet/functional food/supplement countermeasures which optimize nutritional status and exercise countermeasures which optimize physical fitness that, when combined, maximize the effectiveness of each.

Figure 10.1. This figure illustrates the integration of four of the five currently funded projects that are targeted towards the common goal of maintaining muscle mass and strength

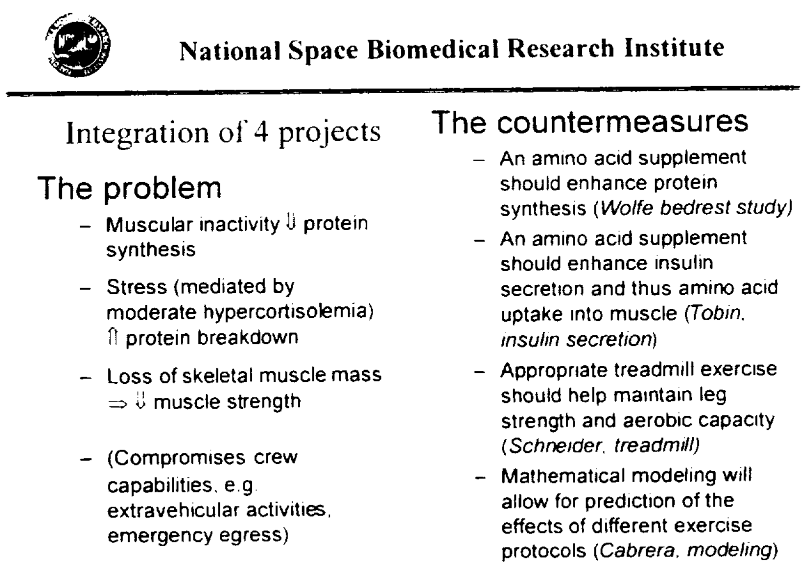


Figure 10.2. Synergy projects based on the Wolfe bed rest study

National Space Biomedical Research Institute

Supplemental collaborative objectives

•immune and inflammatory response
PI: Peter Uchakin, Mercer University

•bone markers of calcium metabolism
PI: Scott M. Smith, NASA, JSC

•amino acid blood levels
PI: Brian Tobin, Mercer University

•oxidative stress
PI: T.P. Stein, UMD-NJ

•herpesvirus-specific immunity
PI: Raymond Stowe, UTMB

•muscle energy production during exercise
PI: Helen W. Lane, NASA, JSC

Wolfe bed rest study

•muscle fiber function
PI: Robert R. Fitts, Marquette University

National Space Biomedical Research Institute
NUTRITION, PHYSICAL FITNESS AND REHABILITATION PROGRAM

Table 10.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
CABRERA/Metabolic Adaptations of Skeletal Muscle to Training/Detraining. A Systems Model	Diminished muscle function	Exercise	Computer Simulations and experimental data on rats and humans	Integrate existing knowledge into computational models of muscle metabolism	Predict effects of muscle mass loss and changes in fiber type distribution on muscle metabolism	Predict effects of detraining and/or exercise training on metabolism and work capacity
LUPTON/Nutritional Countermeasures to Radiation Exposure	Radiation-induced carcinogenesis	Diet/Nutrition	Rat	Test diets in rats injected with a colon specific carcinogen with/without radiation exposure to see which diet is protective against radiation and methylation damage, and how it protects	Predict effects of the optimal diet at each stage of the tumorigenic process and optimize noninvasive recovery of mRNA from exfoliated colon cells to predict and monitor the tumorigenic process	Develop and test dietary supplements that will decrease oxidative and methylation damage to colonic DNA and monitor their effectiveness through a noninvasive technique
SCHNEIDER/Treadmill Exercise as a Countermeasure for Microgravity Deconditioning	• Reduced cardiovascular capacity • Loss of bone • Diminished muscle function	Exercise	Human in flight study	Test different treadmill exercise protocols for maximal effectiveness in maintaining aerobic capacity, muscle strength, and bone mass	Evaluate effectiveness of exercise intervention protocols as related to outcome measures such as ability to do work	Integrate exercise protocols with nutrition protocols for maximum effectiveness
TOBIN/Nutritional Modulation of Pancreatic Endocrine Function in Microgravity	Diminished muscle function	Diet/Nutrition	Cultured pancreatic islet cells (HARV)	Determine nutrient needs of human pancreatic islet cells under different hormonal conditions designed to mimic microgravity and stress	Develop a nutrition intervention to ameliorate the depressed insulin secretion from human pancreatic islet cells	Test the diet intervention strategy in a bed rest/cortisol stressed research program
WOLFE/Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress	Diminished muscle function	Diet/Nutrition	Human bed rest	Determine if a glucose /amino acid supplement provided during bed rest helps to ameliorate depressed protein synthesis, muscle wasting & loss of muscle strength	Optimize the supplement and the timing of the supplement with respect to exercise	Formulate the supplement for timed release, palatability, etc.

National Space Biomedical Research Institute
NUTRITION, PHYSICAL FITNESS AND REHABILITATION PROGRAM

Table 10.2. Integration Activities

	CABRERA	LUPTON	SCHNEIDER	TOBIN	WOLFE
Internal Communication	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons. P. Uchakin from Tobin project is now situated in Wolfe lab.
Integrated Experiment Development	Integrate existing knowledge into computational models of muscle metabolism using data from nutrition and physical fitness, the literature, and the muscle team	Uses the same strain of rat and the same radiation protocol at Brookhaven National Lab as does the Dicello rat long term studies (Radiation Team). Thus results can be compared.	As a result of team meeting discussions, specific outcome measures of muscle strength will be added that can be related to outcomes from Wolfe study. Diet intake will be monitored.	Tobin has redesigned his research protocol as a result of talks with team members to now include myocyte cultures and is also using blood from Wolfe study to determine levels of amino acids to use in his cell culture system. Uchakin, a CoI with Tobin, is now collaborating directly with Wolfe	This bed rest study is highly integrated with a variety of projects. The same amino acid supplement is tested in the Tobin project and we plan to have it tested in the Baldwin rat model (Muscle Team).
Sample Sharing	Data from Wolfe, Lupton, Schneider, Baldwin (muscle team) and others from muscle team	Tobin will use pancreas from Lupton rats. S. Judex (bone team) will use rat hindlimbs, H. Hogan, TAMU, will also use bones.	Data from the experiment will be shared with Cabrera for his prediction models	Will use pancreas from Lupton, will provide pancreatic cells to R Walzem, TAMU, for lipid analysis	There are currently seven "add on" projects to the bed rest study . See discussion of Goal 14 in this report.
Synergistic Studies of Opportunity	Aerobic and resistance exercise training with humans, and applying this to his model	Planned integration with A. Kennedy of radiation team for potential cross-use of each other's diet interventions	Planning with Schneider (who is doing bed rest studies) to have a uniform diet protocol	Future goal is to fly the HARV with pancreatic cells in space to determine how well the results mimic his system on earth	This study maximally capitalizes on synergistic opportunities which have arisen in the course of meetings and telecons to expand the program with "add on" grants.
Development of Computer Model of Integrated Human Function	This is exactly what the project is and should be an integrating force for the entire team.	Data from this project will be used by Cabrera for his prediction equations.	Data from this project will be used by Cabrera for his prediction equations	Currently this research is all ex vivo and not suitable for the integrated function component which we are only doing in animals and humans	Data from this project will be used by Cabrera for his prediction equations

National Space Biomedical Research Institute
NUTRITION AND PHYSICAL FITNESS

Table 10.3. Achieving Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research	■												
Phase 1: Focused Mechanistic Research		■	■	■	■	■							
• Understand muscle protein synthesis under bed rest/cortisol enhanced conditions • Determine the amino acid requirements for muscle protein synthesis													
• Determine the amino acid requirements for insulin secretion under various stress enhanced conditions (*in vitro* HARV) • Determine the proper ratio of amino acids to enhance uptake into myocytes													
Phase 2: Preliminary Countermeasure Development Research		■	■	■	■	■							
• Test amino acid supplementation and how this may promote muscle protein synthesis in humans													
• Study role of amino acid supplements as countermeasure strategy (combining results from Wolfe and Tobin) • Develop predictive equations for estimating work performance as a result of different exercise paradigms													
Phase 3: Mature Countermeasure Development Research					■	■	■	■	■				
• Test different protocols to optimize muscle strength and aerobic capacity in space (Schneider) • Develop integrated exercise and nutritional countermeasure and test in humans													
Phase 4: Countermeasure Evaluation & Validation										■	■	■	
• Testing of integrated exercise and nutritional interventions inflight • Test ability of theoretical predictive equations to actually predict for work performance in humans, in space													
Phase 5: Operational Implementation of Countermeasure Strategy													■

11.0 Radiation Effects

Team Leader: John F. Dicello, Ph.D.
Professor of Oncology
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
Harry and Jeanette Weinberg Bldg., Rm. 1454
401 North Broadway
Baltimore, Maryland 21231-2410
410-614-4194
410-502-1419 FAX
diceljo@jhmi.edu

11.1 INTRODUCTION

The risks to human health inherent in space exploration are enumerated in the NASA Critical Path Roadmap, which lists radiation as one of the four Severe Type I Risks, the most critical type. It follows that the principal aims of the NSBRI Radiation Program are to improve the predictions of risks to human health from space radiations and to provide effective countermeasures that will significantly reduce these risks. The radiation risk areas, in terms of long-term missions, both low-Earth orbit or extra planetary, and their relation to the overall space program are shown in the following figure adapted from NASA's Critical Path Roadmap. As shown, generally, radiation is one of several initiating events of a multistep process that can take years or decades before a clinically relevant consequence manifests itself. The overarching concern is to minimize the radiation exposure to as low as reasonably possible. Because the outcome of exposure is dependent upon multiple initiating agents, as well as, factors in the promotion and progression stages of the diseases, there are multiple risk factors that can alter the outcome. The major consequences are shown graphically in Figure 11.1 and are delineated in the next section.

11.2 RISKS

The following risks in the Radiation Effects Discipline Area of the Critical Path Roadmap have been identified (risk number in parentheses):

- Carcinogenesis Caused by Radiation (38)
- Damage to Central Nervous System from Radiation Exposure (39)
- Synergistic Effects from Exposure to Radiation, Microgravity and other Spacecraft Environmental Factors (40)
- Early or Acute Effects from Radiation Exposure (41)
- Radiation Effects on Fertility, Sterility, and Heredity (42)

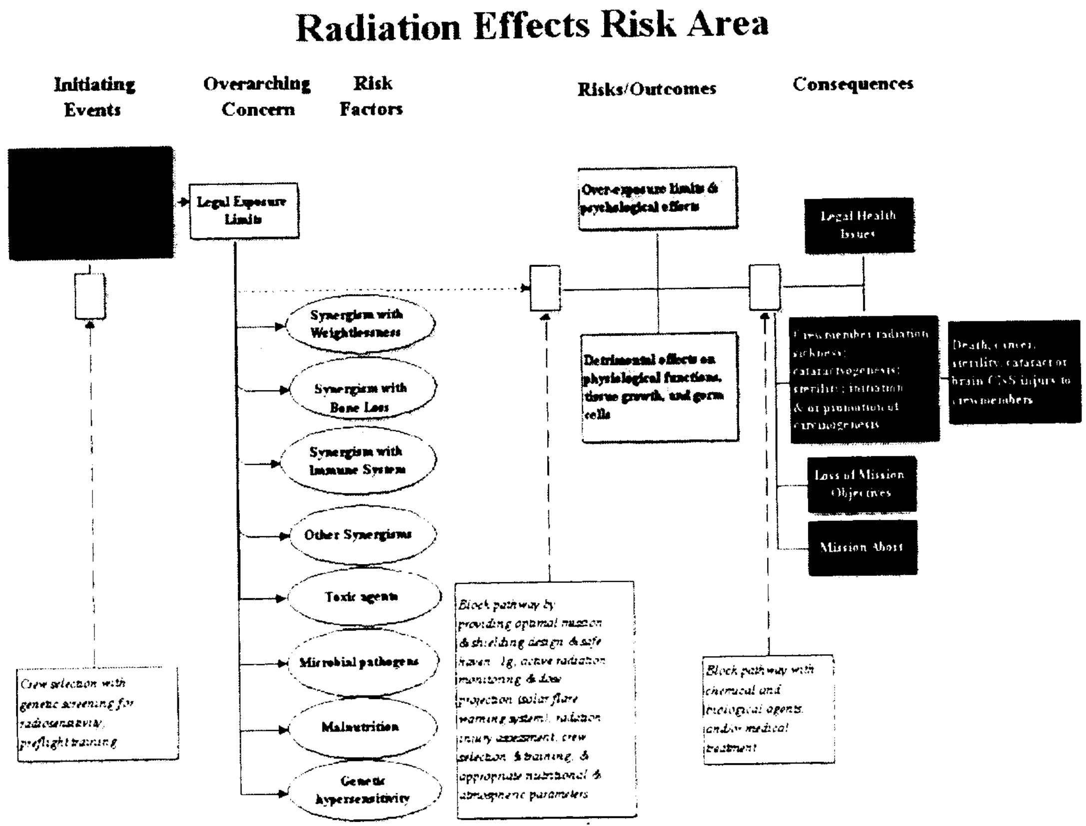


Figure 11.1. Radiation effects risks.

11.3 GOALS

The Radiation Effects Team has the following goals for its program:

<u>Risk-Based Goals</u>

Goal 1: *Reduce risk of carcinogenesis caused by radiation (38)*

Goal 2: *Reduce risk of damage to central nervous system from radiation exposure (39)*

Goal 3: *Reduce risk of synergistic effects from exposure to radiations, microgravity and other spacecraft environmental factors (40)*

Goal 4: *Reduce risk of early or acute effects from radiation exposure (41)*

Goal 5: *Reduce risk of radiation effects on fertility, sterility, and heredity (42)*

Non Risk-Based Goals

Goal 6: *Develop methods for assessing level of health risk, prevention of diseases, & appropriate medical care*

Goal 7: *Develop Earth-based applications*

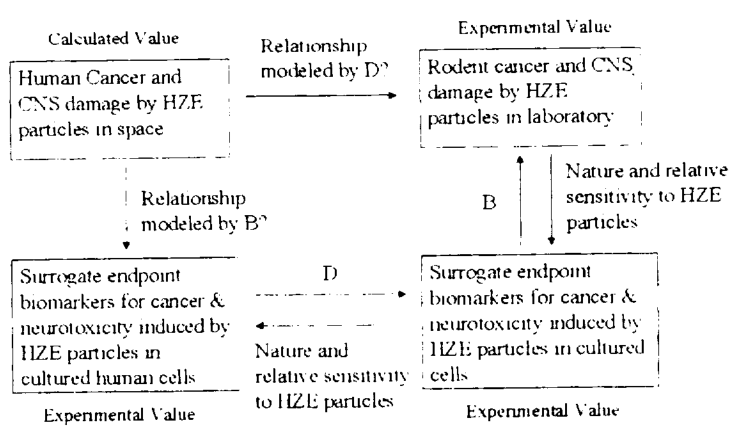
Goal 8: *Integrate research and analysis*

Although all of these goals are part of the Radiation Team and/or NASA's long-term goals, not all are being addressed at this time, as shown in Table 11.3. As part of NASA's mission, it is appropriate, however, that they be enumerated in the design plan to define future directions and areas of new emphasis.

11.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The underlying philosophy of the program's approach is modeled after that proposed in the NASA report on Modeling Human Risk (1997): experimentally determined risks for carcinogenesis and CNS damage in appropriate animal models with corresponding in vitro measurements can be used to validate theoretical relations between animal results and human response. These theoretical relations, then, can be used to extrapolate known responses of humans to acute exposures of low-LET radiations to expected responses to protracted exposures to protons and HZE particles. When such relations have been established, then this same process and these same animal and cell models can be used to determine the potential of pharmaceutical agents, including both chemopreventive drugs and dietary supplements, for reducing risks. This concept is illustrated schematically in the following figure (Fig. 11.2) which is a revision of that proposed in the NASA report on modeling human risk (1997).

Figure 11.2. Philosophy of radiation effects program.



Adapted from Modeling Human Risk: Cell & Molecular Biology in Context, 1997

Description of Current Projects and Progress Towards Risk-Based Goals

Currently, the Radiation Effects Team has six principal projects. In Table 11.1, these projects are summarized, including those risks that are currently being addressed, the experimental system, the countermeasure target, and whether a project is part of the strategic steps of Phase 1, 2 or 3 Activities. A brief description follows of each project and the countermeasures being studied:

PROJECT I: In vivo Studies of Mammary Carcinomas
John F. Dicello, PhD, *Johns Hopkins University*

Critical Path Risk(s): Carcinogenesis caused by radiation (38:1, 3, 5, 6, 7, (8), 9, 10, 11), Addresses Goal 1, Countermeasure Readiness Level: 4
Specific Aim: Determine risk of carcinogenesis in a relevant animal model and supply exposed animals for chemopreventive studies.
Countermeasure: Chemoprevention of cancers by use of pharmaceuticals administered after high-level exposure to radiations. Improved risk factors can be used to optimize spacecraft design for optimal shielding

PROJECT II: Chemoprevention and Radiation-Induced Neoplasms
David L. Huso, DVM, PhD, *Johns Hopkins University*

Critical Path Risk(s): Carcinogenesis caused by radiation (38:1, 3, 5, 6, 7, (8), 9, 10, 11), Addresses Goal 1, Countermeasure Readiness Level: 5
Specific Aims: Studies of the pathology of cancer induced by HZE particles and pharmaceutical intervention.
Countermeasure: Tamoxifen as a model for pharmaceutical intervention in the promotion and progression stages of carcinogenesis to reduce risk after exposure

PROJECT III: Countermeasures for Space Radiation Biological Effects
Ann R. Kennedy, PhD, *University of Pennsylvania*

Critical Path Risk(s): Carcinogenesis caused by radiation (38:1, 3, 9, 10), Early or acute effects from radiation exposure (41:1,3,5,10,11), Addresses Goals 1 and 4, Countermeasure Readiness Level: 4
Specific Aims:
(1) Determine the ability of various dietary supplements to reduce radiation-induced oxidative stress in cultured cells
(2) For the combinations of agents demonstrating efficacy as antioxidants *in vitro*, determine the ability of these agents to decrease radiation induced oxidative stress in Sprague Dawley rats.
Countermeasure: Dietary supplements prior to and after exposure to radiation to reduce the cancer incidence.

PROJECT IV: Risk Assessment and Chemoprevention of HZE Induced CNS Damage
Marcelo E. Vazquez, MD, PhD, *Brookhaven National Laboratory*

Critical Path Risk(s): Damage to CNS system from radiation exposure (39:1, 3, 7, 10, 11), Early or acute effects from radiation exposure (41:1, 3, 5, 10, 11), Addresses Goals 2 and 4, Countermeasure Readiness Level: 3-4
Specific Aims:
(1) Examine cell death in cycling and non-cycling neural cells
(2) To characterize the putative cell signaling cascades induced by high-LET radiation in the apoptotic pathways (ceramide- and p53-dependent).
Countermeasure: Modulate signaling pathways by pharmacological manipulation (trophic factors, free-radical scavengers, p53 modulators)

PROJECT V: CNS Damage and Countermeasures (In vivo Studies)
Marcelo E. Vazquez, MD, PhD, *Brookhaven National Laboratory*

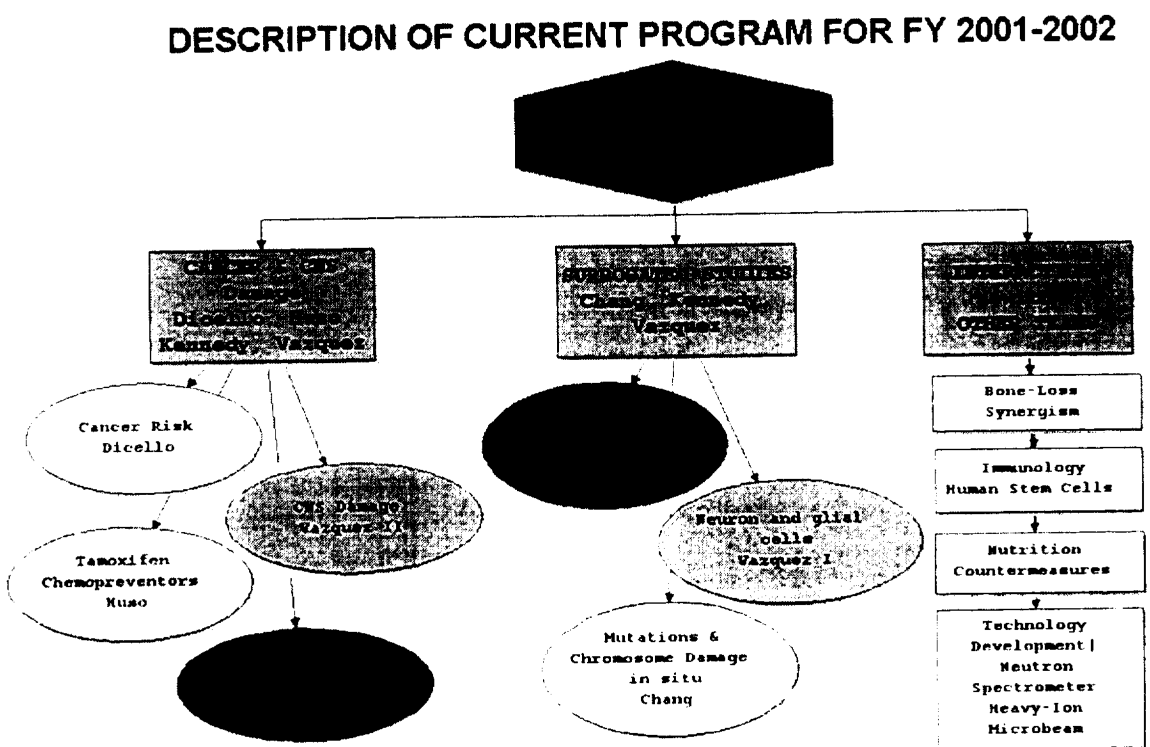
Critical Path Risk(s): Damage to CNS system from radiation exposure (39:1, 3, 7, 10, 11), Early or acute effects from radiation exposure (41:1, 3, 5, 10, 11), Addresses Goals 2 and 4, Countermeasure Readiness Level: 3-4
Specific Aims:
(1) Characterize the behavioral, neurochemical and structural changes induced by heavy ions and protons.
Countermeasure: To protect neural cell populations in vivo using pharmaceuticals, such as neuroprotectants (gangliosides), antioxidants (melatonin) and signal pathways modulators (p53 modulators)

PROJECT VI: Charged Particle Radiation-Induced Genetic Damage in Transgenic Mice
Polly Yee Chang, PhD, *SRI International*

Critical Path Risk(s): Carcinogenesis caused by radiation (38). Damage to central nervous system from radiation exposure (39). Early or acute effects from radiation exposure (41: (3), 5, 10). Addresses Goals 1, 2, and 4, Countermeasure Readiness Level: 2
Specific Aims:
(1) Examine both the dose and temporal-dependence of particle radiation-induced mutation in vivo using the LacZ transgenic mice model system. In particular, acute and long-term tissue specific mutagenic responses of CNS and rapidly renewing organ systems will be determined after exposure to protons and HZE particles.
(2) Examine the impact of genetic backgrounds, e.g. p53 on radiation sensitivity using the p53/lac Z double transgenics.
Potential Countermeasures: Determine if known radioprotective pharmaceuticals (e.g. tamoxifen, anti-oxidants) or cytokines (e.g., interleukins) reduce tissue-specific mutation frequencies or genetic damage *in vivo*. Such alterations in the genome may be precursors of cancer.

A summary diagram, Figure 11.3, describes the current program.

Figure 11.3 Current radiation effects program.



The major themes of this program are the understanding of risks and the development of effective countermeasures for the radiation-induced biological effects identified to be of major concern: radiation-induced cancer and CNS damage. It is also possible that because of the complexity of the space environment. unanticipated effects may occur in organ systems other than the CNS. Thus the major aims will cover five categories:

1. Develop countermeasures for mitigating effects of radiation exposure.
2. Develop markers for determining risks and monitoring the efficacy of countermeasures.
3. Determine carcinogenic and CNS effects for space radiation.
4. Determine acute and long-term pathological responses of rapidly renewing organ systems at risk.
5. Characterize differences in cell and molecular mechanisms for pathological effects for high- versus low-LET radiation in defined model systems.

Progress Towards Non Risk-Based Goals

Figure 11.1 refers to Goal 6, Develop methods for assessing level of health risk, prevention of diseases, & appropriate medical care. At present, this goal is not being explicitly expressed; however, progress towards this goal has been made. We have determined for the first time the risks of carcinogenesis in tissues relevant to humans from protons and HZE particles. We have further shown that relatively non-toxic pharmaceuticals can be used to reduce those risks in animal models in the promotion and progression stages after radiation. In order to extrapolate these risks to humans, we have to examine the interspecies variation in carcinogenesis as a function of particle type. As mentioned previously, it is imperative that the radiation studies of this program be mechanistically based in order to be able to extrapolate results to human models. Developing such appropriate theoretical, human models, that we presently do not have and that are not currently funded as part of this program, should be a major future goal (see elaboration under Goal 8, "integration using modeling"). Input for such models requires not only carcinogenesis studies but also the appropriate genetic, epigenetic, and cytogenetic data to define the mechanisms leading to carcinogenesis. The present results suggest that we could begin formulating ground-based and space-based clinical studies. In this respect we are already looking for less toxic combinations of pharmaceuticals and/or dietary supplements.

Several activities support the early development of Earth-based applications (Goal 7). We currently have an NIH grant (Joseph Lombardo, P.I.) at Johns Hopkins for medical telecommunications that resulted from the NSBRI collaborations. Another NIH program grant (Jerry Williams, P.I.) at JHU to develop novel treatment protocols in radiation therapy is a spin-off from a previous project of our team headed by Dr. Jerry Williams.

Table 11.2 at the end of this document illustrates in tabular form activities that are ongoing in achieving the Team's integration goal, Goal 8. A brief summary of these activities in provided here as well. To aid team integration, the Team holds weekly meetings at Johns Hopkins University School of Medicine and monthly teleconferences integrating experimental development. In terms of overall strategy, four of the team projects described are collaborating on investigating carcinogenesis (3) and CNS damage (1) *in vivo*, and three projects are addressing corresponding cellular effects. Collaborations among team members involve a great deal of integrated experiment development. The team as a group, under the direction of Drs. John Dicello and Marcelo Vazquez, is one of the strongest participants at the NASA biomedical facility of AGS acceleration at Brookhaven National Laboratory (BNL). This participation requires a series of proposals not only to NSBRI but also to each of the home institutions and to BNL for separate reviews and the necessary but not always automatic approval. Similarly, animal research and research involving human cells requires proposals to separate Institutional Review Boards at the home institutions and at the BNL, again requiring approval. The Team also does extensive sample sharing. For instance, Dr. Dicello provides animals and animal tissues for Dr. David Huso's tamoxifen studies. He is also irradiating animals for Dr. Jerry Williams' earlier cytogenetic studies.

We also have been collaborating with researchers on other NSBRI teams, where team goals overlap. There is a strong need for synergistic collaborations within and with other teams, some of which may address achievement of Goal 3. Preliminary experiments to show feasibility have been carried out by Dr. Dicello's group looking at 1) synergies between different types of radiations; 2) synergies arising between radiation and the immune system (with Immunology Team); and 3) synergistic interactions between radiation and bone (with Bone Team). In all cases significant synergistic effects have been observed, although uncertainties associated with the data have been large. However, currently, no additional funding has been available either for feasibility studies or for further research. We have also been collaborating with the team leader for the Education and Outreach since its inception. The Radiation program has included numerous undergraduate, graduate and postdoctoral students and has attracted additional external funding from NASA and the Johns Hopkins University Bloomberg School of Public Health among other sources, as well as, travel grants for the students to scientific meetings.

As a means of integrating their research with the scientific community beyond the NSBRI, Dr. Dicello's group has also had a long collaboration preceding the establishment of the NSBRI with scientists at the Johnson Space Center and Headquarters that has resulted in a continuous productivity of peer-reviewed publications and invited talks. Dr. Francis Cucinotta, JSC, spent his sabbatical leave at Johns Hopkins working with Dr. Dicello. Currently, there is no support within or outside of NSBRI for integration and analyses since it was eliminated as a line item from the NSBRI awards. A theoretically-based research approach is the only practical method by which the cell and animal data can be extrapolated to humans (except for identical responses), so it is an indispensable part of the strategic plan for the Radiation Program and should be supported.

Dr. Dicello's project was also successful in generating new and unique theoretical models to describe genetic and cytogenetic pathways and in vivo carcinogenesis, which contributes to the development of a computer model of integrated human function. Future strategic activities associated with this modeling project and a timeline for these activities are provided in Table 11.3H. Funding for this extensive modeling project is still needed.

Gaps and Weaknesses of the Program

Remaining gaps and weaknesses in the Radiation Effects Team plan have been identified:

1. In vivo data for synergistic effects of mixed fields.
2. Animal studies for protracted exposures.
3. A need for a more comprehensive analysis of human responses to low-dose, protracted exposures.
4. Improved methods for extrapolating animal data to humans too imprecise.
5. Inadequate research on early or acute consequences from radiation exposures (Goal 4).
6. No present research on effects on fertility, sterility, or heredity (Goal 5).

11.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Presented here are the objectives underlying each goal and the strategic activities that we plan to use to achieve the goals and objectives of our program. The timelines for achievement of the activities underlying each goal are presented in Table 11.3.

Goal 1: *Reduce risk of carcinogenesis caused by radiation*

Objective 1A: Assess risk and target level of acceptable risk

- In vivo measurements of carcinogenesis

Objective 1B: Determine mechanisms

- Cellular and Subcellular endpoints as surrogate biomarkers leading to carcinogenesis

Objective 1C: Develop countermeasures

- In vitro testing followed by in vivo studies of pharmaceuticals and dietary supplements

Goal 2: *Reduce risk of damage to central nervous system from radiation exposure*

Objective 2A: Assess risk and target level of acceptable risk

- In vivo measurements of CNS damage

Objective 2B: Determine mechanisms

- Cellular and Subcellular endpoints as surrogate biomarkers leading to CNS damage

Objective 2C: Develop countermeasures

- In vitro testing followed by in vivo studies of pharmaceuticals and dietary supplements

Goal 3: *Reduce risk of synergistic effects from exposure to radiation, microgravity and other spacecraft environmental factors*

Objective 3A: Assess risk and target level of acceptable risk

- In vivo measurements of combined hazards

Objective 3B: Determine mechanisms

- Cellular and Subcellular endpoints for combined hazards in comparison with responses to individual hazards

Objective 3C: Develop countermeasures

- Exercise, dietary supplements, and pharmaceutical intervention

Goal 4: *Reduce risk of early or acute effects from radiation exposure*

Objective 4A: Assess risk and target level of acceptable risk

- Observe acute responses for in vivo measurements of combined hazards

Objective 4B: Determine mechanisms

- Theoretical modeling compared with measurements

Objective 4C:Develop countermeasures

- Minimize dose with shielding and spacecraft design and choice of travel interval

Goal 5: *Reduce risk of radiation effects on fertility, sterility, and heredity*

Objective 5A: Assess risk and target level of acceptable risk

- Use existing epidemiological data for photon exposures

Objective 5B: Determine mechanisms

- Theoretical modeling of existing data base

Objective 5C: Develop countermeasures

- Minimize doses through spacecraft design and choice of travel interval

Goal 6: *Develop methods for assessment of level of health risk, prevention of diseases, and appropriate medical care*
Objective 6A: Develop markers for determining risks and monitoring the efficacy of countermeasures from previous experiment.

Goal 7: *Develop Earth-based applications*
Objective 7A: Translational research to move new discoveries into medical and industrial arena with the Industrial Forum.

Goal 8: *Integrate experimental research with theoretical analysis to be used to extrapolate data to risk and countermeasures in humans.*
Objective 8A: Integrate research within the radiation effects team
- All team projects focused on a major programmatic goal
- Samples and experimental design shared

Objective 8B: Integrate research with other teams, using modeling as well as other approaches.
- Foster collaborations with Bone and Immunology Teams
- Obtain funding for theoretical modeling

Objective 8C: Integrate research with scientists within NASA and outside of NSBRI
- Foster collaborations at JSC

11.6 SUMMARY

The risks to human health inherent in space exploration are enumerated in the NASA Critical Path Roadmap, which lists radiation as one of the four Severe Type I Risks, the most critical type. Most recently, radiation is being categorized as the most serious of these hazards in space. It follows that the principal aims of the NSBRI Radiation Program are to improve the predictions of risks to human health from space radiations and to provide effective countermeasures that will significantly reduce these risks. The major radiation risk area in terms of long-term missions, both low-Earth orbit or extra planetary, is carcinogenesis. Damage to the central nervous system and synergisms of different types of radiation or synergisms of radiation with other hazards including bone loss and reduced immunological response are all areas of concern as well. The current Radiation Effects Team projects are making significant progress towards assessing these risks and potential pharmacological, nutritional, and shielding countermeasures.

The underlying philosophy of the program's approach to experimentally determine risks for carcinogenesis and CNS damage in appropriate animal models with corresponding *in vitro* measurements can be used to validate theoretical relations between animal results and human response. These theoretical relations, then, can be used to extrapolate known responses of humans to acute exposures of low-LET radiations to expected responses to protracted exposures to protons and HZE particles. When such relations have been established, then this same process and these same animal and cell models can be used to determine the effectiveness of potential countermeasures, such as pharmaceutical agents, including both chemopreventive drugs and dietary supplements, for reducing risks.

National Space Biomedical Research Institute
RADIATION EFFECTS PROGRAM

Table 11.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
CHANG/Charged Particle Radiation-Induced Genetic Damage in Transgenic Mice	•Carcinogenesis caused by radiation •Damage to CNS from radiation exposure •Early or acute effects from radiation exposure	•Pharmaceuticals (e.g. tamoxifen, anti-oxidants) •Cytokines (e.g., interleukins)	Transgenic mice	•Examine both the dose and temporal-dependence of particle radiation-induced mutation *in vivo* using the LacZ transgenic mice model system •Examine the impact of genetic backgrounds, e.g., p53, on radiation sensitivity using the p53/LacZ double transgenics	Determine if known radioprotective pharmaceuticals (e.g. tamoxifen, anti-oxidants) or cytokines (e.g., interleukins) reduce tissue-specific mutation frequencies or genetic damage *in vivo*. Such alterations in the genome may be precursors of cancer. Examine potential drugs *in vitro*.	Examine potential potential drugs *in vivo*
DICELLO/In vivo Studies of Mammary Carcinomas	Carcinogenesis caused by radiation	•Chemoprevention of cancers by use of pharmaceuticals administered after exposure to radiations. •Shielding	Sprague Dawley rats	Determine risk of carcinogenesis in a relevant animal model and supply exposed animals for chemopreventive studies	•Obtain improved risk factors which can be used to optimize spacecraft design for optimal shielding and to select clinical trials •Chemoprevention of cancers by use of pharmaceuticals administered after exposure to radiations.	Clinical trials and flight experiments
HUSO/Chemoprevention and Radiation-Induced Neoplasms	Carcinogenesis caused by radiation	Pharmaceuticals (Tamoxifen)	Sprague Dawley rats	Studies of the pathology of cancer induced by HZE particles and use of Tamoxifen as a model for pharmaceutical	Obtain improved risk factors to select appropriate clinical trials	Clinical trials and flight experiments

				intervention in the promotion and progression stages of carcinogenesis to reduce risk after exposure		
KENNEDY/Countermeasures for Space Radiation Biological Effects	•Carcinogenesis caused by radiation •Early or acute effects from radiation exposure	Dietary supplements	•Cultured cells •Sprague Dawley rats	Determine the ability of various dietary supplements to reduce radiation-induced oxidative stress in cultured cells	•Dietary supplements prior to and after exposure to radiation to reduce cancer incidence •For the combinations of agents demonstrating efficacy as antioxidants *in vitro*, determine the ability of these agents to decrease radiation-induced oxidative stress in Sprague Dawley rats	Clinical trials and flight experiments
VAZQUEZ/Risk Assessment and Chemoprevention of HZE Induced CNS Damage	•Damage to CNS from radiation exposure •Early or acute effects from radiation exposure	Pharmacological manipulation	Cells obtained from rats	•Examine cell death in cycling and non-cycling neural cells •Characterize the putative cell signaling cascades induced by high LET radiation in the apoptotic pathways (ceramide- and p-53 dependent)	Modulate signaling pathways by pharmacological manipulation; test use of trophic factors, free-radical scavengers, p53 modulators in modulating signaling pathways	Bases for *in vivo* experiments
VAZQUEZ/CNS Damage and Countermeasures (*In vivo* Studies)	•Damage to CNS from radiation exposure •Early or acute effects from radiation exposure	Pharmacological agents	C57 black mice	Characterize the behavioral, neurochemical, and structural changes induced by heavy ions and protons	Test protective efficacy of pharmaceuticals such as neuroprotectants (gangliosides), antioxidants (melatonin), and signal pathways modulators (p53 modulators) on neural cell populations	Clinical trials and flight experiments

National Space Biomedical Research Institute
RADIATION EFFECTS PROGRAM

Table 11.2. Integration Activities – See discussion under section 11.4, Goal 8

Activities common to all projects unless specified				
Internal Communication	Weekly NSBRI staff meetings	Monthly teleconference of principal investigators	Scheduled NSBRI meetings of investigators at national and international meetings.	
Integrated Experiment Development	Monthly NSBRI luncheon meeting	Collaborations between PIs in Radiation with Technology Team on two projects	Members of several NASA, NCRP, and NAS/NRC committees	
Sample Sharing	Sprague-Dawley rats shared with Tamoxifen project (Huso and Dicello)	Tissue samples shared between Carcinogenesis project and Tamoxifen project	Animals irradiated at Loma Linda used for Gridley's immunology study (Dicello)	Carcinogenesis and Tamoxifen projects agreed to provide animals and tissues for several proposals submitted to NSBRI and NASA
Synergistic Studies of Opportunity	Dicello funded immunological studies at Loma Linda University (Daila Gridley)	Dr. Dicello is collaborating with Dr. Jay Shapiro on the combined effects of radiation and microgravity on bone loss.	Sequential studies at BNL (HZEs) and LLUMC (protons)	
Development of Computer Model of Integrated Human Function	Dicello and, previously, F. Cucinotta at JSC had been carrying out theoretical studies.			

National Space Biomedical Research Institute
RADIATION EFFECTS

Table 11.3a. Achieving Goal 1: Reduce Risk of Carcinogenesis Caused by Radiation (38)

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research Five of the seven principal investigators had extensive research experience with regard to the carcinogenic effects from radiation. The sixth was a senior biologist working on DNA damage, a major pathway to cancer from radiation, and the seventh is an animal pathobgist and veterinarian, a unique resource for these studies													
Phase 1: Focused Mechanistic Research													
• Preliminary data and proposal to measure risk of carcinogenesis in a relevant animal model and tissue for protons and HZEs													
• Preliminary data and proposal for chemopreventive drugs in promotion/progression stage of cancer													
• Preliminary data and proposal for dietary supplements to reduce risk of cancer													
• Preliminary data and proposal to study cytogenetic aberrations to understand the process leading to cancer at low doses, to determine biomarkers of risk for cancer, and to determine chemical pathways that will reduce risk..													
• Preliminary data and proposal to study DNA damage to understandthe process leading to cancer at low doses and to determine biomarkers of risk for cancer.													
• Preliminary data and proposal to study a transgenic mouse to characterize mutation changes in different tissue types.													
Phase 2: Preliminary Countermeasure Development Research													
• Initial studies to measure risk of carcinogenesis in a relevant animal model and tissue for protons and HZEs for pharmaceutical studies and spacecraft design													
• Initial studies of chemopreventive drugs in promotion/progression stage of cancer													
• Initial studies of dietary supplements to reduce risk of cancer													
• Initial studies of cytogenetic aberrations to understand the process leading to cancer at low doses, to determine biomarkers of risk for cancer, and to determine chemical pathways that will reduce risk..													
• Initial studies of DNA damage to understand the process leading to cancer at low doses and to determine biomarkers of risk for cancer.													
• Initial studies of a transgenic mouse to characterize mutation changes in different tissue types leading to drug studies													

Phase 3: Mature Countermeasure Development Research													
• Determine risk of carcinogenesis in a relevant animal model and tissue for protons and HZEs													
• Determine efficacy of a chemopreventive drug in promotion/progression stage of cancer													
• Determine specific dietary supplements to reduce risk of cancer													
• Determine cytogenetic aberrations to understand the process leading to cancer at low doses, to determine biomarkers of risk for cancer, and to determine chemical pathways that will reduce risk.													
• Initial studies of DNA damage to understand the process leading to cancer at low doses and to determine biomarkers of risk for cancer.													
• Determine mutations in different tissues in a transgenic mouse leading to carcinogenesis.													
• Develop pharmacological countermeasure and test with human subjects													
• Determine whether there are synergistic or antagonistic interactions between radiation and other major risks such as bone loss or reduced immunology.													
Phase 4: Countermeasure Evaluation & Validation													
• Testing in space environment													
Phase 5: Operational Implementation of Countermeasure Strategy													

National Space Biomedical Research Institute
RADIATION EFFECTS

Table 11.3b. Achieving Goal 2: Reduce Risk of Damage to Central Nervous System from Radiation Exposure (39)

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research	■	■											
Phase 1: Focused Mechanistic Research		■	■	■	■	■							
• Preliminary data and proposal to measure effects of radiation on CNS cells *in vitro* for protons and HZEs													
• Preliminary data and proposal to measure effects of radiation on CNS *in vivo* for protons and HZEs													
Phase 2: Preliminary Countermeasure Development Research		■	■	■									
• Initial studies to measure effects of radiation on CNS cells *in vitro* for protons and HZEs leading to drug studies in-vitro													
• Initial studies to measure effects of radiation on CNS *in vivo* for protons and HZEs leading to in-vivo drug studies													
Phase 3: Mature Countermeasure Development Research					■	■	■	■	■				
• Develop integrated exercise, nutritional, and pharmacological countermeasure and test in humans													
• Determine whether artificial gravity, in conjunction with the exercise, nutritional, and pharmacological countermeasure above, further reduces muscle atrophy in humans													
Phase 4: Countermeasure Evaluation & Validation										■	■	■	
• Testing in a space environment													
Phase 5: Operational Implementation of Countermeasure Strategy													■

National Space Biomedical Research Institute

RADIATION EFFECTS

Table 11.3c. Achieving Goal 3: Reduce Risk of Synergistic Effects from Exposure to Radiations, Microgravity, and Other Spacecraft Environmental Factors (40)

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Experimental observation of antagonistic effects of protons and iron ions for carcinogenesis *in vivo*													
• Demonstrated dietary restriction reduced cancer and extended life of our rats													
• Experimental observation of abscopal effects *in vivo*													
• Experimental observation of apparent adaptive response *in vitro* and *in vivo*													
• Funded preliminary study of potential synergistic effects of radiation and immunology..													
Phase 2: Preliminary Countermeasure Development Research													
• Effect of dietary supplements on oxidative stress													
• Proposal submitted to NASA for Bone/Radiation collaboration													
• Studies initiated in Nutrition and Immunology Teams. Based upon initial data obtained by Dicello's project.													
Phase 3: Mature Countermeasure Development Research													
• Clinical trial of dietary supplements													
• Determine whether microgravity affects chemo-effectiveness of drugs or dietary supplements.													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of drugs in Space													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 11.3d. Achieving Goal 4: Reduce Risk of Early or Acute Effects from Radiation Exposure (41)

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
These effects are considered Type II, rank 4 risks in NASA's Strategic Plan and are not being explicitly examined at the present time with resources available. Our research on carcinogenesis and CNS damage, however, will provide some data to further assess problems in these three areas.													
Phase 1: Focused Mechanistic Research													
Phase 2: Preliminary Countermeasure Development Research													
Phase 3: Mature Countermeasure Development Research													
Phase 4: Countermeasure Evaluation & Validation													
Phase 5: Operational Implementation of Countermeasure Strategy													

Table 11.3e. Achieving Goal 5: Reduce Risk of Radiation Effects on Fertility, Sterility, and Heredity (42)

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
These effects are considered Type III risks in NASA's Strategic Plan and are not being explicitly examined at the present time with resources available. Our research on genetics and biomarkers, however, will provide some data to further assess problems in these three areas.													
Phase 1: Focused Mechanistic Research													
Phase 2: Preliminary Countermeasure Development Research													
Phase 3: Mature Countermeasure Development Research													
Phase 4: Countermeasure Evaluation & Validation													
Phase 5: Operational Implementation of Countermeasure Strategy													

National Space Biomedical Research Institute

RADIATION EFFECTS

Table 11.3f. Achieving Goal 6: Methods for Assessing Level of Health Risk, Prevention of Diseases, & Appropriate Medical Care

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
This strategy being pursued presently to achieve this goal is to reduce the level of radiation exposure, to determine and measure appropriate biomarkers, and to find drugs, diet, and environmental factors that can be used to reduce risk.													
Phase 1: Focused Mechanistic Research													
• Propose chemopreventive drugs in promotion/progression stage of cancer													
• Propose chemopreventive dietary supplements to reduce risk of cancer													
• Propose chemopreventive drugs to reduce risk of CNS damage													
Phase 2: Preliminary Countermeasure Development Research													
• Begin *in vivo* studies of Tamoxifen as a chemopreventive drug in the promotion/progression stages.													
• Propose chemopreventive dietary supplements to reduce risk of cancer													
• Propose chemopreventive drugs to reduce risk of CNS damage													
Phase 3: Mature Countermeasure Development Research													
• *In vivo* studies of Tamoxifen as a chemopreventive drug in the promotion/progression stages.													
• Cell/animal studies of dietary supplements to reduce risk of cancer													
• Cell/animal chemopreventive drugs to reduce risk of CNS damage													
Phase 4: Countermeasure Evaluation & Validation													
Phase 5: Operational Implementation of Countermeasure Strategy													

National Space Biomedical Research Institute
RADIATION EFFECTS

Table 11.3G. Achieving Goal 7: Potential Earth-Based Applications

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Feasibility Research													
• Propose broad-band neutron detector for Tech Team													
• Propose network-based remote treatment planning for radiotherapy to NIH													
• Propose chemopreventive drugs in promotion/progression stage of cancer													
• Propose microbeam of energetic heavy ions for Tech Team													
• Propose chemopreventive dietary supplements to reduce risk of cancer													
• Propose chemopreventive drugs to reduce risk of CNS damage													
Phase 2: Development Research													
• Initiate broad-band neutron detector in Tech Team leading to design changes in spacecraft and selection of drug categories needed													
• NIH funds network-based remote treatment planning													
• Begin *in vivo* studies of Tamoxifen as a chemopreventive drug in the promotion/progression stages.													
• Initiate design of microbeam of energetic heavy ions in Tech Team													
• Propose chemopreventive dietary supplements to reduce risk of cancer													
• Propose chemopreventive drugs to reduce risk of CNS damage													
Phase 3: Mature Research and Development													
• Tech Team flies broad-band neutron detector in planes and balloons													
• NIH clinical trials of remote treatment planning for radiotherapy													
• *In vivo* studies of Tamoxifen as a chemopreventive drug.													
• Prototype of microbeam of energetic heavy ions in Tech Team													
• Cell/animal studies of dietary supplements to reduce risk of cancer													
• Cell/animal chemopreventive drugs to reduce risk of CNS damage													
Phase 4: Evaluation & Validation													
Phase 5: Operational Implementation Strategy													

National Space Biomedical Research Institute
RADIATION EFFECTS

Table 11.3H. Achieving Goal 8: Integrate Experimental Research with Theoretical Analysis to be Used to Extrapolate Data to Risk and Countermeasures for Humans.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Integrate Research in the Radiation Team													
• Request proposals on this topic, review, and fund													
• Develop theoretical model to relate cell biomarkers (genetic, cytogenetic, epigenetic, and abscopal) in animals to carcinogenesis in animals													
• Develop theoretical model to relate animal carcinogenesis to human carcinogenesis													
• Develop theoretical model to relate cell biomarkers (genetic, cytogenetic, epigenetic, and abscopal) in animals to CNS damage in animals													
• Develop theoretical model to relate animal CNS to human CNS													
Phase 2: Preliminary Countermeasure Development Research													
• Apply model with new data to obtain improved risk assessments and models to evaluate effect of drugs in humans													
• Request proposals on this topic, review, and fund													
• Apply model with new data to obtain improved risk assessments													
Phase 3: Mature Countermeasure Development Research													
• Initiate shielding designs based upon model calculations of risk													
• Develop pharmaceutical strategy based upon model predictions													
Phase 4: Countermeasure Evaluation & Validation													
• Modify existing spacecraft and design new vehicles according to new criteria													
• Initiate ground-based clinical trials of chemopreventives and dietary supplements.													
Phase 5: Operational Implementation of Countermeasure Strategy													

12.0 Smart Medical Systems

Team Leader: Jeffrey P. Sutton, M.D., Ph.D.
Director, Neural Systems Group
Massachusetts General Hospital
Harvard-MIT Division of Health Sciences
and Technology
Bldg. 149, 13th Street, 9th Fl.
Charlestown, MA 02129-2000
617-726-4350/731-2388
617-726-4078 FAX
sutton@nmr.mgh.harvard.edu

12.1 INTRODUCTION

Health problems associated with space travel may be related to the effects of microgravity, radiation and other risks to the body that are particular to space flight. They may also be independent of these effects, arising in association with a given demographic population, toxic environmental exposure or trauma. Complex interactions between these factors, as well as potential differences in the way disorders present and respond in microgravity relative to Earth, pose formidable challenges. The unique medical circumstances and limited health care resources in space suggest that novel strategies are required for in-flight physiological monitoring and medical assessment, diagnosis and treatment on long duration missions.

The Smart Medical Systems Team (SMST) aims to take a leadership role in the research and development of an advanced, integrated and autonomous system for astronaut health assessment, maintenance and medical care. This includes the delivery and evaluation of medical interventions and other countermeasures to reduce the deleterious effects of space travel and enhance the overall well-being of astronauts. To accomplish this task, the SMST works closely with other NASA efforts in space and critical medicine. It is anticipated that the countermeasure program of the SMST will have significant impact and applications for Earth-based health and medical care.

12.2 RISKS

The following risks have been identified in the Critical Path Roadmap under Clinical Capabilities (risk number in parentheses).

- Trauma and Acute Medical Problems (43)
- Toxic Exposure (44)
- Altered Pharmacodynamics and Adverse Drug Reactions (45)
- Illness and Ambulatory Health Problems (46)
- Development and Treatment of Space-Related Decompression Sickness (47)
- Difficulty of Rehabilitation Following Landing (48)

12.3 GOALS

Risk-Based Goals: Development of Methods for Health Assessment and Medical Care

Goal 1: Methods to reduce risk of trauma and acute medical problems

Goal 2: Methods to reduce risk of toxic exposure

Goal 3: Methods to reduce risk of altered pharmacodynamics and adverse drug reactions

Goal 4: Methods to reduce risk of illness and ambulatory health problems

Non Risk-Based Goals

Goal 5: Develop a platform for suite of medical devices

Goal 6: Develop Earth-based applications for non-invasive, portable physiological sensing and medical diagnostic and therapeutic devices

Goal 7: Integrate research and analysis

12.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The SMST was formed in 2000, and funded in 2001, following peer-review of applications for research to mitigate risks most closely associated with the Clinical Capabilities discipline of the Critical Path Roadmap as listed in Section 11.2. The emphasis has been on addressing the four highest priority risks (Goals 1 to 4) in the discipline, with the requirement that Goal 5 be developed to integrate the projects together as a prototypical smart medical system, that can be demonstrated and implemented. Achievements toward Goal 6 are already being realized, even though the team has only recently been established, and Goal 7 is partially addressed in Goal 5, as well as in other contexts described later.

Given the team's goals, collaborations have been essential. These have been initiated and fostered across the NSBRI and with NASA flight surgeons, astronauts, medical operations personnel, engineers and researchers at the Johnson Space Center (JSC). The team has also developed a working collaboration with biosensor and other groups at the Ames Research Center (ARC), the Jet Propulsion Laboratory (JPL) and other NASA Centers. It has engaged in a working relationship with the NASA Chief Health and Medical Officer.

Collaborations are a cornerstone for the team to meet its objectives and to strategically utilize its assets to help mitigate risks, especially those delineated in Goals 1 to 4. At present, the SMST has eight projects headed by seven principal investigators. Five projects (led by Drs. Crum, Davies, Klempner, Soller and Sutton) address research and development of novel biometric sensors that are lightweight, portable, low power, non-invasive and unobtrusive. These projects have applications for physiological and medical monitoring of astronauts, as well as for the assessment of countermeasures that potentially diminish the deleterious effects of long duration space travel (Goals 1, 2 and 4). Dr. Davies' project also has applicability to the risk of ameliorating the difficulty of rehabilitation following landing (currently a non-goal risk - Section 11.2). One project (led by Dr. Putcha) develops a novel pharmacological drug delivery system for near term countermeasure administration (Goal 3), while another project (led by Dr. Crum) develops a revolutionary new form of non-invasive surgery (Goal 1). A NASA echocardiographic resource project (led by Dr. Thomas) is supported by the SMST (Goals 1 and 4), and is jointly supervised with the Cardiovascular Alterations Team. Three projects (led by Drs. Klempner, Sutton and Thomas) develop "smart" algorithms for minimal user evaluation and interpretation of real time physiological and medical data (Goals 1 to 5 and Goal 7).

The current program consists of eight multi-disciplinary projects (3 animal, 1 human + animal, 2 human + computation, 1 pathogen, 1 resource) that integrate engineering, computation and biomedicine with innovation in technology and medical care. All of the projects fit within the objectives and strategic activities of the SMST (Section 11.5). Although the team is newly formed, there is preliminary planning for flight tests of some technologies, and for applying research discoveries to enhance medical care on Earth (Goal 6). A synopsis of the projects follows, with the major attributes being summarized in Table 11.1.

Crum et al.: Guided High Intensity Focused Ultrasound for Mission-Critical Care
This project seeks to develop a lightweight, portable, smart medical device that can adequately control internal bleeding, as well as address a number of other medical conditions that require surgery. This device will use diagnostic ultrasound for guidance and High Intensity Focused Ultrasound (HIFU) for therapy. Specifically, an image-guided transcutaneous device for acoustic hemostasis and bloodless surgery is proposed.
Countermeasure Target(s): Revolutionary surgical advance for use in trauma and for monitoring and assessment of other medical problems.

Davies et al.: Vascular Genomics in Gravitational Transitions
This ground-based project will address, at the level of gene expression, the structural and regulatory changes in murine vascular tissues associated with (a) exposure to simulated microgravity, (b) return to normal posture, and (c) prolonged exposure to hypergravity, and its acute reversal. Changes in RNA expression in regions of the vascular tree known to be of particular relevance to human orthostatic intolerance, and of critical importance in normal blood vessel regulation, will be investigated.
Countermeasure Target(s): Training and other interventions to minimize effects of vascular change, with pre-, in- and post-flight applications.

Klempner et al.: Smart Medical System for Microorganism Detection
This proposal involves the development of a novel smart medical system to detect and identify bacteria through the use of novel sensors and includes three steps: (a) development of "fingerprinting" phage display libraries which can detect, identify, quantify and discriminate bacterial species in environmental and biological specimens; (b) application of phage displayed peptides and antibody fragments in a microarray to the surface of a microsensor to demonstrate,

using optical readout and colorimetric reflectance, the sensitivity and specificity for detecting and discriminating between bacterial species using surface "fingerprints"; and (c) development of algorithms from the microarray response for real-time identification and discrimination of bacterial species.
Countermeasure Target(s): Novel monitoring and diagnostic capabilities with environmental manipulation and pharmacological countermeasure possibilities.

Putcha et al.: Microcapsule Gel Formulation for Intranasal Promethazine HCl
The goal of this project is to develop an intranasal dosage formulation of promethazine hydrochloride that will provide crewmembers with a non-invasive means of self-administering space motion sickness medications. The research involves the (a) development of a microencapsulated, pH-balanced gel dosage formulation and a combination form with a corticosteroid for intranasal administration, (b) establishment of release kinetics and shelf life of the optimized dosage forms, and (c) assessment of bioavailability, nasal mucosal irritability and toxicity of the selected dosage forms in rats.
Countermeasure Target(s): Novel drug delivery system for pharmacological agent administration.

Soller et al.: Noninvasive Measurement of Blood And Tissue Chemistry
This project uses near infrared spectroscopy and novel algorithms to non-invasively assess blood and tissue for the measurement of oxygenation, pH, glucose and hematocrit in humans, irrespective of skin color and gender. These parameters are important in diagnosing and treating hypoxia and trauma that may arise from exposure to radiation, toxic chemicals and blunt or sharp injury. They may also be useful in evaluating exercise as a countermeasure for extended weightlessness.
Countermeasure Target(s): Physiological and medical monitoring and diagnosis of blood and tissue parameters. Some parameters, such as muscle pH, are relevant for optimizing exercise countermeasures.

Sutton et al.: Near Infrared Brain Imaging for Space Medicine
This project develops and implements a non-invasive, low power, portable, functional imaging technology for monitoring brain activity in remote harsh environments, including microgravity. The device uses diffuse optical tomography, which is validated in the project using functional magnetic resonance imaging. Performance on motor tasks of varying complexity under normal and sleep-deprived conditions are conducted with tomographic functional imaging to assess cortical activity in humans during simulated flight tasks, including docking. The technology is also being developed to assess patients with altered intracranial pressure. The sensor work interfaces with a system for automated assessment, warning, and countermeasure evaluation.
Countermeasure Target(s): Physiological and medical monitoring and diagnosis, with countermeasures to adjust scheduling and performance expectations.

Thomas et al.: Diagnostic 3D Ultrasound Algorithms for Space Applications
This project seeks to develop, optimize and validate diagnostic ultrasound in manned space flight, with aims focused on (a) serial 3D examinations to enhance current diagnostic capabilities, (b) utilizing reconstruction and real-time techniques, (c) registering anatomical images from 2D and 3D ultrasound with those obtained from prior ultrasound examination and

from magnetic resonance and computed tomographic imaging, (d) abstracting, in an automated fashion, anatomical changes in ultrasound studies, (e) compression algorithms, and (f) assessing the ability of novice examiners to obtain 3D sonographic data sets (cardiac, renal) following minimal training.

Countermeasure Target(s): Physiological and medical monitoring and diagnosis, with early countermeasure intervention, such as pharmacological agents or nephrolithiasis, when indicated.

Thomas et al.: Echocardiographic Resource for Microgravity Studies

This resource project in ultrasound experimentation and training is a collaboration with the Cardiovascular Alterations team. The goal is to establish an Echocardiographic Core Facility to the NASA research and clinical communities, capable of applying standard and novel analysis techniques in a rigorous fashion to echocardiographic data obtained from selected ground-based experimental models, pre- and post-flight examinations, and eventually from in-flight acquisitions.

Countermeasure Target(s): Physiological and medical monitoring and diagnosis, and training of naïve users in medical image acquisition, with multi-systems applications (e.g., cardiovascular, bone, renal).

The integration activities among the projects just listed, both within the SMST and between the SMST, other NSBRI teams and groups outside the NSBRI, are summarized in Table 11.2. From a technology, modeling and physiological system perspective, the relationships are also illustrated in Figure 11.1. Specifically, each of the eight SMST projects is represented along the middle row of Figure 11.1. The projects are coded to depict (a) NSBRI cross-team interactions (Soller with Cabrera (Nutrition, Physical Fitness and Rehabilitation)), (b) NASA interactions (Davies with Luzod (ARC); Putcha (JSC); Sutton with Marshburn (JSC)), (c) NSBRI cross-team and NASA interactions (Klempner with Fox (Immunology, Infection and Hematology Team) and Pierson (JSC); Thomas with Cohen (Cardiovascular Alterations Team) and JSC)), and (d) none of the above (although Crum has strong ties to the Department of Defense medical technology programs).

The bi-directional arrows in Figure 11.1 represent relationships (a) among projects within the SMST and (b) between SMST projects and the other NSBRI teams. These relationships are broken down into two main categories: Technology; and Physiological Systems and Effects. Across the top row, interactions between SMST projects and the Technology Development Team and core Integrated Human Function activities are shown. These interactions correspond roughly to experimentation (Technology Development Team) and theoretical or modeling (core Integrated Human Function) interactions. Arrows pointing to particular boxes *from* SMST projects *to* boxes in the upper row show how SMST projects contribute to NSBRI developments in other specific domains. For example, the Klempner, Soller and Sutton projects all develop novel spectrographic devices that complement one or more projects being developed in the Technology Development Team (specifically, projects headed by Potember and by Maurer).

Arrows that originate *from* boxes in the upper row of Figure 11.1 and project *to* SMST projects represent links among projects *within* the SMST. The relationships are incomplete and are evolving, sometimes with added benefit to the overall NSBRI scientific program. For example, ultrasound technologies link projects by Crum and Thomas, although Thomas' projects do not develop hardware. The functional magnetic resonance imaging (fMRI) aspects of Sutton's project adds to the (non-functional) MRI developments in the Technology Development Team; hence the half shaded box in Figure 11.1. The chemical engineering and functional genomic and proteomic approaches on the SMST complement other core technology developments within the NSBRI program.

Bi-directional arrows between the boxes representing the SMST projects and the system teams along the bottom row of Figure 11.1 work similarly to those just described. There is synergy with every system team, especially the Cardiovascular Alterations Team. There is also an emerging emphasis on brain and neurobehavioral alterations within the SMST (Sutton project). At present, there is no synergy with the Radiation Effects Team, although there is scientific overlap with that team.

SMST – Technology, Physiological Systems and Interactions

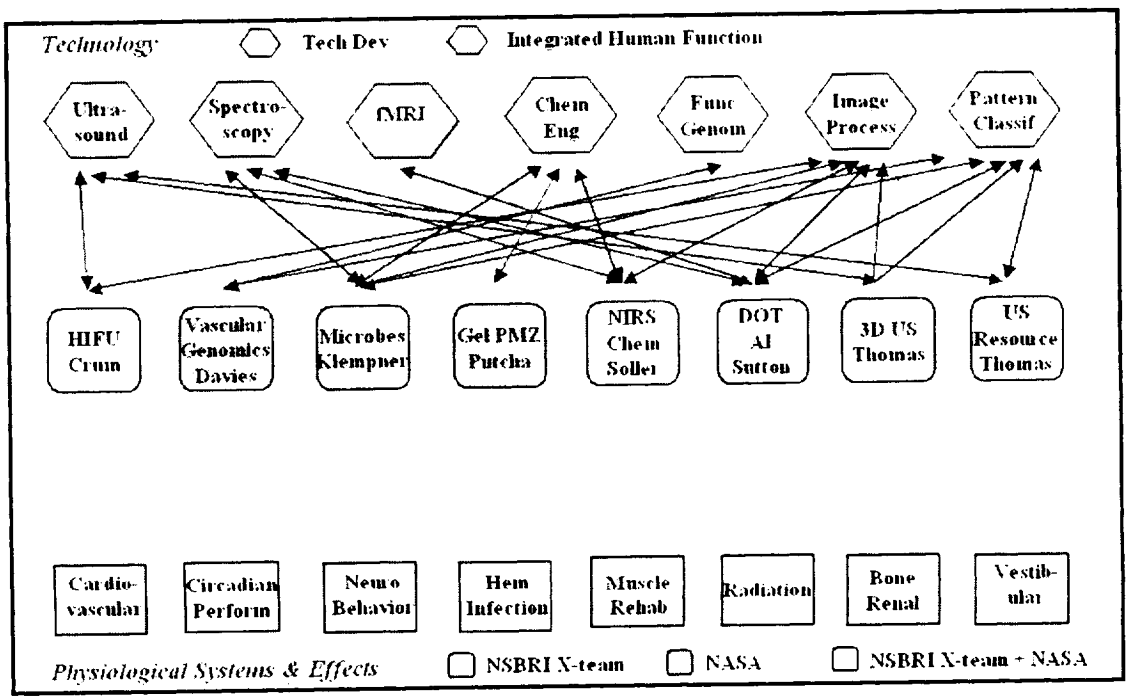


Figure 11.1

In October 2001, the SMST provided a live demonstration of new technologies and added value across projects to the Team Leaders of the other NSBRI teams and to the External Advisory Council. Considerable progress was made by the SMST since October 2001. In March 2002, the Council reported that the SMST:

- "has been remarkably successful in realizing substantial progress and rapid maturation of several of it major projects."

- "has achieved proof-of-principle or near proof-of-principle countermeasure status of several of the systems within its development domain,"
- "has in many ways succeeded in the fundamental mission of the NSBRI, namely, to engage in basic research that leads to new technologies uniquely suited to the critical needs of NASA space flight demands,"
- "should have as its highest priority the definition of flight-test trajectories for its most successful technologies," and
- "should (have next stage goals that are) highly focused and implemented with a certain sense of urgency" given the team's "success and the current critical stage of development of the NSBRI."

Prototypical Smart Medical System

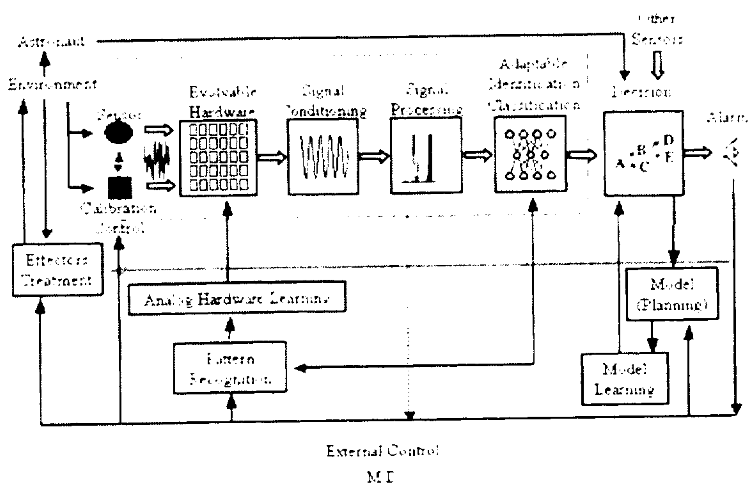


Figure 11.2

To follow through on achieving Goals 1 to 7, the SMST has developed a model prototype and concept of operations to identify gaps, weaknesses, strengths, needs and progress toward mature countermeasures. The model is summarized in Figure 11.2. In this figure, information from the environment and astronauts is sensed by a suite of small, lightweight, low power, portable, non-invasive, unobtrusive, intelligent ,sensors with pattern recognition capabilities. These sensors feed automatically analyzed, rather than raw, data into decision-making algorithms, that also have cognitive input from the astronauts themselves. There is a model of the system, which is where the NSBRI integration core activities fit into the team's plans. The model not only (a) assesses input from multiple sources, but it (b) pre-plans notification for onboard alarms and information transfer to the ground, (c) looks at contingencies and outcomes for effectors and treatments prior to the administration of countermeasures, (d) assesses the effectiveness of treatments and countermeasures, (e) monitors consequences of actions and countermeasures, and (f) interfaces with models for pattern recognition and analog hardware learning. Since feedback loops exist which are independent of external and M.D. control, the system is, in principle, autonomous. Moreover, the design is achievable, to varying degrees, and proposes a revolutionary new health care system for space, which is central to the research charge assigned to the SMST.

While there are other features of the system described in Figure 11.2, the main points in summary are:

- Enhanced small sensor platforms with pattern recognition and wireless capabilities
- Adaptable system of systems for sensor integration
- Algorithms and models for human assisted monitoring, countermeasure assessment and decision making
- Common platforms for sensing and countermeasure delivery

Tables 11.3a and 11.3b provide projected timelines for achieving Risk-based Goals 1 to 4 using the model of Figure 11.2. Non-risk based Goals 5 to 7 are achieved in parallel to the Risk-based Goals as described in Section 11.5.

12.5 OBJECTIVES AND STRATEGIC ACTIVITIES

The objectives underlying each goal are presented below, along with strategic activities that will be used to achieve the goals and objectives.

Goal 1: Methods to Reduce Risk of Trauma and Acute Medical Problems

Objective 1A. Assess risk and target level of acceptable risk

- Determine the full range of risks to trauma and acute medical problems using evidence based medicine and other approaches. All team members have been acquiring such information from published reports, JSC personnel, and current and former astronauts and flight surgeons.
- Determine the full range of current clinical capabilities taking into account international requirements and resources (Putcha, Klempner, Soller, Sutton, Thomas projects; JSC personnel).

Objective 1B. Determine mechanisms

- Identify technologies suitable for non-invasive physiological assessment (all projects).
- Identify capabilities of sensor technologies for use in trauma (Crum, Soller, Sutton, Thomas projects).
- Identify promising new non-invasive surgical interventions (Crum, Soller, Sutton, Thomas projects).
- Assess validity of sensors based on gold standards in health and disease (Crum, Klempner, Soller, Sutton, Thomas projects).
- Further understanding of signal and effector mechanisms in relation to novel sensor developments (Crum, Soller, Sutton projects).

Objective 1C. Develop countermeasures

- Test sensors for normal anatomical and physiological non-invasive monitoring in animals and humans (Crum, Klempner, Soller, Sutton, Thomas projects).

- Test sensors for anatomical and physiological non-invasive monitoring in animals and humans during trauma and acute medical conditions (Crum, Klempner, Soller, Sutton, Thomas projects).
- Develop time-derivative pattern recognition and other algorithms for near automated detection of significant medical alterations based on sensor data (all projects).
- Refinement of non-invasive surgical capabilities integrated with image guided detection, interpretation and assessment of treatment efficacy (Crum project).
- Human subject demonstration of sensor-algorithm devices for trauma and acute medical problem assessment (Crum, Klempner, Soller, Sutton, Thomas projects).
- Human subject demonstration of sensor-effector (treatment) devices for trauma and acute medical problems (Crum, Soller, Thomas projects).
- Evaluation of sensor-algorithm-effector "smart" system in simulated space flight conditions (e.g., KC135) (Soller, Sutton, Thomas projects).

Goal 2: Methods to Reduce Risk of Toxic Exposure

Objective 2A. Assess risk and target level of acceptable risk

- Determine the full range of risks to toxic exposure based on environmental factors and evidence based medicine from NASA Centers, including JSC, ARC and JPL (e.g., eNose project). Team members have been acquiring such information from published reports, JSC personnel, and current and former astronauts and flight surgeons (Klempner, Sutton projects).
- Determine the full range of current capabilities for management of toxic exposure taking into account international requirements and resources (Klempner, Sutton projects; JSC personnel).

Objective 2B. Determine mechanisms

- Identify emerging technologies suitable for management of toxic exposures in the space environment (Klempner, Sutton projects with input from JSC, ARC and JPL personnel).
- Investigate mechanisms and determine validity of approaches in reducing risk of toxic exposure (Klempner, Sutton projects in collaboration with biotechnology companies, including SRU Biosystems).

Objective 2C. Develop countermeasures

- Test technologies suitable for toxic exposure monitoring in remote harsh environments (Klempner project, collaboration with JSC, ARC biosensors group, JPL).
- Tests sensors on animals for toxic exposures and medical sequelae of exposures (Klempner project, collaboration with JSC, ARC biosensors group, JPL).
- Human subject demonstration of novel technologies for assessment of toxic exposures (Klempner project, collaboration with JSC and ARC biosensors group).
- Evaluation of "smart" systems for assessment of toxic exposure in simulated space environment (Klempner, Sutton projects, collaboration with JSC personnel).

Goal 3: Methods to Reduce Risk of Altered Pharmacodynamics and Adverse Drug Reactions

Objective 3A. Assess risk and target level of acceptable risk

- Determine the full range of risks and implications of space flight alterations in human physiology concerning pharmacology for clinically useful medications. This requires interactions with JSC scientists, flight surgeons and astronauts. Team members have been acquiring such information (Klempner, Putcha, Sutton, Thomas projects).
- Determine the full range of current pharmacological practices taking into account international requirements and resources (Putcha project; JSC personnel).

Objective 3B. Determine mechanisms

- Identify emerging technologies suitable for establishing the effects and implications regarding absorption, distribution, metabolism, clearance, excretion, clinical efficacy, side effects and drug interactions for clinically useful medications (Putcha, Sutton, Thomas projects).
- Investigate mechanisms and determine validity of approaches for quantifying altered pharmacodynamics and adverse drug reactions (Putcha project; this area requires further support).

Objective 3C. Develop countermeasures

- Test technologies suitable for non-invasive drug delivery of clinically relevant medications for space flight (Putcha project).
- Establish clinical efficacy and side effect profiles of appropriate medications for space flight (Putcha project).
- Determine space and radiation hardness of appropriate medications (this area requires further support).
- Human subject demonstration of novel drug delivery system with established efficacy and high benefit to risk ratio (Putcha project in collaboration with JSC flight surgeons and astronauts).

Goal 4: Methods to Reduce Risk of Illness and Ambulatory Health Problems

Objective 4A. Assess risk and target level of acceptable risk

- Determine the full range of risks of illnesses and ambulatory health problems using evidence based medicine. All team members have been acquiring such information from published reports, JSC personnel (in collaboration with the Director of the Space and Life Sciences Directorate) and current and former astronauts and flight surgeons.
- Determine the full range of current clinical capabilities taking into account international requirements and resources (Crum, Klempner, Putcha, Soller, Sutton, Thomas projects; JSC personnel).

Objective 4B. Determine mechanisms

- Identify emerging technologies suitable for management of illnesses and ambulatory health problems in the space environment (Crum, Klempner, Putcha, Soller, Sutton, Thomas projects).

- Investigate mechanisms and determine validity of approaches in reducing risk of illness and ambulatory health problems (Crum, Klempner, Putcha, Soller, Sutton, Thomas projects).

Objective 4C. Develop countermeasures

- Test technologies suitable for conducting a nominal health and fitness examination, and for performing ongoing health monitoring, in remote harsh environments (Crum, Klempner, Putcha, Soller, Sutton, Thomas projects).
- Tests sensors on animals for physiological monitoring (Crum, Klempner, Putcha, Soller, Thomas projects).
- Human subject demonstration of novel technologies for assessment of nominal health and fitness examination, and ongoing health monitoring, in simulated space environment (Crum, Klempner, Putcha, Soller, Sutton, Thomas projects).
- Evaluation of "smart" systems for assessment of nominal health and fitness examination, and ongoing health monitoring, in simulated space environment (Crum, Klempner, Putcha, Soller, Sutton, Thomas projects).

Goal 5: Develop a Platform for Suite of Medical Devices

Objective 5A Assess and develop platform prototypes

- Identify adaptable, reconfigurable hardware that is software intense and able to support a suite of medical devices (Crum, Klempner, Sutton, Thomas projects; this area requires further support).
- Develop software capable of providing local computation on sensors with integrative abilities across the entire suite of sensors (Sutton project; this area requires further support).
- Develop models of the entire network that can process data streamed in real-time, predict outcomes and recommend actions, including countermeasure delivery (Sutton project; this area requires further support).

Objective 5B. Implement platforms and assess capabilities

- Test hardware and software prototypes by adding a single sensor-algorithm-effector system to the platform and ensuring that the system remains functional (Crum, Davies, Klempner, Sutton, Thomas projects; this area requires further support).
- Add several sensor-algorithm-effector systems to the platform and ensure that each system remains functional (Soller, Sutton projects; this area requires further support).
- Link systems to provide added value to physiological monitoring, prediction and countermeasure delivery (Sutton project in collaboration with JSC medical operations; this area requires further support).
- Expand system to automate monitoring and countermeasure delivery in significant risk scenarios, including trauma, toxic exposure, illness and ambulatory health problems (Crum, Soller, Sutton projects in collaboration with JSC medical operations; this area requires further support).

Goal 6: Develop Earth-based Applications for Non-invasive, Portable Physiological Sensing and Medical Diagnostic and Therapeutic Devices

Objective 6A. Identification and demonstration

- Identify promising developments within and between projects, and identify the need(s) for applying these developments to Earth-based problems (all team projects).
- Demonstrate promise of efficacy and superiority of technologies to solve Earth-based problems (all team projects).

Objective 6B. Leveraging and transition

- Secure additional support from government, academic and/or industry to leverage NSBRI funding and to firmly establish efficacy and superiority of technologies to solve Earth-based problems (all team projects).
- Protect intellectual property.
- Engage NSBRI Industry Forum and other avenues to perform due diligence and possible commercialization.

Goal 7: Integrate Research and Analysis

Objective 7A. Integrate research within the Smart Medical Systems Team

- Continue current integration efforts among team PIs, co-investigators and key NASA personnel affiliated with team projects, as summarized in Table 11.2.

Objective 7B. Integrate research with other teams

- Continue current integration efforts with other teams and with integrated human function modeling efforts, as summarized in Figure 11.1.
- Continue coordinated technology development efforts with the Technology Development Team.
- Continue coordinated interactions and collaborations with the Cardiovascular Alterations, Human Performance Factors, Sleep and Chronobiology, Neurobehavioral and Psychosocial Factors, Immunology, Infection and Hematology, Muscle Alterations and Atrophy, Nutrition, Physical Fitness and Rehabilitation, Bone Loss and Neurovestibular Adaptation Teams (mapping of SMST projects to other teams shown in Figure 11.1).
- Coordinate with the Radiation Team regarding the effects of space radiation on medical illness in animals as a prelude to assessing and monitoring the effects in humans.

Objective 7C. Integrate research with investigators not formally associated with the NSBRI

- Although all of the projects on the SMST involve collaborations among leading investigators from different schools, universities, companies and Federal agencies, team members continue to seek out expertise from scientists not formally part of the NSBRI who can contribute to many of the areas under study. The number of investigators who initially were not associated with the NSBRI and who now collaborate with the SMST exceeds the number of investigators originally supported on the team. The SMST continues to serve as a nidus in an emerging area of space and Earth-based biomedical research.

12.6 SUMMARY

The SMST is a collaborative effort within the NSBRI and with NASA that firmly embraces the countermeasure development paradigm to deliver critical aspects of an advanced, integrated and autonomous system for astronaut health assessment, maintenance and medical care. The success of the team is dependent upon new enabling technologies, the establishment of risk priorities based on hard evidence and opportunities to demonstrate countermeasure efficacy on the ground and in a space medicine environment. The importance of this research is clear, as the risk of Trauma and Acute Medical Problems is one of the four Type I risks on the Critical Path Roadmap. The team currently focuses on the top four out of six risks (Risk-Based Goals 1 to 4) listed under Clinical Capabilities in the Critical Path Roadmap. Modeling and applications for Earth-based care are active areas of investigation and achievement.

Tables 11.3a and 11.3b summarize the plans to achieve Goals 1 to 4. While there is a critical mass of investigators to implement this plan, there is a need to supplement the work in pharmacology and in the systems engineering to develop a platform for a smart medical system. Moreover, it should be recognized that further support is required to foster the critical interface between members of the SMST and the flight surgeon and NASA engineering communities, especially with respect to meeting medical requirements and achieving feasible device implementation.

With adequate adjustment in program support, it is anticipated that the SMST will continue its successful course as noted by the External Advisory Council in March 2002. There is enormous potential in the team's individual projects, the added value across team projects and interactions with other teams. The SMST is well positioned to make significant contributions to Earth-based clinical care. Figure 11.1 summarizes the implemented strategy for interactions and Figure 11.2 proposes the strategic model for a revolutionary form of a smart medical system for space and for Earth.

Table 11.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
CRUM/Guided High Intensity Focused Ultrasound for Mission-Critical Care	Trauma, acute medical problems	Monitoring, med assessment Surgery	Image guided HIFU for acoustic hemostasis	Determine efficacy of HIFU on tissue for bloodless surgery	Develop integrated imaging – HIFU system	Planning for human demonstration of system
DAVIES/ Vascular Genomics in Gravitational Transitions	Rehabilitation following landing	Training	Hypergravity mice, vascular RNA	Understand vascular gene, protein effects in hyper-g		
KLEMPNER/Smart Medical System for Microorganism Detection	Trauma, acute med Toxic exposure Illness, ambulatory health problems	Monitoring, med assessment Pharmacological agents	Phage displayed ligands Colorimetric resonant sensors	Establish microbial phage libraries of space fungi and sensitivity of reflectance biosensor	Develop and test novel sensor to detect and analyze phages	
PUTCHA/Microcapsule Gel Formulation for Intranasal Promethazine	Altered pharmacodynamics	Pharmacological agents	Microencapsulation Kinetics and bio-availability in rat		Develop and test microencapsulated promethazine	Planning of human studies for drug delivery system

SOLLER/Noninvasive Measurement of Blood and Tissue Chemistry	Trauma, acute med Illness, ambulatory health problems	Monitoring, med assessment Exercise	Near infra-red spectroscopy and algorithms	Refine NIRS technology for tissue pH and hematocrit determination	Utilize NIRS for non- invasive tissue moni-toring during exercise	
SUTTON/Near Infrared Brain Imaging for Space Medicine	Trauma, acute med Illness, ambulatory health problems	Monitoring, med assessment Performance adjustments	Diffuse optical tomography, simulated docking task, ICP changes	Develop DOT system and validate using fMRI to detect regional brain activity and ICP changes	Integrate DOT assessment of brain function during simulated docking task	
THOMAS/Diagnostic 3D Ultrasound Algorithms for Space Applications	Trauma, acute med Illness, ambulatory health problems	Monitoring, med assessment Pharmacological agents	Ultrasound and algorithms in animal and human models	Identify and adapt new algorithms for real-time evaluation of cardiac and renal echo data	Develop and test algorithms for semi-automated interpretation	
THOMAS Echocardiographic Resource for Microgravity Studies	Trauma, acute med Illness, ambulatory health problems	Monitoring, med assessment Training	Training paradigms		Testing of training protocols to use echo equipment and analyze	Plans to test system during space flight

National Space Biomedical Research Institute
SMART MEDICAL SYSTEMS PROGRAM

Table 11.2. Integration Activities

	CRUM HIFU for mission critical care	DAVIES Vascular genomics in g transitions	KLEMPNER Smart microorganism detection sys	PUTCHA Microcapsule drug formulation	SOLLER Non-invasive blood & tissue chemistry	SUTTON Near infrared brain imaging for space med	THOMAS Diagnostic 3D ultrasound for space	THOMAS Echo-cardiographic resource
Internal Communication	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings	Monthly team telecon; Biannual team meeting; NSBRI retreat; Biannual NASA meeting; National scientific meetings
Integrated Experiment Development	Sensor aspects link to both THOMAS projects	Vascular studies link Cardiovascular Alterations team	Algorithms link to SUTTON project; Phage library studies link to IHH team	Promethazine development links to Neurovestibular Adaptation team	Sensor links to SUTTON project; Applications links to Muscle team	Sensor links to SOLLER project; Algorithms link to KLEMPNER and THOMAS projects	Sensor links to CRUM project; Algorithms link to SUTTON project; Echo links to CV team	Sensor links to CRUM project; Algorithms link to SUTTON project; Echo links to CV team

Sample Sharing			Specimen sharing with JSC microbiology		Collaboration with CABRARA project	Cognitive task sharing with JSC flight surgeons	Vascular investigations link to DAVIES project	Resource is shared within NSBRI and NASA
Synergistic Studies of Opportunity	Studies with DoD / DARPA	Bioengineering Center, U Penn	SRU Biosystems, biotechnology industry	Pharma industry collaborations	Medical assessment for diabetics, surgical patients	Neuro monitoring in ICU, Harvard	Cardiac, renal imaging apps in med practice; flight apps	Resource of National value
Development of Computer Model of Integrated Human Function	Image / model guided surgery	Data mining	Neural nets for pattern recognition		Algorithms for pattern identification	Neural nets, software engineering platform	Algorithms for individualized astronaut models	Modeling for training purposes

Table 11.3a. Achieving Goal 1: Methods to Reduce the Risk of Trauma and Acute Medical Problems

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Identify technologies suitable for non-invasive physiological assessment • Identify capabilities of sensor technologies for use in trauma • Identify promising new non-invasive surgical interventions • Assess validity of sensors based on gold standards in health and disease • Establish with NASA Medical Ops personnel levels of risks in humans													
Phase 2: Preliminary Countermeasure Development Research													
• Test sensors for normal anatomical and physiological non-invasive monitoring in animals and humans													
• Test sensors for anatomical and physiological non-invasive monitoring in animals and humans during trauma and acute medical conditions • Develop time-derivative pattern recognition and other algorithms for near automated detection of significant medical alterations based on sensor data • Refinement of non-invasive surgical capabilities integrated with image guided detection, interpretation and assessment of treatment efficacy													

Phase 3: Mature Countermeasure Development Research													
• Human subject demonstration of sensor – algorithm devices for trauma and acute medical problem assessment													
• Human subject demonstration of sensor – effector (treatment) devices for trauma and acute medical problems													
Phase 4: Countermeasure Evaluation & Validation													
• Evaluation of sensor – algorithm – effector "smart" system in simulated space flight conditions													
Phase 5: Operational Implementation of Countermeasure Strategy													

National Space Biomedical Research Institute
SMART MEDICAL SYSTEMS PROGRAM

Table 11.3b. Achieving Goals 2-4: Methods to Reduce the Risk of Toxic Exposure, Altered Pharmacodynamics and Adverse Drug Reactions, and Illness and Ambulatory Health Problems

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Identify emerging technologies suitable for management of toxic exposures, drug delivery and alterations, and nominal health exam. in space environment • Investigate mechanisms and determine validity of approaches in health problems • Establish with NASA Medical Ops personnel levels of risks in humans													
Phase 2: Preliminary Countermeasure Development Research													
• Test technologies suitable for health monitoring in remote harsh environments													
• Test sensors for toxic exposures and medical sequelae of exposures • Investigate novel drug delivery and other pharma concerns to reduce drug adversity in space environment													
Phase 3: Mature Countermeasure Development Research													
• Human subject demonstration of novel technologies for assessment of health and medical problems, including													

exposure to toxins • Determine in human trials countermeasure effectiveness of new pharma approaches relevant for space													
Phase 4: Countermeasure Evaluation & Validation													
• Evaluation of "smart" systems for assessment of health and medical problems in simulated space flight conditions • Establish efficacy of new pharma approaches, including microencapsulation													
Phase 5: Operational Implementation of Countermeasure Strategy													

13.0 Technology Development

Team Leader: Harry K. Charles, Jr., Ph.D.
Assistant Department Head for Engineering
Technical Services Department
Applied Physics Laboratory
Johns Hopkins University
11100 Johns Hopkins Road
Laurel, MD 20723-6099
240-228-8050
240-228-6119 FAX
harry_charles@jhuapl.edu

13.1 INTRODUCTION

The Technology Development Program (Team) of the National Space Biomedical Research Institute (NSBRI) is chartered with developing technologies that will lead to a better understanding of the barriers to long-duration space exploration and assist in the development of countermeasures to assure safe and productive missions. The primary focus of the Technology Development Program is directed toward those technologies that support the ground-based and space-based research of the other NSBRI research teams and space life science research community at large. Accordingly, it creates systems and tools such as sensors, instruments, devices, and intelligent software. Requirements for these tools and technologies are predicated on the carefully developed needs of the other research teams. In particular, the Technology Development Team selects projects that: (1) support the investigation of the effects of spaceflight on human physiology and behavior; (2) apply this information toward the development of techniques, technologies, instruments, and countermeasures that will sustain humans during future long-duration space missions; and (3) benefit the quality of life and medical care on Earth.

Synergism is a key element of the program and the Technology Development Team strives to bring the engineering and biological science disciplines together in the identification and development of devices, instrumentation, and systems that address the fundamental research issues critical to the human exploration of space. A unique feature of the Technology Development Team's projects are their ability to bring an integrated systems engineering perspective (cross discipline) to bear on technology development as it supports the basic research. An important by-product of this integrated approach is the cross-education of the basic and applied science researchers in engineering and technology disciplines and the applied research and development engineers in biological and medical science.

13.2 IDENTIFYING TECHNOLOGY NEEDS

Identifying technology and technology development projects that are important to the requirements of the other NSBRI teams and the human exploration of space is a critical element of the Technology Development Team's charter. These technology identification activities fall in three general areas: (1) assessing the developments in science, technology, and engineering by industry, academia, and government that may impact the conduct of both space- and ground-based research in support of the human exploration of space; (2) monitoring the risks to spaceflight and NASA's humans in space roadmap to ensure that the current and future technological developments align with the major risk areas; and (3) fostering close communications between NASA, the NSBRI, and the industrial and academic communities to focus the new technologies and revolutionary developments on specific methods of risk reduction and countermeasures.

While all fields of engineering and applied science are rapidly changing as new materials, tools, and processes come on line, a few areas important to medical and biological sciences and NSBRI research can be identified. These areas include miniaturized devices and sensors, engineered materials, wireless communications, information processing and storage, and autonomous control and operation. The world of microelectronics continues its revolution with more and more active devices being placed on a single chip (i.e., a piece of semiconductor material the size of a human fingernail). The processing and science used to achieve the fantastic densities of active devices on a single chip (100 million to 1 billion) has been applied to several adjunct fields which hold promise in the biological arena, especially sensors. In particular, microelectromechanical systems (MEMS) can produce miniaturized mechanical parts that move under the action of an applied electric field or other stimulus. Such technology offers great possibilities for detectors and samplers that can be used to collect biological samples and provide on a chip analysis work. Other miniaturized and materials technologies will lead to entire analysis systems on chip. Nanotechnology and its associated self-assembly techniques will be a major underpinning of all advanced materials and composite structures. It will have far reaching effects on the biological and medical worlds ranging from the impregnation of bandage material with silver nanoparticles to promote wound and burn healing while preventing infection to the development of the fully-instrumented human by utilizing smart garments composed of composites with embedded nanofibers for sensing and control of the body environment.

The wireless communications explosion will have a significant impact on human communications as well as the control and readout of scientific information. Wireless interfaces will do much to improve clutter in cramped spacecraft as well as speed data collection and improve the comfort of astronauts during the experimental process. Advances in signal processing and information storage and processing will allow vast amounts of information to be stored on board the spacecraft as well as effective data compression for scientific information transmission. The exploitation of autonomous systems and automated control offer significant advantages for reducing the experimental burden on both the research scientist and the astronaut. Such systems range from the robotic control of machines and machine processes (e.g., blood sampling and analysis) to improving the quality of health delivery during long-duration space missions by using smart medical systems.

Since such a myriad of potentially useful technologies, devices, and instruments could have significant impact on an astronaut's health and his ability to perform his mission, it is important for the Technology Development Team to identify the most important of NASA's risk factors for humans in space and then from these risk factors identify technology applications and devices that might produce significant risk countermeasures or aid human adaptation or health care in prolonged flight environments.

The Critical Path Roadmap (CPR) provides the foundation needed by NASA to ensure that human spaceflight now and in the future is as safe, productive, and healthy as possible (within the mission constraints) regardless of the mission duration or destination. The CPR provides a framework for risk identification, risk prevention, and the need for viable countermeasures associated with humans in long-duration spaceflight. The Technology Development Team uses this roadmap as one means of prioritizing project selection. For example, bone loss in microgravity is considered one of the most serious risk factors (Type 1). Two NSBRI research teams are addressing bone loss and the causal or associated muscle alteration in space. The Technology Development Team has ongoing projects that directly support the efforts of both the bone and muscle teams.

Using the roadmap alone is not sufficient to identify all technology needs of the NSBRI research teams as well as the needs for human spaceflight. The Technology Development Team actively engages members from the other research teams, the medical science community, and NASA to assess additional technical requirements. Through various individual team leader and working group interactions, the needs are identified, distilled, and then focused into a technology development program.

13.3 GOALS

The Technology Development Team has the following goals for its program:

Goal 1: *Identifying new technological advancements and developments that can have a major impact on space biomedical research and astronaut health.*

Goal 2: *Contribute to risk reduction in each CPR priority area by developing new medical instruments and devices for both ground- and space-based research and countermeasure development.*

Goal 3: *Exploit the developments and advances made by Technology Development Team projects to improve the quality of life and health care delivery on Earth.*

Goal 4: *Promote the transfer of NSBRI-developed technological advances to industry for the benefit of Earth-based medical care.*

Goal 5: *Integrate technology development needs across other NSBRI teams, medical science community, and NASA through service and communication to become recognized as an important service arm that helps these researchers develop needed tools and instrumentation.*

13.4 DESCRIPTION AND EVALUATION OF THE CURRENT PROGRAM

Description of Current Projects

The risks associated with long-term exposure to microgravity and a high radiation environment are numerous; they represent the basis for the research program pursued by the NSBRI. Most of the ongoing NSBRI research is vertically integrated within a specific thrust area. For instance, the research teams typically have a core research topic that is combined with several special topic areas to form a disciplined approach to addressing a number of related issues.

The Technology Development Program is implemented in a different manner. The funded projects are selected, among other reasons, for their ability to provide necessary and enabling technologies for the basic research areas. Thus, the thrust area is laterally integrated with the other research areas. Figure 13.1 is a diagram showing the interaction between the eight current Technology Development Team projects and the other ten NSBRI research teams. As can be seen in Figure 13.1, the current Technology Development Team projects support nine of these remaining ten research areas.

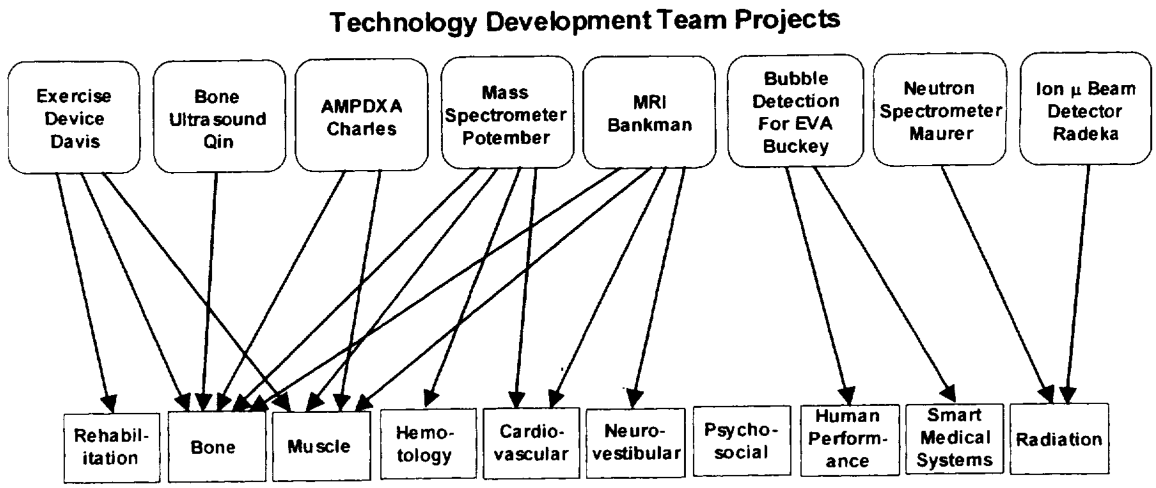


Figure 13.1. Mapping of current NSBRI Technology Development Team projects into the remaining ten NSBRI research areas.

The Technology Development Team generally focuses on projects that will deliver a specific product (e.g., sensor, instrument, etc.) in a specified period of time, typically one to three years. Of particular interest are projects that have strong technology transfer potential to industry so that the products of the development can be made available to support the research activities of other teams and achieve maximum societal benefit. Projects under the Technology Development Team umbrella are encouraged to interact with industry early in the development cycle. The NSBRI's Industry Forum can foster such interactions.

Proposals to the NSBRI Technology Development Program are expected to be of sufficient maturity (i.e., NASA Phase A (Conceptual Design)) so that: (1) the critical research issues can be readily identified, (2) the relevance of the technology development to the key research needs of the other NSBRI research teams and human spaceflight is evident, and (3) the technical approach and development plan directly lead to a deliverable (instrument, sensor, countermeasure device, etc.) within a reasonable timeframe.

Currently, there are eight projects under the umbrella of the NSBRI Technology Development Team: three projects continuing from the first research cycle (1998-2000) and five new projects that were nominally started in February 2001. Some projects had slightly later starts due to funding transfer issues. Due to budget cuts and change in Principal Investigators, one project, the Space Qualifiable MRI, has been delayed to Summer 2002. As shown in Figure 13.1, the Technology Development Team projects address research needs and risk reductions in nine of the ten NSBRI basic research areas. The research activities for each of the Technology Development Team projects are listed in Table 13.1 and described below.

Project 1

PI/Project Title: Harry K. Charles, Jr., Ph.D.

Advanced Multiple Projection Dual Energy X-ray Absorptiometry (AMPDXA) System

Need(s) Addressed: Provide accurate measurement of bone and muscle loss both in space and on Earth. Measure the location of the bone loss and assess the integrity of the bone structure.

Countermeasures Target: Provide highly accurate bone mass loss and structural information so that appropriate countermeasures can be developed, applied, and monitored.

Project Description: The purpose of the Advanced Multiple Projection Dual Energy X-ray Absorptiometry (AMPDXA) Scanning System project is to design, build, and test a precision scanning system for monitoring the deleterious effects of weightlessness on the human musculoskeletal system during prolonged spaceflight. The instrument uses dual energy X-ray absorptiometry (DXA) principles and is designed to measure bone mineral density (BMD), decompose soft tissue into fat and muscle, and derive structural properties (cross-sections, moments of inertia). Such data permits assessment of microgravity effects on bone and muscle and the associated fracture risk upon returning to planetary gravity levels. Multiple projections, coupled with axial translation, provide three-dimensional geometric properties suitable for accurate structural analysis. This structural analysis, coupled with bone models and estimated loads, defines the fracture risk. The scanner will be designed to minimize volume and mass (46 kg goal), while maintaining the required mechanical stability for high-precision measurement. The AMPDXA will be able to detect 1% changes in bone mass and geometry and 5% changes in muscle mass.

Two instruments (the Laboratory Test Bed (LTB) and a Clinical Test System (CTS)) have been constructed to date. The LTB has been used to develop source and substrate parameters and to test human bone segments. The CTS will allow human patient testing. The LTB has been fully operational for the last three years. It has allowed the AMPDXA project to develop sources, detectors, and software algorithms necessary for the high-precision detection of BMD and bone structure. In this current period, the LTB has allowed the refinement of our BMD and structure extraction algorithms as well as continued progress on the high-resolution separation of soft tissue from bone. Multiple-projection analysis enables the user to evaluate bone structural properties (e.g., bending strength) independent of subject position and orientation. Empirical evaluations to date have demonstrated an average coefficient of variation in the maximum and minimum moment of inertia of less than 3%. It is projected that further processing refinement will reduce the error in a three-projection estimate to <1%; adding more projections will also reduce the error.

The CTS is operational and initial human testing trials are about to begin. Initial results of the CTS (using phantoms and cadaver parts) have shown even greater precision than the highly accurate LTB results.

Project 2

PI/Project Title: Richard H. Maurer, Ph.D.
Neutron Spectrometer

Need(s) Addressed: Monitor the neutron radiation environment inside spacecraft, large space habitats, and on planetary surfaces.

Countermeasure Target: Provide highly accurate neutron radiation monitoring so that appropriate countermeasures can be developed, applied, and monitored.

Project Description: A Neutron Energy Spectrometer is being developed to monitor the flight radiation environment on the International Space Station (ISS), an interplanetary transport vehicle, or on a planetary surface. Detector types were selected for the complete neutron energy range and experimentally validated the concept for the low- and high-energy intervals. The effectiveness of our charged particle discrimination system was demonstrated. Data analysis and modeling efforts have verified the experimental results to date and the procedure for deconvolving deposited energy spectra into incident neutron energy spectra. The engineering prototype instrument was successfully flown on a NASA aircraft, demonstrating the robustness and operational capability of our design. A balloon flight is planned that will yield scientifically interesting data on the high-energy neutron environment. The balloon altitude was selected to simulate the incoming or downward neutron environment of the surface of a planet like Mars.

Project 3

PI/Project Title: Richard S. Potember, Ph.D.
Miniature Time-of-Flight Mass Spectrometer

Need(s) Addressed: Develop a miniaturized instrument that can quantitatively measure critical biomarkers from breath, body fluids, products of infection, etc.

Countermeasure Target: Provide a highly accurate measure of human biomarkers associated with many of the deleterious effects and conditions caused by microgravity and prolonged spaceflight so that appropriate countermeasures can be developed, applied, and monitored.

Project Description: The long-term objective of the Miniature Time-of-Flight Mass Spectrometer (TOFMS) project is to design, build, and launch a flight-qualified TOFMS for use on space platforms such as the Shuttle, ISS, or a planetary mission. The TOFMS can identify and quantitatively measure critical biomarkers associated with the deleterious effects of microgravity and long-duration spaceflight. The biomarkers can be determined from the analysis of breath, body fluids, products of infection, and, perhaps, DNA repair products and DNA mutations. As currently configured, the system appears to be of particular value to both the Bone and Muscle Teams, but biomarkers important to several other research teams can also be obtained. The TOFMS system being developed is small (less than 1 cubic foot), lightweight (less than 5 kg), low power (less than 50 W), and rugged. This NSBRI-sponsored TOFMS is building upon technology developed for DARPA to analyze chemical and biological weapons, while being optimized for astronaut use and the identification and quantification of biomarkers. To date, the TOFMS has shown spectra of compounds ranging from under 100 to beyond 10,000 atomic mass units (amu). Sensitivities for such biomarkers in the parts per million to parts per trillion range have been achieved.

Many of the biomarker identification procedures are complex, requiring special protocols and associated laboratory equipment. To carry the equipment and chemical supplies required to monitor the health of an astronaut would be weight prohibitive, would necessitate specialized training, and would require a significant fraction of the astronaut's time. The TOFMS provides a small, efficient, broadband diagnostic instrument that can rapidly identify biomarkers important for successful human space exploration.

Project 4

PI/Project Title: Jay C. Buckey, Jr., M.D.
Improved Bubble Detection for Extra-Vehicular Activity

Need(s) Addressed: Careful monitoring and understanding of the bubble nucleation process associated with decompression sickness is required to reduce astronaut risks associated with extra-vehicular activity.

Countermeasure Target: Provide an understanding of blood bubble nucleation and growth so that effective countermeasures can be developed, applied, and monitored.

Project Description: The Improved Bubble Detection for Extra-Vehicular Activity (EVA) project goal is to improve current bubble detection methods. The assembly of the ISS requires extensive and unprecedented extra-vehicular activity. Because spacesuits operate at low internal pressures, the astronauts are highly susceptible to decompression sickness (DCS) (gas bubbles in the blood). A range of pre-breathe strategies, as well as suit gas mixtures and pressures, are employed to mitigate the risk. During ISS construction, in-suit Doppler bubble monitoring will be provided to detect conditions that increase DCS risk. Doppler bubble detection, while effective, has three primary limitations: (1) it is motion sensitive; (2) it detects only moving bubbles; and (3) it does not detect bubbles with diameters less than 80 μm.

The Improved Bubble Detection for EVA project will exploit two transcutaneous ultrasonic bubble detection and sizing instruments under development by NASA. These instruments utilize bubble resonance (not Doppler) techniques, thus allowing the instruments to measure stationary bubbles as well as bubbles of smaller size. One instrument is optimized for intravascular bubble detection in the size range of 30 to 200 μm. The other monitors extravascular bubbles in the 1- to 10-µm-size range. Both instruments in *in-vitro* trials have demonstrated bubble detection at their lower range limits.

Project 5

PI/Project Title: Yi-Xian Qin, Ph.D.
Scanning Confocal Acoustic Diagnostic (SCAD) System

Need(s) Addressed: Measurement of bone loss in space so that appropriate countermeasures can be developed, applied, and monitored.

Countermeasure Target: Provide measurement of bone material properties and relate to countermeasure development and processing.

Program Description: The Scanning Confocal Acoustic Diagnostic (SCAD) System project is focused on the measurement of bone loss is space. On Earth, early diagnosis and proper treatment of progressive bone loss (and/or poor bone quality) can dramatically reduce the risk of bone fracture. Ultrasound systems have the potential for determining the material properties of bone in a safe, repeatable, and highly accurate manner. Limitations in the performance of current ultrasound systems restrict their application to first-order screening, rather than the clinical standard upon which osteoporotic diagnosis and treatment regimens are based.

The SCAD is usable not only for ground-based determination of bone's physical properties; but, because of its low weight and size, it is also suitable for monitoring subtle changes in bone density and strength during extended spaceflight. The SCAD project is divided into four basic parts: (1) development of the SCAD system hardware, (2) correlation of SCAD-determined sound velocity and attenuation measurement with micro-CT bone BMD and structure, (3) prediction of the risk of trabecular bone failure associated with osteoporosis in the animal model, and (4) correlation of SCAD-derived BMD and structural modules with DXA measurements.

Project 6

PI/Project Title: Veljko Radeka, Ph.D.
Heavy Ion Microbeam and Micron Resolution Detector

Need(s) Addressed: The micron resolution detector, together with the microbeam, will allow the localized position of an ion impact within a cell to be determined. This is an enabling technique for radiobiology studies.

Countermeasure Targets: Understanding of the effects of radiation damage within the cell so effective countermeasures can be developed.

Program Description: The Heavy Ion Microbeam and Micron Resolution Detector System is aimed at studying radiation effects at the cellular level. Using microbeam irradiation facilities, it is now possible to place discrete numbers of particles in defined cellular and extracellular locations. Such facilities permit heavy-ion radiobiologists to explore the impact of signal transduction between cellular compartments as well as issues related to intercellular communication at low limiting fluences where not all cells in a population have been traversed. A high-energy, heavy-ion microbeam will allow an important unanswered question to be addressed, i.e., whether neurons that survive transversal by high-energy heavy ion (HZE) particles develop changes as a late consequence of the damage they incurred. These low-fluence studies will increase the understanding of the consequences of exposure to high, linear energy transfer (LET) radiation, such as encountered in the space radiation environment. (See the NES project above.) Currently, the microbeam detector has been designed and simulated.

The purpose of the Heavy Ion Microbeam and Micron Resolution Detector project is to allow such radiation studies as described above to take place by developing the following tools: (1) a microbeam (diameter 10 μm) of heavy ions (e.g., iron) at energies higher than existing ion microprobes (3 GeV/nucleon), and (2) an electronic position-sensitive detector for heavy ions with a position resolution better than 1 μm. Interactions between the Heavy Ion Microbeam and Micron Resolution Detector project and the Radiation Team have taken place.

Project 7

PI/Project Title: Brian L. Davis, Ph.D.
Dynamic Exercise Countermeasure Device (DECD)

Need(s) Addressed: Demonstrate that proper in-flight exercise can counter the microgravity-induced bone and muscle loss.

Countermeasure Target: Develop a direct countermeasure to bone and muscle loss in space.

Program Description: The Dynamic Exercise Countermeasures Device (DECD) is aimed at developing a countermeasure to bone and muscle loss in space. Bone demineralization (bone mass loss) is a well-documented physiologic effect of long-duration spaceflight and microgravity. Animal experiments on Earth have clearly indicated that: (1) certain bone strains and strain rates stimulate bone deposition, and (2) repetitive loading of the lower extremity can increase osteonal bone formation even as proximally as the vertebral column. Such studies have also indicated that a relatively small number of appropriate weight-loading cycles may be sufficient to stimulate bone deposition. Based on prior research with weight-loading experiments upon the foot, a dynamic exercise countermeasure device that utilizes jumping as the mode of exercise for the astronauts is under development. The DECD project is divided into three phases: (1) develop a lightweight, vibration-isolated exercise device, suitable for use on the ISS, that will permit dynamic jumping exercise within microgravity; (2) perform system testing using zero-gravity simulation; and (3) verify DECD efficacy in true microgravity through KC-135 experiments. Currently, a prototype device is in operation.

Project 8

PI/Project Title: Isaac Bankman, Ph.D.
Space Qualifiable Magnetic Resonance Imaging (MRI) System

Need(s) Addressed: MRI needed in space for animal studies and peripheral (limb) measurements on humans.

Countermeasure Target: Provide highly accurate bone and soft tissue measurements to verify countermeasures in space-based animal studies.

Program Description: The goal of the Space Qualifiable Magnetic Resonance Imaging (MRI) System is to develop a proof-of-concept engineering model of a space-qualified MRI system for small animals and astronaut limbs with a mass of less than 130 kg and low average power (<1 kW quiescent and <1.2 kW when scanning). An on-board processor or personal computer can be adapted to display the collected information. MRIs provide high-resolution, high-quality anatomical information without ionizing radiation, so they can be safely and repeatably used to track changes without deleterious effects.

As a result, the study of physiological alterations in space and the development, verification, and maintenance of countermeasures will be significantly enhanced. Mice and small rat models are useful surrogates to carry out in-orbit physiological studies. In-flight MR imaging of these animals will be of particular benefit to countermeasure development by several of the NSBRI research teams. Measurement of alterations in the limbs of the astronauts, especially the lower limbs, will provide partial confirmation of countermeasure effectiveness and of the utility of

Earth-based animal models. The MRI system is particularly amenable to the study of soft tissue and bone. To date, magnet trade-off studies and initial system designs have taken place.

Evaluation of Program

The seven active NSBRI Technology Development Team projects are making significant progress against their development goals. The three continuing projects have operating instruments, while the relatively new projects are in various phases of instrumentation development. For example, the two AMPDXA instruments (LTB and CTS) are operational and the CTS is being readied for human trials. In addition, commercialization discussions are underway to transfer the technology to industry. The neutron spectrometer is being readied for a high altitude balloon flight after completing several successful aircraft flight tests. The TOFMS has identified with high sensitivity several biomarkers associated with bone and muscle loss. The heavy ion microbeam and detector system has been designed and the detector fabricated. When completed, this resource will address several very current and significant issues in cellular biology. The SCAD system is operational and is performing correlation studies between measurements in the extremities and the weight-bearing bones. The bubble detection project has developed prototype equipment that has detected microbubble formation at various nucleation sites within the body. The DECD is in its second prototype design phase. Each of the projects and prototype instruments is addressing the major goals of the Technology Development Team, the NSBRI, and NASA by either developing research tools that facilitate the measurement and analysis of critical parameters necessary for the research of the other NSBRI teams or creating direct countermeasures to the risks encountered in long-duration spaceflight.

The Technology Development Team is constantly on the alert for technological developments and advancements (Goal 1) that will have impact on both the NSBRI and space life science research. For example, working closely with the Bone Team, the Technology Development Team was able to identify two major impediments to the development of countermeasures for bone demineralization: understanding of the bone mineral loss process and being able to monitor the instantaneous conditions of the subjects' bones. The TOFMS (Project No. 3) has been adapted to monitor the biomarkers for bone loss. While the TOFMS was developed under DARPA funding for solids analysis, newly invented methods of sample preparation and fixing techniques has allowed its applicability to biological specimen analysis. Historically, space-based monitoring of such biomarkers has typically relied on collection of specimens (urine, blood, etc.) and then storage of the specimens until Earthly return. Specimen analysis may, under good conditions, be completed many months after completion of the mission, but certainly does not afford the ability to provide closed-loop monitoring and control of countermeasures (Goal 2).

The AMPDXA project (No. 1) and the SCAD project (No. 5) specifically address the monitoring issue. Both these projects have completed engineering model instrumentation developments (Goal 2) and have demonstrated the ability to provide quantitative information that is critical to the current and future research of the Bone Team. These devices have been designed to be directly adaptable for in-space use. Size, weight, and power are currently, or soon will be, appropriate for routine launch and regular use on-orbit or in missions beyond Earth. Using advanced automation techniques (Goal 1), these devices and their associated analysis methods can be operated by individuals with very little training. Thus, the devices have broad utility in both space- and Earth-based applications.

The bone demineralization conditions that astronauts experience in space are similar to those that exist in clinical populations (e.g., age-related osteoporosis, quadriplegic, etc.) on Earth. Thus, the research supported by the AMPDXA, SCAN, and TOFMS is expected to have a direct positive influence on health care delivery on Earth (Goal 3). In addition, the technology itself has demonstrated better performance than commercially available devices. In particular, commercialization (Goal 4) of a clinical version of the AMPDXA is being pursued that has great potential to improve screening and treatment for age-related osteoporosis.

Muscle alteration research faces the same challenges of loss mechanism determination and monitoring as noted above for bone. Both the AMPDXA and TOFMS provide the same capabilities (i.e., monitoring and biomarker determination, respectively) in support of risk reduction for muscle as they do for bone. Advanced AMPDXA muscle algorithms (Goal 1), coupled with a radical new x-ray source (Goal 1), offer a promise of similar precision measurements of muscle as has been demonstrated for bone. The DECD (Project No. 7) offers the potential to directly countermeasure muscle loss in space (Goal 2).

Exposure to radiation in space is a threat that can lead to an increased risk of cancer and DNA damage. A significant portion of the exposure, between 30-60%, results from neutron sources that are extremely difficult to monitor, let alone characterize, in real-time. The absence of a portable, quantitative, real-time neutron spectrometer results in an exposure safety risk for astronauts (Goal 1). The Neuron Energy Spectrometer Project (No. 2) is developing a spectrometer (Goal 2) that can supply information on the neutron environment to the Radiation Effects Team in support of assessing radiation damage and cancer risk. The prototype of this unit is operational and has just completed several flight tests in F15 aircraft. The Ion Microbeam Project (No. 6) will address radiation damage at the cellular level.

Orthostatic intolerance can result in syncope when an individual is subjected to gravitational influence after exposure to microgravity. This situation can pose severe risks to astronauts who have to execute unassisted emergency procedures or extraterrestrial landings. The need to predict, prevent, or control orthostatic intolerance and its effects is significant to the space program. Both the TOFMS and the MRI project (No. 8) have the ability to provide near real-time monitoring of parameters related to orthostatic intolerance. The TOFMS can detect various heart-related biomarkers and the MRI will be able to monitor soft tissue, including vein and artery blood volumes and fluid shifts, in animals and potentially on the extremities of the astronauts. Previously in the first research cycle, the Technology Development Team created the cardiovascular systems identification (CSI) instrumentation (Goal 2). The CSI is a self-contained, automated device for measuring and characterizing alterations in cardiovascular regulation. The CSI is being commercialized and transfer to industry is underway (Goal 4) for use in Earth-bound clinical settings (Goal 3).

To identify and appropriately fund these pipeline projects requires constant interaction between the NSBRI research teams and the Technology Development Team. To promote this integration, which satisfies much of Goal 5, the Technology Development Team established the Technology Working Group (TWG) as a formal mechanism for this liaison. Meetings of the TWG will be conducted more frequently with expanded participation from academia, industry, and government. In addition, Technology Development Team participation in the annual retreats of the other teams will also foster cooperation and the synergism necessary to identify the technical requirements (Goal 1). Such input from NSBRI research teams, coupled with strong industrial and academic input, will allow the Technology Development Team to develop calls for research that address technological solutions for the risk factors associated with long-duration spaceflight that are in concert with the established research goals of the other NSBRI teams. Part of the strategic growth plan for the Technology Development Team will be the ability to direct key technology development efforts in addition to or in conjunction with the projects received in response to the research announcements. Such responses may leave gaps in the envisioned technology development requirements. A recent meeting of the TWG identified over thirty instruments or technology development needs of the space research community that are not currently being addressed by the NSBRI Technology Development Program. These gaps offer opportunities to foster important research that could accelerate the overall space effort. Support sources for such selected top-down driven research will have to be developed.

The Technology Development Team also envisions itself as a bridge between the other NSBRI research teams and the extensive resources for technology development that exist within the participating institutions as well as in academia and industry. Bridging activities will include information exchanges on technology, contacts for development efforts, etc. Integration activities, as mentioned above, are described in Table 13.2. Table 13.3 presents the phases of technology development and insertion for the current Technology Development Team projects.

13.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Summarized below are the objectives underlying each goal and the strategic activities that the Technology Development Team plans to use to achieve the goals and objectives of its program.

Goal 1: *Identify new technological advancements and developments that can have a major impact on space biomedical research and astronaut health.*

Objective 1A: Technology assessment to determine most applicable developments:

- Increase the Team's interdisciplinary membership, both in the skill base of its members and the diversity of participating institutions.
- Have team members attend conferences, meetings, and other forums where advanced technology and its applications are discussed.
- Participate in NASA space life sciences programs, conferences, and forums on the issues associated with long-duration human spaceflight.
- Establish ties with non-NSBRI institutions that have technology ideas and resources necessary for solving the issues surrounding human spaceflight.

Objective 1B: Risk assessment to determine the most urgent needs:

- Continue interactions with NASA and the other NSBRI research teams.
- Conduct more frequent TWG meetings with expanded participation from academia, industry, and government.
- Participate in the annual retreats of other NSBRI research teams.

Goal 2: *Contribute to risk reduction in each critical path roadmap priority area by developing new medical instruments and devices for both ground- and space-based research and countermeasure development.*

Objective 2A: Current monitoring and capability development activities:

- Complete projects developing instrumentation to monitor bone and muscle loss (AMPDXA, SCAD, and MRI projects).
- Demonstrate that precision measurement of bone loss and structure will shed light on the bone loss mechanisms in space.
- Complete neutron radiation monitoring instrument.

- Complete development of heavy ion microbeam to facilitate cellular level radiation damage research.
- Complete TOFMS and demonstrate its ability to monitor biomarkers for major human risk factors.
- Verify the origin of the bubbles present in decompression sickness and develop effective measurement equipment.

Objective 2B: Current countermeasure development activities:

- Complete development of dynamic countermeasures device and verify the exercise and jumping loads will inhibit bone and muscle loss in space.
- Expand program to include more projects that directly develop countermeasures.

Goal 3: *Exploit the developments and advances made by Technology Development Team projects to improve the quality of life and health care delivery on Earth.*

Objective 3A: Technology readiness:

- Publish results of instrument development and experimental results.
- Work with medical researchers to demonstrate the utility and versatility of the instrumentation development.
- Develop funding mechanisms to allow prototype-developed instruments to be placed in appropriate clinical settings.

Objective 3B: Technology market penetration:

- Develop presentations and marketing material (literature) that not only touts the progress on current projects, but also makes the entire NSBRI team aware of the technological resources available at participating institutions.
- Expand Technology Development Program to include all ten NSBRI research areas with better balance between the areas. Currently, nine of these areas have overlap with the technology projects, but the technology projects are heavily focused in a few areas.

Goal 4: *Promote the transfer of NSBRI-developed technological advances to industry for the benefit of Earth-based medical care.*

Objective 4A: Establish ties with industry:

- Work closely with members of the NSBRI Industry Forum on the performance and capabilities of the developed instruments.
- Serve as a resource to bring NASA's needs and industry's capabilities together in the solution to health risks associated with long-term spaceflight.

Objective 4B: Facilitate technology transfer:

- Develop sources of funding to help in the investigator's technology transfer process.
- Make instrument developers aware of opportunities for direct funding from NASA and other sources once projects have reached a certain level of maturity.
- Provide information on how to pursue technology transfer (licensing, start-up company, etc.).

Goal 5: *Integrate technology development needs across other NSBRI teams, medical science community, and NASA through service and communication to become recognized as an important service arm that helps these researchers develop needed tools and instrumentation.*

Objective 5A: Develop support to other teams:

- Develop calls for research that address technological solutions for the risk factors associated with long-duration spaceflight that are in concert with the established research goals of other teams.
- Identify gaps left in the NSBRI's technology development requirements from the proposal responses.
- Develop support resources for filling these gaps to effectively foster and accelerate the overall goals of the other teams.

Objective 5B: Technology awareness:

- Facilitate information exchanges and provide technology information to the other teams.
- Serve as resource to help facilitate technology liaison with industry, academia, or government laboratories.

13.6 SUMMARY

The objective of the Technology Development Program of the National Space Biomedical Research Institute is to develop devices, instrument systems, and associated algorithms and software that lead to a better understanding of the barriers to long-duration space exploration and assist in the development of countermeasures to assure safe and productive space missions. The primary focus of the Technology Development Program is directed towards those technologies that support the ground-based and space-based activities of the other NSBRI research teams. The unique feature of this program is the opportunity to bring an integrated system engineering perspective to bear on the technological developments necessary to support basic research. Multidisciplinary development teams have been established to work on strategically focused projects that integrate individuals and institutions with vastly different capabilities into a cohesive team.

Identification of the technology development research needs of the NSBRI teams and space life sciences community in general is made through vigilant review of current technology development advances that may impact or advance NSBRI research; monitoring of the Critical Path Roadmap; and creating forums for discussion and communication on technological needs with NSBRI teams, NASA, industry, and academia.

In the next 3- to 5-year time span, the Technology Development Team should be able to point to many successes from its current program. Indications are that several of its projects are reaching high enough technology readiness levels that sources of funding other than the NSBRI should be available to carry these developments into space, or be widely available to support Earth-based research and, in some cases, to be part of the medical health care delivery system. While these successes are extremely important, it is also just as important to keep the pipeline filled with high-quality, on-going development efforts that address the technology needs of the other NSBRI research teams and support the overall requirements of the NASA Space Life Science Program.

Summary Diagrams

Table 13.1 summarizes the Technology Development Team's project research activities and phases of development.

Table 13.2 summarizes the Technology Development Team's project integration activities.

Table 13.3 summarizes the phases in technology development and insertion for the current Technology Development Team projects.

National Space Biomedical Research Institute
TECHNOLOGY DEVELOPMENT TEAM

Table 13.1. Technology Development Program – Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasures Target	Experimental Systems	Phase I (1)	Phase 2 (2)	Phase 3 (3)
Charles/AMPDXA	• Bone loss • Muscle loss	• Not applicable • Allows countermeasure effectivity measurement	• X-ray	• Laboratory test bed	• Clinical test unit • Human Testing	• Protoflight Design
Maurer/NES	• Radiation • Cancer	• Not applicable • Measures environment	• Radiation detectors	• Accelerator measurements	• Aircraft & balloon flights	
Potember/TOFMS	• Broad applicability • Bone loss	• Not applicable • Analysis tool • General purpose	• Mass spectrometry	• Understand biomarkers	• Detect biomarkers	• Hardware • Protoflight
Buckey/Bubble Detection	• Crew health • Decompression sickness	• Not applicable • Measurement tool	• Ultrasonic detection	• Bubble detection measurements		
Qin/SCAD	• Bone loss	• Not applicable • Measurement tool	• Ultrasound	• Ultrasound • Propagation studies	• Clinical test unit	
Davis/DEDC	• Muscle loss • Bone loss	• Jumping • Exercise training	• Mechanical exercise system	• Bone stress-strain studies	• Exercise machine • KC-135 flights	
Radeka/Microbeam/ Detector	• Radiation • Cellular damage	• Investigative tool	• Neutron source • Radiation detectors			
Bankman/Space MRI	• Muscle loss • Bone loss	• Not applicable • Measurement tool	• Magnetic resonance			

(1) Equipment Development Mechanistic Studies
(2) Equipment Operational Proof-of-Concept
(3) Protoflight Instrument Countermeasure

National Space Biomedical Research Institute
TECHNOLOGY DEVELOPMENT TEAM

Table 13.2. Technology Development Program – Integration Activities

Activity	Charles AMPDXA	Maurer NES	Potember TOFMS	Buckey Bubble Detection	Qin SCAD	Davis DEDC	Radeka Microbeam Detector	Bankman Space MRI
Internal Communication	• Telecons • Retreats • Team meeting	• Telecons • Retreats • Team meeting	• Telecons • Retreats • Team meeting	• Telecons • Retreats • Team meeting	• Telecons • Retreats • Team meeting	• Telecons • Retreats • Team meeting	• Telecons • Retreats • Team meeting	• Telecons • Retreats • Team meeting
NSBRI Teams	• Retreat • Working groups • Individual	• Retreat • Working groups • Individual	• Retreat • Working groups • Individual	• Retreat • Working groups • Individual	• Retreat • Working groups • Individual	• Retreat • Working groups • Individual	• Retreat • Working groups • Individual	
Information Sharing	• Reports • Papers • Patents	• Reports • Papers • Patents	• Reports • Papers • Patents	• Reports • Papers • Patents	• Reports • Papers • Patents	• Reports • Papers • Patents	• Reports • Papers • Patents	
Synergistic Studies/ Opportunities	• With SCAD • With Bone	• With Radiation • With Microbeam	• With Bone, Muscle & Cardiology	• With Crew Health • With SCAD	• With AMPDXA • With Bone	• With Human Fitness	• With Radiation • With NES	

Program about to start.

National Space Biomedical Research Institute
TECHNOLOGY DEVELOPMENT TEAM

Table 13.3. Technology Development and Insertion

Technology Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Need Identification													
• AMPDXA (Advanced DXA) • Neutron Spectrometer • Time of Flight Mass Spectrometer • SCAD (Ultrasound) • Microbeam/Detector • Bubble Detection • DECD (Exercise Countermeasure) • Space MRI													
Phase 1: Preliminary Instrument/Experiment Design													
• AMPDXA (Advanced DXA) • Neutron Spectrometer • Time of Flight Mass Spectrometer • SCAD (Ultrasound) • Microbeam/Detector • Bubble Detection • DECD (Exercise Countermeasure) • Space MRI													
Phase 2: Prototype Instrument/Preliminary Tests													
• AMPDXA (Advanced DXA) • Neutron Spectrometer • Time of Flight Mass Spectrometer • SCAD (Ultrasound) • Microbeam/Detector • Bubble Detection • DECD (Exercise Countermeasure) • Space MRI													

Table 13.3. Technology Development and Insertion (continued)

Technology Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 3: Proof of Concept Experiments/Testing				■	■	■							
• AMPDXA (Advanced DXA)													
• Neutron Spectrometer													
• Time of Flight Mass Spectrometer													
• SCAD (Ultrasound)													
• Microbeam/Detector													
• Bubble Detection													
• DECD (Exercise Countermeasure)													
• Space MRI													
Phase 4: Engineering for Flight or Widespread Use						■	■	■	■				
• AMPDXA (Advanced DXA)													
• Neutron Spectrometer													
• Time of Flight Mass Spectrometer													
• SCAD (Ultrasound)													
• Microbeam/Detector													
• Bubble Detection													
• DECD (Exercise Countermeasure)													
• Space MRI													
Phase 5: Technology Transfer/Insertion								■	■	■	■		
• AMPDXA (Advanced DXA)													
• Neutron Spectrometer													
• Time of Flight Mass Spectrometer													
• SCAD (Ultrasound)													
• Microbeam/Detector													
• Bubble Detection													
• DECD (Exercise Countermeasure)													
• Space MRI													

Appendix B

14.0 EDUCATION AND PUBLIC OUTREACH

Team Leader: Marlene MacLeish, Ed.D.
Professor, Medical Education
Morehouse School of Medicine
720 Westview Drive, SW
Atlanta, GA 30310-1495
404-756-5706
404-752-1043 FAX
macleim@link.msm.edu

14.1 INTRODUCTION

NASA's space program has enjoyed extraordinary success over the past 40 years. Program accomplishments and discoveries have broadened our understanding of the solar system and universe, as well as life on Earth. The space program has helped to advance human civilization by advancing fields as diverse as telecommunications, navigation systems and lightweight construction materials and medicine. With the establishment of the National Space Biomedical Research Institute (NSBRI) in 1997, NASA expanded its goal, to enhance health and healthcare delivery on Earth through research that will allow humans to engage safely in long-term space exploration beyond Earth orbit.

NSBRI discoveries and research are beginning to produce countermeasures to the harmful effects of microgravity and space radiation. Simultaneously, NSBRI will bring discoveries and products of clinical benefit to mankind on Earth, enhancing treatments for health issues such as muscle wasting, osteoporosis, shift-related sleep disorders and radiation-related conditions. The Institute also is researching ways to deliver improved medical care on space missions with new technologies and remote-treatment advances.

The mission of the NSBRI Education and Public Outreach Team is to communicate the significance and excitement of space life sciences to local, national and international audiences, while transferring and disseminating knowledge gained via the biomedical advances achieved by NSBRI Research Teams. This mission is being accomplished through an integrated array of programs focusing on students and educators at all grade levels, as well as the general public.

NSBRI Education and Outreach Team members include some of the nation's most prestigious research institutions, all leaders in educational outreach programming: Baylor College of Medicine (BCM), Massachusetts Institute of Technology (MIT), Morehouse School of Medicine (MSM), Mount Sinai School of Medicine (MSSM), Rice University (RU), Texas A&M University (TAMU), University of Texas-Medical Branch (UTMB) and University of Washington (UW).

14.2 NEED

Each decade brings new challenges and participants who work to advance the mission of NASA's space program. Unfortunately, the initial stunning success of the space program may have fostered the impression that space travel has few associated risks. These perceptions are not accurate and must be addressed to assure public support.

The NSBRI Education and Public Outreach Team strives to promote understanding of and support for both NASA's and NSBRI's activities by working across the educational continuum to share the new discoveries resulting from NSBRI-led research. Through teacher professional development, innovative curricular materials and university courses, and use of various media, Team members are strengthening NASA's connection to the public. In addition, NSBRI's Education and Public Outreach is addressing NASA Administrator Sean O'Keefe's strong commitment to motivating young people to pursue careers in science, technology and engineering through the excitement of space exploration.

14.3 GOALS

The Education and Public Outreach Team develops and implements activities that address five major programmatic goals, developed jointly by Team partners, in coordination with the NSBRI leadership, to assure that Team projects address overarching NSBRI objectives.

Goal 1: *Design and conduct a variety of teacher professional development programs to help teachers understand space life sciences and change their practices and behaviors to improve the learning experiences they provide students.*

Goal 2: *Develop curricular materials that span the educational continuum; are aligned with national science standards; provide accurate, balanced, effective and inquiry-based instruction; and expand students' understanding of on-going NSBRI research.*

Goal 3: Increase science literacy and public awareness of the real-life impacts of NSBRI research through media, informal science activities, direct mailings and magazine stories.

Goal 4: *Promote educational access and career awareness in space life science fields among high school and undergraduate students as well as high school teachers.*

Goal 5: *Integrate NSBRI-focused teacher professional development, curricular materials, scientific literacy initiatives, and educational and career access activities among all Education and Public Outreach Teams, other NSBRI Teams and public venues.*

14.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The Educational and Public Outreach Team is comprised of experienced educators and scientists from some of the most noted research institutions in the nation. It is establishing NSBRI as a leading resource for teacher professional development programs and quality science education materials that bring the excitement and importance of NSBRI space life science research into the nation's classrooms and homes. Hundreds of teachers and thousands of students are benefiting from programs and activities conducted by the Education and Public Outreach Team. The public is being reached through media programs and national magazine articles.

NSBRI Education and Public Outreach Team members are expanding the scope of their projects by partnering with local and national organizations. Team partners include: public schools and school districts in 24 states, Atlanta Public Television and Radio, Emory University, Fernbank Science Center Museum, Excellence in Education, Harvard Medical School, Houston Public Television, Houston Independent School District, Johnson Space Center, New York Public Schools, New York Hall of Science, North Forest (TX) Independent School District, Space Center Houston, Spelman College, Texas Alliance for Science, Mathematics and Technology, Texas Rural Systemic Initiative, the Texas Statewide Systemic Initiative and the Washington NASA Space Grant.

The Education and Public Outreach Team continues to conduct activities that address the five program goals. The wide range of Team projects are designed to address the ultimate mission of communicating the significance and excitement of space life sciences to a variety of audiences, while transferring and disseminating knowledge gained via the biomedical advances achieved by NSBRI Research Teams. Table 14.1 (below) delineates which primary activities of each

TABLE 14.1. CURRENT NSBRI EDUCATION AND OUTREACH PROJECTS

PI/PROJECT	GOAL ADDRESSED			
	Teacher Professional Development	**Curriculum Development**	**Science Literacy/Public Awareness**	**Career Awareness and Access**
William A. Thomson, PhD *From Outer Space to Inner Space: Sharing NSBRI Progress with the Community*	Summer and School Year Teacher Professional Development at Conferences and Meetings	Elementary/Middle School Curriculum Materials	Educational Television and News Stories; Space Center Houston	Television Stories; Space Center Houston
Dava J. Newman, PhD *Space Biomedical Sciences and Engineering Curr. and Outreach Project*		Undergraduate and Graduate Courses; K-12 materials	Modular "Knowledge Station" (Interactive Exhibit)	Modular "Knowledge Station" (Interactive Exhibit)
Marlene MacLeish, EdD *Secondary and College Education for the Next Generation of Space Life Scientists*	Year-long Residency Program for Secondary School Teachers; Problem-Based Teacher Field Test Program	Undergraduate Courses; Secondary School Curriculum	NSBRI-Film Archive	NSBRI-Film Archive; Undergraduate Summer Research Program
Patrick J Gannon, PhD *Defying Gravity: Enduring Life In Space*	Science Teacher Teaming Teacher Workshops; Summer Program	9th Grade Curriculum	Museum Exhibits; Newsletters; Websites	Museum Exhibits; Newsletters; Websites
Roland B. Smith, EdD *Outreach Program for the Professional Development of Students and Teachers on Studies Related to Biomedicine in Outer Space*	Year-long Program for 20 Secondary School Teachers	Teacher-Developed Secondary Curriculum Units	Museum Exhibits, Websites	Summer Research Experiences for High School Students
Robert James, PhD *Teacher Academy Project*	Master NSBRI Teacher/ Teacher Workshops	Middle School Online Curriculum Projects	Texas Legislative Conferences	Annual Youth Symposia for Middle and High School Students
Deborah L. Illman, PhD *Northwest Outreach Program on Space Biomedical Research*			NSBRI Magazine Stories. Science Communication Workshops; Writer-in-Residence Program	NSBRI Magazine Stories-- Middle School "SciScape" Inserts-- (Some experiences for high school students)

Education and Public Outreach Team partner institution/project satisfy which goals. Goal 5, *Integration*, does not appear in this Table, as integration is not so much a separate aim as an overarching characteristic that applies to all Education and Public Outreach Team objectives.

Program Description

Following is a brief description of each Education and Public Outreach Team partner institution/project and its activities. It expands upon Table 14.1 and explains the general activities used to address the team's goals.

Baylor College of Medicine (BCM)—*From Outer Space to Inner Space: Sharing NSBRI Progress with the Community*. BCM, Space Center Houston, Houston Public Television and the Houston Independent School District are collaborating to convey the excitement and promise of NSBRI space life sciences research to students, teachers and the general public through coordinated formal and informal educational opportunities that will be embedded within local and state science education reform programs.

This partnership engages scientists and educators in the production, evaluation and dissemination of a planned series of elementary and middle school curriculum materials based on NSBRI research themes. It also produces bimonthly, nationally distributed radio stories on NSBRI research areas. The partnership reaches thousands of students, teachers and members of the general public each year. It also generates public awareness and appreciation of the benefits of NSBRI research. Project activities are aimed at middle school (grades 5-8), which has been identified as a particularly weak link in the K-12 science/mathematics education continuum.

Measurable project objectives are: (1) collaboratively create, evaluate and disseminate three interdisciplinary teaching units (one per year) on NSBRI research themes for middle school students; (2) improve teacher practice and content knowledge through multiple professional development opportunities conducted in formal and informal educational settings; (3) develop an online workshop resource for NSBRI scientists to use for outreach to teachers, students and the community-at-large; and (4) create and implement cost-effective models for communicating NSBRI research to local and national populations through television and radio short-format news and newsmagazine stories.

<u>Massachusetts Institute of Technology (MIT)—*Space Biomedical Sciences and Engineering Curriculum and Outreach Project*</u>. MIT is developing curricular materials to educate a generation of scholars in space life sciences by transferring NSBRI space life sciences research into undergraduate courses and to younger students and the public. One graduate course has been developed and is being piloted at MIT: *Sensori-Neural Systems: From the Vestibular Periphery to Motor Responses, Perception and Adaptation*. Five course faculty are affiliated with other NSBRI research projects. One undergraduate course also will be developed: *Space Biomedical Engineering and Life Support Systems*. Its modular materials will cover eight of twelve NSBRI research areas and will be designed for adoption among NSBRI consortium institutions.

K-12 modular labs and activities will be developed for teachers to insert in established anatomy and physiology classes. These labs emphasize space biomedicine and engineering skills. The integration of these modules focuses on an end-term student designed project of an exercise machine that will counter the physiological effects of long-term space flight: "*Spacercise*". For the public, MIT will design a knowledge station that allows learners to interact with curricular materials via state-of-the-art information technology and a physical platform designed specifically to facilitate human interaction and learning.

Intended outcomes are to: (1) provide multi-level space life sciences curriculum; (2) excite and educate the public about the wonders of science, engineering and medicine by disseminating knowledge gained through NSBRI research; and (3) develop a set of innovative pedagogical strategies that represent the application of tested learning principles as a basis for comprehensive educational evaluation tools. In addition, the project will develop multimedia tools that are particularly suited to active learning accessible through the Internet. The evaluation plan will assess learning and knowledge transfer of curriculum that makes use of these technological advances as well as assessment of the new student (or 'learner') population.

<u>Morehouse School of Medicine (MSM)—*Secondary and College Education for the Next Generation of Space Life Scientists*</u>. The MSM program is multi-faceted. *The MSM-Fernbank Museum Space Station Teacher Institute* admits two science teachers into a yearlong residency at MSM to develop, test and disseminate secondary problem-based curriculum supplements. Teachers work with scientists and physicians to develop problem-based field test capabilities and

to write a cardiovascular case, *Bobby's Beat.* They attend the Texas A&M Teacher Academy to learn this method and develop leadership skills.

The *MSM-Georgia Institute of Technology SECME Program* delivers a teacher professional development module on the Human Body in Space at the annual SECME national meeting, and also sponsor a noted space scientist lecture to address the estimated one thousand attendees. The *Summer Research Program* enrolls four undergraduate students, selected from a national applicant pool, to engage in a research-intensive internship at MSM. One MSM medical student is sponsored to undertake clinical research in the Harvard Medical School Sleep and Circadian laboratory headed by an NSBRI scientist. A longitudinal database is maintained to measure the outcome of the program.

The *NSBRI Film Archive* contains more than 150 hours of video relating to NASA's Neurolab mission, NSBRI team science, and the Human Body in Space course. This one-of-a-kind repository will be used to develop interactive Internet accompaniments to the proposed textbook and the problem-based cases written by the teacher fellows. It also will support the outreach and pubic affairs of the entire NSBRI enterprise. An electronic, undergraduate curriculum on the human body and weightlessness will use a multidisciplinary perspective to support national undergraduate, science education standards and space life sciences at the college level.

<u>Mount Sinai School of Medicine (MSSM)—*Defying Gravity: Enduring Life in Space*</u>. MSSM is developing a 9th grade, space-based science and mathematics curriculum that links human health in Earth's gravity and in space's microgravity. It explores scientific knowledge essential to formulate countermeasures; provides working models of scientific and mathematical principles; and includes hands-on laboratory sessions with group discussion to demonstrate current paradigms and unifying principles that relate research to space biomedicine and hypothesis testing. The curriculum integrates mathematical principles to concepts in the biological and physical sciences and technology, and to data collection, organization, analysis and graph design.

Defying Gravity is being developed by educators from MSSM Teacher's Summer Institute 2001: A Space Research Odyssey. It will be field tested at the New York City Life Sciences Secondary School, among an underrepresented and academically challenged student population. Products derived will include: a hard copy of the curriculum; an interactive Internet version of the stand-alone curriculum with downloadable text, images and digital video/audio sessions; a live scientist discussion room; teacher's lounge email FAQ and questions; interactive CD ROMs of selected curricular components; a *High School Teaching for Biomedical Scientists handbook*; a hands-on exhibit at the New York Hall of Science; and National multi-media outreach and dissemination via MSSM and NSBRI/Public Broadcasting Services (PBS) television channels.

<u>Rice University/University of Texas Medical Branch (RU/UTMB)—*Outreach Program for the Professional Development of Students and Teachers on Studies Related to Biomedicine in Outer Space*</u>. This collaboration attracts young people to space-related enrichment programs, promotes excellence and innovation in America's science education system, and enhances the scientific background of teachers, students, their families and the community as a whole. It consists of the Academic Development of High School Students (Summer Student Research Program) and the Teacher Institute for the Advancement of Space Science Education (Teacher Professional Development Institute).

Students and teachers are partnered with ongoing space biomedicine research projects conducted at Rice and UTMB. The *Teacher Institute* selects 16 secondary school teachers in a yearlong program to enhance their knowledge of space biomedicine through interactive discussions with researchers; a one-day, hands-on research experience; and special tours of NASA Johnson Space Center and Space Center Houston. Teachers use their knowledge to design a space biomedicine mini-module/unit plan to be taught in class and refined for publication on the Rice, UTMB and NSBRI educational resources web sites. The *Student Research component* enrolls 12 high school summer students to conduct research projects in Rice and UTMB science labs, participate in a field trips, and meet researchers engaged in a wide variety of space biomedicine research.

Texas A&M University (TAMU)—*Teacher Academy Project*. The NSBRI *Teacher Academy Project (NSBRI TAP)* prepares Master Teachers to assist their peers in infusing cutting-edge, space-based science activities into middle school. The specific objectives are to: (1) establish a national cadre of 90 middle level science teachers and prepare them to provide staff development that will reach 1,800 middle level science teachers; (2) identify and provide access to extant teaching resources for middle level science educators; and (3) develop supportive partnerships to access and utilize the resources and skills of key organizations, and work collaboratively with other NSBRI member institutions to improve the quality of middle level science in the classrooms of teachers who participate in NSBRI activities.

NSBRI TAP will select a cadre of master teachers to help develop a summer institute. These teachers will utilize recent NSBRI scientific discoveries to create curricular supplements, attend a leadership and staff development training module, and engage in follow-up activities and conferences to obtain certification as master teachers and Fellows of the Academy. Academy Fellows will form a national professional development staff that trains all middle level science teachers to implement space-based science. It is anticipated that extensive collaborations with other Education and Outreach teams will occur with respect to resource sharing and support with the identification of master teachers. *TAP* also will produce a national cadre of 90 master teachers who are successful in helping at least 1,800 of their peer space science teachers to implement space-based science in their classrooms. Both qualitative and quantitative data will be collected, with on-going analysis of the data shared with the Director.

The University of Washington (UW)—*Northwest Outreach Program on Space Biomedicine Research*. The UW program leverages an existing communication/education program, *Northwest Science & Technology*, at UW to: (1) transfer/disseminate space biomedical knowledge to homes and classrooms throughout the Northwest; (2) increase literacy about science in general, and about space biomedical research and terrestrial applications in particular, among the general public, teachers and students; (3) prepare scientists and future reporters and public information officers to communicate more effectively about science and space biomedicine issues to general audiences; and (4) attract young people to careers in NSBRI space biomedical research.

The program will develop and disseminate articles on space biomedical research via *Northwest Science & Technology (NWS&T)* magazine, a new regional science publication with a circulation of almost 30,000 in the Pacific Northwest region and beyond. Student writers will write, adapt and disseminate special materials on space biomedical research for middle school students and their parents and teachers via an insert in *NWS&T*. In addition, the UW program will deliver a series of three summer science writing workshops for NSBRI consortium members.

The Education and Public Outreach Team institutions enjoy a significant amount of synergistic interaction with each other and with other NSBRI Research Teams. Such interactions, which work towards achieving Goal 5, *integration*, are delineated in Table 14.2. Goal 5, itself, does not appear in this Table, as integration is not so much a separate aim as an overarching characteristic that applies to all Education and Public Outreach Team objectives.

Table 14.2. Integration Activities by NSBRI Research Area/Education and Public Outreach Goals

	EDUCATION AND PUBLIC OUTREACH GOALS			
NSBRI RESEARCH AREAS	**Teacher Professional Development**	**Curriculum Development**	**Science Literacy/Public Awareness**	**Career Awareness and Access**
Bone Loss	BCM, TAMU, RU/UTMB	BCM, MIT, MSSM	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW, TAMU
Cardiovascular Alterations	TAMU	MIT, MSM	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW, TAMU
Human Performance Factors, Sleep and Chronobiology	BCM, TAMU	BCM, MSSM	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW
Immunology, Infection and Hematology	RU/UTMB	MSSM	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW
Integrated Human Function		MIT	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW
Muscle Alterations And Atrophy	BCM, TAMU, RU/UTMB	BCM, MIT, MSM RU/UTMB	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW, TAMU
Neurobehavioral and Psychosocial Factors	TAMU, RU/UTMB	MIT, MSSM RU/UTMB	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW
Neurobehavioral Adaptation	TAMU, RU/UTMB	MIT, MSSM	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW
Nutrition, Physical Fitness and Rehabilitation	BCM, TAMU	BCM, MIT, MSM	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW
Radiation Effects	TAMU, RU/UTMB	MSSM, TAMU RU/UTMB	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW, TAMU
Smart Medical Systems		MIT	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW
Technology Development	TAMU	MIT	BCM, MIT, MSM, MSSM, RU/UTMB, TAMU, UW	MIT, MSM, RU/UTMB, UW

***BCM:** Baylor College of Medicine; **MIT:** Massachusetts Institute of Technology; **MSM:** Morehouse School of Medicine; **MSSM:** Mount Sinai School of Medicine, **RU/UTMB:** Rice University/The University of Texas Medical Branch; **TAMU:** Texas A&M University; **UW:** University of Washington*

Evaluation of Current Program

Gaps. The NSBRI External Advisory Council and the 2000 NSBRI Site Visit Team made five recommendations for the Education and Public Outreach Team: (1) improve dissemination, feedback and assessment methodologies; (2) establish a coordinated development plan; (3) establish university level education programs; (4) articulate the Team's unique abilities to contribute to national education; (5) promote diversity. The addition of MIT to the Education and Outreach Team will help to establish university-level education. MIT will develop and test two graduate level courses, one of which will be offered to undergraduate students. The remaining recommendations are being addressed in the strategic objectives outlined in Section 14.5.

Team members have collaboratively established the strategic goals and objectives for NSBRI Education and Outreach. Through retreats and conference calls, team members have identified the challenges of building a national identity for NSBRI through educational outreach. It was agreed that the quality of materials and activities and the extent to which they are disseminated would be initial defining factors for all NSBRI sponsored educational activities. Once planned and implemented, presentations and publications will document the programmatic impacts.

14.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Below is a brief description of strategic activities to achieve NSBRI Education and Public Outreach Team objectives and goals. Table 14.3 provides a timetable for completion of these activities.

Goal 1: *Design and conduct a variety of teacher professional development programs to help teachers understand space life sciences and change their practices and behaviors to improve the learning experiences they provide students.*

Objective 1A. Enhance the space-based science and technological readiness, skill and teaching impact of educators by providing professional development that focuses on partnerships with scientists and increased teacher content knowledge.

- Create a national Teacher Academy.
- Offer school-year and summer professional development opportunities for K-12 teachers.
- Involve scientists in professional development for teachers.
- Implement teacher mentorship programs within schools.
- Sponsor year-long internships for teachers.

Objective 1B. Utilize NSBRI-generated resources to empower educators to teach all students more effectively and communicate these new instructional resources to peers in education.

- Align curriculum materials based on NSBRI research to national science standards.
- Develop science education reform leaders within the scientific and K-12 education communities.
- Design, create and deploy Internet-based teaching and science education resources.

Goal 2: *Develop curricular materials that span the educational continuum; are aligned with national science standards; provide accurate, balanced, effective and inquiry-based instruction; and expand students' understanding of on-going NSBRI research.*

Objective 2A. Develop and implement high-quality NSBRI-based science, mathematics, and reading/language arts instructional materials designed to facilitate measurable success for all students, apply best understandings of how students learn, and incorporate assessment as an integral component.

- Produce a 9th grade space science program.
- Develop elementary/middle school instructional programs focusing on NSBRI research.
- Create problem-based cases for high school and undergraduate students.
- Facilitate the development of teacher-generated classroom materials.
- Design and implement studies that examine the effectiveness of NSBRI-sponsored Internet-based curriculum materials, as compared to traditionally formatted materials.

Objective 2B. Promote excellence, achievement and systemic change in education through the dissemination of materials described in Goal 2, Objective A.

- Offer local, regional and national teacher professional development on NSBRI materials.
- Partner with NASA for teacher professional development and materials dissemination.
- Partner with informal education centers and museums for teacher professional development and materials dissemination.
- Advertise materials in appropriate journals.
- Direct mail materials to schools.

Goal 3: *Increase science literacy and public awareness of the real-life impacts of NSBRI research through media, informal science activities, direct mailings and magazine stories.*

Objective 3A. Increase scientific literacy by involving scientists in community education and bringing NSBRI and space-based science into classrooms and homes.

- Involve NSBRI and other scientists in teacher professional development and community outreach activities.
- Produce NSBRI-related exhibits and activities at informal education centers and museums.
- Generate TV news and magazine stories focusing on NSBRI advances and research.

Objective 3B. Create and support stimulating, informal space life sciences education programs outside of school to develop and maintain public interest in, and awareness of, NSBRI scientific and technological developments.

- Develop, publish and disseminate NSBRI science activities for families through available media.
- Produce NSBRI-related exhibits and activities at museums and informal education centers.

Objective 3C. Foster healthy behaviors and attitudes among students and families, and increase opportunities for families to become more involved in their children's learning through family-school-community partnerships.

- Produce NSBRI-related exhibits and activities at museums and informal education centers.
- Develop, publish and disseminate NSBRI science activities for families through available media.
- Produce NSBRI-related TV health education segments and TV news stories.

Objective 3D. Develop and implement a media plan to include, but not be limited to: public affairs announcements and programs for radio and television, brochures, posters, video-documents and websites, and a national writer-in-residence program.

- Share NSBRI research and educational opportunities through public media.
- Produce NSBRI-related TV health education segments and TV news stories.
- Continue to build a film archive of NASA footage from SpaceLab missions.
- Print quarterly NSBRI-focused magazine stories for dissemination to lay and professional audiences.

Goal 4: *Promote educational access and career awareness in space life science fields among high school and undergraduate students as well as high school teachers.*

<u>Objective 4A</u>. Attract more young students (especially those from underrepresented groups) to careers in space life sciences, engineering and technology-based fields.

- Conduct summer internship programs for students from underrepresented groups.
- Give targeted presentations on NSBRI activities for undergraduate students.
- Develop undergraduate and graduate courses focusing on NSBRI research.
- Establish NSBRI as a national leader in development and deployment of K-16 Internet distance education.
- Offer online graduate programs in space life science education for K-12 science, mathematics, physical education and language arts teachers.

<u>Objective 4B</u>. Establish partnerships with external groups that bring additional funding support to NSBRI activities and assist the Education and Public Outreach Team to disseminate and promote space-life science education programs.

- Integrate NSBRI activities into existing funded programs, such as NSF-funded systemic initiatives.
- Develop and submit new applications to create and conduct new NSBRI-related projects.
- Establish an International Society of Space Life Sciences Educators, with fellowships for members.
- Create a Center for Research in Space Life Science and Health Education to infuse NSBRI research into educational practice in schools and study ways to increase student motivation in science education and career pursuits.
- Enter into commercial partnerships with publishers, software manufacturers and broadcast media corporations to disseminate information and materials nationally that describe and promote application of NSBRI educational activities.

Goal 5: *Integrate NSBRI-focused teacher professional development, curricular materials, scientific literacy initiatives, and educational and career access activities among all Education and Public Outreach Teams, other NSBRI Teams and public venues.*

<u>Objective 5A</u>. Integrate NSBRI materials, programs and findings across all institutions of the NSBRI Education and Public Outreach Team.

- Establish a peer review process for educational relevance and practice, alignment with NSBRI research themes and national science standards, and also for accuracy, balance and potential bias.
- Create and deploy Internet-based educational resources to include downloadable slide presentations, streaming video and links to other NASA-based educational resources.
- Hold annual workshops to share findings and products developed among Education and Public Outreach Team institutions.

<u>Objective 5B</u>. Integrate NSBRI materials, programs and findings among all other NSBRI Teams.

- Establish a process for NSBRI scientific review of materials and activities developed by the Education and Public Outreach Team.
- Engage NSBRI scientists in the development of educational materials and the design and conduct of teacher professional enhancement activities.
- Hold annual communications workshops with NSBRI scientists to develop strategies to work with schools and the general public.
- Work with NSBRI research teams to identify potential partners and scientific resources at NASA.

Objective 5C. Integrate NSBRI materials, programs and findings into venues outside of NSBRI.

- Generate and broadcast television features that share the findings and contributions of NSBRI-based research with the general public.
- Establish partnerships with professional societies, state and national governments and informal science organizations to disseminate and promote NSBRI educational materials and activities.
- Develop mechanisms to integrate NASA-developed educational materials into NSBRI outreach activities.

14.6 SUMMARY

The Education and Public Outreach Team develops and implements activities that address the five major programmatic goals identified below. Team partners developed these strategic goals in coordination with the NSBRI leadership, to assure that Education and Public Outreach Team activities address overarching NASA and NSBRI objectives.

Goal 1: *Design and conduct a variety of teacher professional development programs to help teachers understand space life sciences and change their practices and behaviors to improve the learning experiences they provide students.*

Teachers are the critical link between curricula, students and their parents. NSBRI teacher professional development activities are designed to help teachers understand space life sciences and change their practices and behaviors to improve the learning experiences they provide students. They also help biomedical space scientists to understand the complex issues involved in instructing today's youth. Teacher Professional Development activities include workshops, summer institutes and research experiences.

Examples of activities being conducted include the numerous NSBRI-focused workshops being carried out by Baylor College of Medicine in Texas and around the US, including activities being coordinated jointly with Space Center Houston for hundreds of teachers in the Houston area, and partnerships with school districts making NSBRI materials part of their curricula. Morehouse School of Medicine's Teacher Institute is a partnership with the Georgia Institute of Technology, DeKalb School System, Fernbank Science Museum, Atlanta Educational Telecommunications Collaborative, Inc., and NSBRI's Teacher Academy at Texas A&M University. Rice University and The University of Texas Medical Branch at Galveston have teamed to create a two-week summer science institute for Houston-area teachers, and Texas A&M is impacting teachers profoundly through its Teacher Academy Project. Master Teachers come from around the US to participate in this project, which provides teachers with intensive field experiences, insight from science and educational experts and new resources to use in their classrooms.

Goal 2: *Develop curricular materials that span the educational continuum; are aligned with national science standards; provide accurate, balanced, effective and inquiry-based instruction; and expand students' understanding of on-going NSBRI research.*

NSBRI curriculum development activities are occurring across the educational continuum from primary grades through graduate preparation. At the K-12 levels, materials are being developed that are aligned to the national science standards. These materials are addressing the need for accurate, balanced, effective and inquiry-based materials for the nation's classrooms. At the undergraduate and graduate levels, courses are being developed to expand students' understanding of on-going NSBRI research.

There is a great deal of emphasis on curriculum development among Education and Public Outreach partner institutions. For example, Mount Sinai School of Medicine is carrying out a wide array of innovative curriculum development activities involving New York City museums, scientists, teachers and students, both in the summer and during the school year, through its *Defying Gravity* program. Meanwhile, Baylor College of Medicine is producing NSBRI-focused teacher activity guides under the *From Outer Space to Inner Space* program. These guides relate directly to NSBRI science objectives and seek to share the excitement of space life sciences via innovative classroom activities. In addition, TAMU is developing and field testing three online modules on energy (radiation).

Goal 3: *Increase science literacy and public awareness of the real-life impacts of NSBRI research through media, informal science activities, direct mailings and magazine stories.*

Promoting greater understanding and awareness of NSBRI space life sciences research is essential for public support. Numerous activities are underway. They include television and radio news programs, informal science activities at museums, direct mailings of informational posters to schools and magazine stories designed to expand public understanding of how NSBRI research will impact long-term space exploration and the everyday world.

Promoting public awareness of NSBRI activities and increasing science literacy are strengths of the Education and Public Outreach Team. In fact, all activities of the Team address these very important goals. However, some Team activities are designed and conducted specifically for this purpose. The University of Washington's journal, *Northwest Science & Technology Report*, is reaching out to readers (including general public, students and educators) in the northwest US with stories and information about NASA and space life sciences. Morehouse School of Medicine's Multimedia Archive contains NSBRI research, NASA's Neurolab Mission and other topics. This footage has been used by the Discovery Channel, ZDF-German TV, Atlanta and DeKalb public schools, and others. Simultaneously, Baylor College of Medicine has produced numerous *Radio HealthLine* stories, distributed to radio stations around the nation, and numerous news-format stories for KUHT, Public Broadcasting in Houston, all focusing on NSBRI-related research and health issues.

Goal 4: *Promote educational access and career awareness in space life science fields among high school and undergraduate students as well as high school teachers.*

There are many barriers to promoting diversity and access to careers in the space life sciences. Activities within this theme include research experiences for high school and undergraduate students as well as high school teachers in NSBRI laboratories. Courses focusing on NSBRI research areas will assist in promoting undergraduate and graduate students' interest in space life sciences research careers.

All partners in the Education and Public Outreach team are involved in promoting access and career awareness. Some of the more prominent Team activities in this area include Mt. Sinai's multi-faceted *Defying Gravity* program, Morehouse's Undergraduate Summer Research project, the Rice University/University of Texas Medical Branch Student Research Seminar, the inserts included in the *Northwest Science & Technology Report* by the University of Washington to attract young readers to science and space biomedical research, and Texas A&M University's annual Youth Symposia on careers in science for several hundred Texas middle and high school students. The scope of these diverse programs is wide, covering the educational spectrum, from young students to undergraduates, not to mention educators and the general public, as well as all demographic groups.

Goal 5: *Integrate NSBRI-focused teacher professional development, curricular materials, scientific literacy initiatives, and educational and career access activities among all Education and Public Outreach Teams, other NSBRI Teams and public venues.*

Integration of NSBRI-focused programs, materials and activities may be the most important goal of Education and Public Outreach Team. As mentioned earlier in this Strategic Plan, the Team's mission is to communicate the significance and excitement of NSBRI research to diverse audiences, while transferring and disseminating knowledge gained by NSBRI Research Teams. In fact, this aim is the specific driving force behind most, if not all, Team activities.

Member institutions of the Education and Public Outreach Team already have begun to share their NSBRI products among each other. Examples include Texas A&M University's Teacher Academy, curricular materials developed by Morehouse School of Medicine and Baylor College of Medicine, and University of Washington's *Northwest Science & Technology Report*. Further, several team activities—such as those related to media or teacher professional development—are being introduced to public audiences. Of course, these examples are but of few of the NSBRI Education and Public Outreach Team products that we anticipate integrating into the NSBRI community and beyond. Schools, universities, informal educational organizations and the general public have demonstrated a great interest in space and the science of space exploration. Our Team is harnessing our varied specialties, experiences and resources to share the excitement and real-world implications of NSBRI with students and the American public.

It also is important to note that there necessarily will be much integration of NSBRI research into education and public outreach efforts. The transfer of NSBRI research team findings is critical to our efforts to promote space exploration, generate excitement and enhance public education of NSBRI activities and goals. The work of the Education and Public Outreach Team in addressing our five goals already has begun to further public understanding of, and interest in, the benefits gained from NASA-sponsored NSBRI research. Such understanding and interest are essential as NASA competes for limited federal resources.

TABLE 14.3: TIMETABLE FOR COMPLETION OF TEAM STRATEGIC GOALS AND OBJECTIVES ("X" = completed; "Y" = to be completed in year indicated)													
GOAL/OBJECTIVES	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Goal 1: Design and Conduct Teacher Professional Development													
Objective 1A. *Enhance space-based science and technological readiness, skill and impact of educators*													
• Create a national Teacher Academy		X											
• Offer school-year and summer professional development for K-12 teachers		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Involve scientists in professional development for teachers		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Implement teacher mentorship programs within schools		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Sponsor year-long internships for teachers		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objective 1B. *Utilize NSBRI-generated resources to empower educators*													
• Align curriculum materials based on NSBRI research to national science standards		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Develop science education reform leaders within the scientific and K-12 education communities		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Design, create and deploy Internet-based teaching and science education resources		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Create a Center for Research in Space Life Science and Health Education					Y	Y	Y	Y	Y	Y	Y	Y	Y
Goal 2: Develop Curricular Materials													
Objective 2A. *Develop and implement high-quality NSBRI-based instructional materials*													
• Produce a 9th grade space science program		X	X	Y	Y								
• Develop elementary middle school instructional programs focusing on NSBRI research		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Create problem-based cases for high school and undergraduate students		X	X	Y	Y								
• Facilitate the development of teacher-generated classroom materials		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Design/implement studies to examine effectiveness of NSBRI-sponsored Internet-based curriculum materials			X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objective 2B. *Promote excellence, achievement and systemic change via dissemination of NSBRI materials*													
• Offer local, regional and national teacher professional development on NSBRI materials		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Partner with NASA for teacher professional development and materials dissemination		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Partner with informal education centers & museums for professional development and materials dissemination		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Advertise materials in appropriate journals			Y	Y	Y								
• Direct mail materials to schools		X	X										
Goal 3: Increase Science Literacy and Public Awareness of NSBRI Research													
Objective 3A. *Increase scientific literacy, involve scientists and bring NSBRI to classrooms*													
• Involve NSBRI and other scientists in teacher professional development and community outreach activities		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Produce NSBRI-related exhibits and activities at informal education centers and museums		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Generate TV news and magazine stories focusing on NSBRI advances and research			X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objective 3B. *Create and support informal space life sciences education programs outside of school*													
• Develop, publish and disseminate NSBRI science activities for families through available media				Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Produce NSBRI-related exhibits and activities at museums and informal education centers		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objective 3C. *Foster healthy behaviors attitudes among students and families, increase family involvement*													
• Produce NSBRI-related exhibits and activities at museums and informal education centers		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Develop, publish and disseminate NSBRI science activities for families through available media		X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Produce NSBRI-related TV health education segments and TV news stories		X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objective 3D. *Develop and implement a media plan*													
• Share NSBRI research and educational opportunities through public media		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Produce NSBRI-related TV health education segments and TV news stories			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Continue to build a film archive of NASA footage from SpaceLab missions		X	X										
• Print quarterly NSBRI-focused magazine stories for dissemination to lay and professional audiences			X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Goal 4: Promote Educational Access and Career Awareness in Space Life Science Fields													
Objective 4A. *Attract more young students to space life sciences, engineering and technology-based fields*													
• Conduct summer internship programs for students from underrepresented groups		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Give targeted presentations on NSBRI activities for undergraduate students		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Develop undergraduate and graduate courses focusing on NSBRI research		X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Establish NSBRI as a national leader in development and deployment of K-16 Internet distance education					Y	Y	Y	Y	Y	Y	Y	Y	Y
• Offer online graduate programs in space life science education for K-12 teachers			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objective 4B. *Establish partnerships with external groups*													
• Integrate NSBRI activities into existing funded programs		X	X	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Develop and submit new applications to create and conduct new NSBRI-related projects				Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Establish an International Society of Space Life Sciences Educators, with fellowships for members					Y	Y	Y	Y	Y	Y	Y	Y	Y
• Create a Center for Research in Space Life Science and Health Education					Y	Y	Y	Y	Y	Y	Y	Y	Y
• Enter into commercial partnerships to disseminate NSBRI information and materials nationally					Y	Y	Y	Y	Y	Y	Y	Y	Y

Appendix C

REVIEW OF THE NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE STRATEGIC RESEARCH PLAN

Washington, D.C.

June 10-11, 2002

Review Committee

Chairperson: Judith Vaitukaitis, M.D.
Steve Beckwith, Ph.D.
Carolyn Huntoon, Ph.D.
Carol Scott-Conner, M.D., Ph.D.
James Snow, Jr., M.D.
Frank Sulzman, Ph.D.
Judith Tintinalli, M.D., M.S.

Consulted By Teleconference:

Allan Tobin, Ph.D.

Office of Biological and Physical Research
National Aeronautics and Space Administration

TABLE OF CONTENTS

EXECUTIVE SUMMARY

After an open national competition in 1997, the National Aeronautics and Space Administration (NASA) selected a consortium of seven academic institutions, led by Baylor College of Medicine, to conduct biomedical research to define adverse medical and biologic consequences associated with space travel and to identify approaches or countermeasures to prevent, minimize and reverse those adverse processes. That consortium became known as the National Space Biomedical Research Institute (NSBRI). In the first five years of its existence, the Institute has made outstanding progress.

It has:

- Developed a comprehensive research strategy that addresses key medical, physiological and technical issues associated with space travel;
- Recruited distinguished investigators from across the nation; and
- Established links to the key NASA end users, including astronauts, flight surgeons, engineers, other federal agencies, industry, and international partners.

The primary mission of the NSBRI continues to be the development of countermeasures that mitigate the health risks and consequences of space travel. The Institute plays an essential enabling role for NASA by providing unique capabilities for focused, basic and applied research that leads to development of effective countermeasures and techniques that bridge the expertise of the biomedical research community, complemented by the engineering and operational expertise of NASA. The progress of the Institute underwent independent review at its 3-year milestone and the independent committee recommended support for an additional five years. In response to weaknesses described in that report, the Institute formulated a 5-year Strategic Plan to address weaknesses cited in that initial review.

The National Aeronautics and Space Administration subsequently constituted this independent Review Committee to examine the responsiveness of NSBRI to the shortcomings cited in the 3-year review. The membership of the Review Committee appears in Attachment 1. The Review Committee's charge was to review the Strategic Plan and provide recommendations to NASA, including the soundness of the Institute's approaches to identify and resolve biomedical problems related to the health, safety and performance of astronauts during and after space flight. These issues have been elaborated in the recent Institute of Medicine report "Safe Passage", 2001 and The National Research Council report, "A Strategy for Research in Space Biology and Medicine in the New Century", 1998.

The Institute is entering an important phase, now that its infrastructure and research agenda have been established. With current and planned long-duration space flights on the International Space Station (ISS), NASA has an increasing need for the capabilities of the NSBRI, especially in the context of loss of NASA technical personnel over the years. The benefits of the NSBRI Program to NASA and to health care on earth are potentially very significant. NASA must therefore commit to adequate and stable funding for the Institute to be able to develop effective countermeasures to enhance safety of prolonged and recurrent space travel.

During its deliberations, the committee reviewed the NSBRI Strategic Plan (May, 2002) in the context of the November 2000 External Review. The committee received presentations by Dr. John Rummel, Dr. Ronald White, Dr. Bobby Alford, and Dr. Jeffrey Sutton. The committee has provided critiques and recommendations in the following eleven topics: Organizational Structure, NSBRI Teams, Research Management, Research Priorities, Radiation Health Research, Bioinfomatics, Peer Review, Relationships with Complementary Programs, November 2000 External Review, President's Management Agenda, and Budget.

Topic 1: Organizational Structure

Critique:

The organizational structure of NSBRI requires clarification. The Committee could not clearly identify the lines of authority and responsibilities for senior management. Furthermore, the Strategic Plan does not adequately describe how programmatic authorities and responsibilities are distributed between NSBRI and NASA as well as how research priorities are set by those organizations.

The NSBRI advisory system appears to be functioning well in that it provides effective programmatic oversight and advice.

The NASA External Review for teams and the 5-year review for the Institute are so intertwined that the 5-year review cannot be accomplished without a concurrent review of the research conducted by team members.

Recommendations:

To optimize the research goals of NSBRI, the Institute needs to define and perhaps further strengthen its management structure and clarify the roles, responsibilities and duration of appointments for the senior management.

The Committee recommends that the NASA Chief Scientist's Review of the Institute be preceded by the review of the individual teams by no more than 2 to

4 months. This approach will streamline the review process and decrease the burden of these periodic reviews, distributed over several years. The Review Committee suggests that this recommendation supercede the recommendation of the 2000 NASA Chief Scientist's Review.

Topic 2: NSBRI Teams

Critique:

The Strategic Plan describes the two basic criteria -- scientific merit and research relevance to the NSBRI mission -- on which applications are selected. Team leaders may recommend funding of those applications relevant to the scientific thrust of their team to top NSBRI management.

The Strategic Plan does not clarify that research team members are geographically dispersed, remain at their own institutions, and are not grouped at one site. In essence they form "virtual teams." Investigators are invited to become members of a team relevant to their research proposal after their grant application is selected by NSBRI for funding.

The selection of the team leaders requires amplification. Further, the role and effectiveness of the team leaders is unclear as well as their "value added" or impact on leading the research teams. Finally, it is not clear how and whether the team leaders can ensure that projects within each team relate to each other as well as other NASA research.

Recommendations:

To optimize the team approach, NSBRI needs to pay closer attention to team management and the selection of the team leaders. NSBRI should develop a plan defining the selection, training and function of team leaders, their term of office, and their roles and responsibilities. NSBRI should consider the inclusion of NASA technical experts as potential team members. This plan should be developed in the next 6 months. Separately, NSBRI may consider evaluation of their research team approach through an independent third party to define best practices and optimize the current team approach or modify the current structure. Further, NSBRI should construct a set of simple metrics allowing them to compare team performance over time and across disciplines. (See Management of Research section below.)

These metrics may be used to determine the best allocation of resources among the teams to further the goals of the Strategic Plan.

<u>Topic 3</u>: Management of Research
The NSBRI plays a unique role in the development of countermeasures by supporting research that is more applied than that solicited through the NASA Research Announcements.

<u>Critique</u>:

At this early stage of the evolution of the NSBRI research program, it is appropriate that much of the research addresses lower Countermeasure Readiness Levels (CRL).

<u>Recommendations</u>:

The NASA and the NSBRI should develop metrics to track the development of countermeasures. The following metrics are suggested:

- What is the distribution of tasks by CRL or TRL (Technology Readiness Level)?
- What is the distribution of tasks and funding by criticality (likelihood & consequences)?
- How many tasks are being flown to test countermeasures or develop baseline data?

Over the next 5 years, the research program should move aggressively toward a much larger proportion of higher CRLs.

<u>Topic 4</u>: Research Priorities
The Strategic Plan states that the primary goal of the NSBRI is the Countermeasure Research Program. Secondary goals are education, training and outreach, along with cooperative research and development.

<u>Critique</u>:

The Committee strongly agrees that the top priority of the Institute should continue to be Countermeasures Research. The development of countermeasures for the health and safety of the astronaut is paramount. Health risks associated with increased flight duration may not have been adequately defined. In that setting, additional countermeasures for longer duration missions undoubtedly will need to be developed. The level of NASA's financial support for the Institute's research program is insufficient to support the level of research required to define risks and their countermeasures.

<u>Recommendations</u>:

The Committee recommends that NSBRI continue to maintain Countermeasures Research as its primary research focus.

At this time, efforts in education should emphasize graduate and post-graduate support in research environments in NSBRI consortia member laboratories. As the Institute and its research programs mature, educational efforts may expand to K-12. Cooperative Research and Development, Education, Training, and Outreach should be secondary to the research focus. Some elements of Cooperative Research and Development may be incorporated into the Countermeasures Research.

Topic 5: Radiation Health Research

NASA and the November 2000 External Review Report have emphasized the importance of radiation effects for humans on long duration space flights.

Critique:

NASA has developed a strategic plan for radiation health and the Johnson Space Center, as the lead Center, has developed an implementation plan. These plans take into account the NASA's distributed nature of activities and programs relevant to radiation health such as materials science, solar space physics, astrophysics, space operations, etc. Further, NASA has committed to developing and operating a beam line at the Department of Energy's Brookhaven National Laboratory (BNL), which will be used to simulate unique aspects of the space radiation environment. The NSBRI has a modest program in radiation effects, but its relation to the broader NASA program should be further refined. Since the BNL is one of the member institutions of the NSBRI, there is a good opportunity for the Institute to play a key role in the NASA efforts.

Recommendations:

NASA and the NSBRI should clarify the role that the radiation effects team should play in the overall program to reduce health risks associated with exposure to space radiation.

NSBRI should consider the addition of NASA JSC technical experts on radiation to the radiation effects team.

Topic 6: Bioinfomatics

Bioinformatics is essential for research in the 21st century. The nature of research is evolving rapidly and commonly requires high throughput technologies that generate vast volumes of data that require special bioinfomatics capabilities for rapid analysis. The current plan fails to include a comprehensive bioinfomatics plan. Bioinfomatics is an essential infrastructure component required by all research teams.

Critique:

Important previous space flight information and other research data exist in NSBRI, JSC and with individual investigators. Bioinfomatics is a crosscutting discipline with sets of analysis tools that span all the research of the NSBRI. The Strategic Plan does not include a functional approach.

Recommendations:

Bioinformatics should be a prominent part of NSBRI's Strategic Plan. Tools should be developed to model and visualize data and to assess whether unexpected relationships may be present in existing databases for factors not yet identified. A comprehensive approach needs to be developed. Both NASA and the Applied Physics Laboratory at Johns Hopkins, a member of the consortium, hold world-class expertise in this area that should be tapped. The Strategic Plan should be modified to include bioinformatics as a key crosscutting set of tools essential for modern research.

Topics 7: Peer Review

Critique:

The recently modified Peer Review process is fair and objective.

Recommendations:

Continue to maintain the high quality and objectivity of the Peer Review process.

Topic 8: Relationships with Complementary Programs

Critique:

There are several programs in the nation that are complementary to the NSBRI. Many Federal agencies support preclinical research into the mechanisms responsible for microgravity-associated risks and other space flight effects. For example, the National Institutes of Health is the premiere funding agency for the study of bone and muscle abnormalities and various other disease conditions. Development of many procedures and technologies for space flight applications can be adapted from such complementary research programs for effective therapies to restore or promote health on Earth.

Recommendations:

Leverage NASA's investment in space travel related health risk research in collaboration with related federal research programs. Whenever possible, develop a collaboration with federal agencies on research, for example, in areas such as bone, muscle, metabolism, and health monitoring technologies. One would expect that many technologies and countermeasures developed to minimize or prevent the consequences of space travel can be adapted to have practical value in health care delivery, just as electronic developments in the formative NASA years resulted in several technologic spinoffs to society's benefit.

Topic 9: November 2000 External Review

Critique:

The Review Committee concludes that NSBRI has effectively addressed the major concerns raised in the first NASA Chief Scientist's Review.

Topic 10: President's Management Agenda

The overall goals, objectives, and approaches are being utilized by NASA and the NSBRI as related to the President's Management Agenda.

Critique:

The establishment of the NSBRI is entirely consistent with the President's Management Agenda in terms of strategic management of human capital, competitive outsourcing, improved financial performance, expanded electronic government, and budget performance and integration.

However, without stable and appropriate funding from NASA, the NSBRI will not realize its potential and satisfy the President's Management Agenda.

Recommendations:

NASA should provide stable and sufficient funding for the NSBRI (See Budget section below).

Topic 11: Budget

Critique:

The overall NSBRI budget is inadequate for the scope of research needed to assure the *safety and health* of astronauts, especially in view of the unknown risks of future long-term space travel and travel into deeper space. NSBRI is operating in an environment in which the projected level of research funding is uncertain and varies sharply from year to year. It is essential that a grant-awarding entity for programmatic research have reasonable stability of financial support. Instability will lead to expert investigators moving to other research and will possibly place future astronauts at unacceptable risks for prolonged and deep space travel.

A chaotic situation that exists because the proposed reduction in funding for FY 2003 is severe and instability in the funding process disrupts the continuum of research, makes it impossible to achieve the goals of Countermeasure Research. The funding decrease threatens the pool of investigators leading this field. Furthermore, the baseline budget in the Strategic Plan is inadequate to meet the goals of the Strategic Plan. Even the full program budget fails to meet the needs in view of the proposed increased duration and repeated space flights.

The complexity and implications of NSBRI research programs are comparable to clinical research supported by the NIH, but the average allocation per project at NIH is significantly greater than that for the NSBRI-funded projects. The original budgetary discussions of an annual NSBRI budget of 50 million to 100 million dollars, in addition to the baseline Biomedical Research Program, would be appropriate to support research into the health risks associated with space flight. The need is urgent because health risks are likely to increase cumulatively with each subsequent International Space Station mission. Furthermore, data that can be collected and analyzed now will provide the substrate for future refinements of the health care system in space, will improve crew selection and rehabilitation, will improve health care maintenance in space, and will affect environmental and engineering adaptations for future long-range space missions.

Recommendations:

NASA should increase and stabilize the NSBRI budget. This is essential to the success of the program and the development of the next generation of researchers. Although NSBRI funding restoration and increase is recommended, it should not be at the cost of NASA's Biomedical Research and Countermeasures Program. Without adequate funding, many talented investigators will abandon this research area and promising researchers will pursue more attractive research areas. The foregoing will preclude future safe space travel.

The Institute should consider the use of NIH-style center support mechanisms to provide an appropriate funding mechanism for more complex research queries that require a research team with complementary expertise required to develop novel research tools and technologies required by the team. A new NASA investment in 2-3 comprehensive centers of this type can lead to an integrative approach into developing countermeasures that are complex and essential and unlikely to be effectively addressed by the classic individualized R01 approach. This approach may include NASA engineers, physicists, and computer programmers working side-by-side with NSBRI investigators. The R01 mechanism remains essential for research that is hypothesis-driven and not heavily dependent on advanced technologies.

NASA Peer Review Services

Attachment 1

NSBRI Strategic Research Plan Review Meeting
Universities Space Research Association
(Washington Design Center)
300 D St. S.W., Suite 801
June 10-11, 2002

Review Committee

Panel Chair:

Judith Vaitukaitis, M.D.
Director, National Center for Research Resources
National Institutes of Health
Bldg 31, Room 3B11
9000 Rockville Pike,
Bethesda, MD 20892-2128
Tel: 301-496-5793, Fax: 301-402-0006
Email: judyv@ncrr.nih.gov

James Snow, M.D.
33506 Tuckahoe River Rd.
Easton, MD 21601
Tel: 410-479-2903
Email: jsnow@crosslink.net
(Former Director, National Institute on Deafness and Communication Disorders)

Steve Beckwith, Ph.D.
Director, Space Telescope Science Institute
3700 San Martin Drive,
Baltimore, MD 21218
Tel: 410-338-4710
Email: svwb@stsci.edu; laguerre@stsci.edu

Frank Sulzman, Ph.D.
59 Wingam Drive
Islip, NY 11751-4114
Tel: 631-277-4171
Email: fsulzman@netzero.net
(Former Deputy Director, Life Sciences Division, NASA Headquarters)

Carolyn Huntoon, Ph.D.
20 Broadview Drive
Barrington, RI 02806
Tel: 401-245-8062
Email: clhuntoon1@aol.com
(Former Director, NASA Johnson Space Center)

Judith Tintinalli, M.D., M.S.
Professor and Chair
Department of Emergency Medicine
University of North Carolina
CB#7594
Chapel Hill, NC 27599-7594
Tel: 919-966-5643
Fax: 919-966-3049
Email: jet@med.unc.edu

Carol Scott-Conner, M.D., Ph.D.
Professor and Head
Department of Surgery
University of Iowa
1515 JCP, 200 Hawkins Drive
Iowa City, IA 52240
Tel: 319-356-0330
Email: carol-scott-conner@uiowa.edu

By Teleconference:

Allan Tobin, Ph.D.
Director, Brain Research Institute
University of California – Los Angeles
2506 Gonda Center
695 Charles E. Young Drive
Los Angeles, CA 90095-1761
Tel: 310-825-5061, Fax: 310-267-0341
Email: atobin@mednet.ucla.edu

Appendix D

SA-02-070 June 21, 2002

TO: NASA Headquarters
Attn: Code U/Associate Administrator for Biological & Physical Research

FROM: AA/Director

SUBJECT: Response to Committee Report on National Space Biomedical Research Institute (NSBRI) Strategic Plan

As noted in my letter to you dated June 18, 2002, please find enclosed the NSBRI's response to each of the recommendations cited in the June 10-11, 2002, report regarding the external review of their strategic plan. We have asked the NSBRI to respond to recommendations that only they can specifically address. The report also included recommendations regarding actions related to NASA, and we are providing the Johnson Space Center's (JSC) response to these recommendations below. We fully understand that the recommendations related to the NASA budgetary actions must await Research Maximization and Prioritizations and NASA Headquarters' policy decisions.

Our response to the following report items:

Topic 5: Radiation Health Research

The management of the NASA Radiation Health Research Program has been the topic of discussion for several years between NASA Headquarters and JSC. Currently, JSC has approved strategic and implementation plans for this research area and has an identified civil servant manager, Dr. Frank Cucinotta. The newly identified Headquarters' initiative in radiation research appears to expand the radiation effort beyond the current plan and provides resources for additional competitive radiation research. Originally, one of the options discussed was to assign the NSBRI a more significant role in the overall planning and management of the Agency biomedical radiation effort. While this was never formally implemented, the external review committee has correctly identified the need to further incorporate NSBRI's radiation research into the Agency's radiation plan and activities.

NASA has recently committed significant resources to developing and operating a beam line at the Department of Energy's Brookhaven National Laboratory, and this organization is a full member of the NSBRI's consortium. In response to the review committee's recommendation, JSC, in concert with its NSBRI partner, would actively support NASA Headquarters in determining the appropriate roles, responsibilities, and resource assignments in this high priority research area, including sponsoring a planning workshop for all the major stakeholders.

Topic 10: President's Management Agenda and Topic 11: Budget

The review committee's recommendations in both of these topic areas revolve around the committee's conclusion that not only is the approximate $30M/year baseline budget request of the NSBRI inadequate, but that their requested augmentation above the $30M/year baseline (that reaches $55M/year by FY07) is also inadequate to accomplish the scope of research needed to assure the safety and health of astronauts.

As JSC had identified in its background materials provided to Headquarters in support of this review, considerable Agency discussion had centered on the need for this science institute to be funded in the range of $50M to $100M/year. It should be pointed out, however, that previous planning estimates at the high end of this range included optional functions and tasks that are not currently being required of the NSBRI (e.g., increased science management of International Space Station biomedical research and Agency biomedical research, in general). The question is, what is the appropriate level of Agency funding for the NSBRI, given the current mission requirements for human space flight as well as ensuring that the Agency can adequately address in a reasonable timeframe the human element of any future discussions for missions beyond low-Earth orbit.

It is our opinion that the NSBRI's augmented program request provides a reasonable balance in light of the Agency's current fiscal environment. However, should priorities and Agency policies permit, the original request for the NSBRI in 1999 that was included within the overall Bioastronautics Initiative should be considered. This request had the following budget profile: FY01/$35M, FY02/$48.8M, FY03/$62.9M, FY04/$71.7M, and FY05/$76.2M. This funding scenario was based on a robust program that permitted addressing a greater percentage of the identified risks and associated critical questions as well as established a comprehensive, integrated approach to data mining, systems analysis, and modeling. It is funding at these levels that begin to establish the human sub-system element on a par with other spacecraft sub-systems. This profile could be re-visited as required.

Summary

JSC is committed to supporting the Agency's responsibility for assuring the health, safety, and optimum performance of flight crews. The Agency science institute approach and the NSBRI, in particular, provides an excellent model on how to engage the external scientific community in solving important biomedical issues.

The knowledge and technologies from this activity have wide applicability to Earth-based health care concerns. It is encouraging to note that even though this approach was initiated in 1995, it complements the President's Management Agenda in several important areas.

We fully support the external review committee's recommendations and are prepared to implement the NSBRI to the funding level that is finally decided upon. Should that level be less than the requested $30M/year baseline, we would recommend re-evaluating and re-establishing the mission and objectives that NASA has currently provided to the NSBRI. In such a scenario, we would have to develop an alternate approach on how to accomplish the essential focused space biomedical research necessary to provide for crew safety, health, and optimum performance.

If you have any questions, please contact Dr. John Rummel at 281-483-7317.

Jefferson D. Howell, Jr.

Enclosure

SA-02-070

cc:
BA/R. K. Gish
SA/D. R. Williams
HQ/UB/G. C. Fogleman
HQ/A/R. M. Senke
HQ/CIC/T. K. Grimes

SA/JARummel:jrc:06/21/02:37317

SA-02-070

bcc:
AL/M. G. Winchell
SA/C. F. Sawin
SA/C. M. Stegemoeller
SA/J. L. Robinson

Baylor College of Medicine
Attn: Dr. Bobby Alford
Executive Vice President, Dean of Medicine
One Baylor Plaza, NA-102
Houston, TX 77030-3498

SA/JARummel:jrc:06/21/02:37317

Strategic Plan Review
NSBRI CRITIQUE/RESPONSE
6/21/02

TOPIC 1: ORGANIZATIONAL STRUCTURE

Recommendations:

To optimize the research goals of NSBRI, the Institute needs to define and perhaps further strengthen its management structure and clarify the roles, responsibilities and duration of appointments for the senior management.

The Committee recommends that the NASA Chief Scientist's Review of the Institute be preceded by the review of the individual teams by no more than 2 to 4 months. This approach will streamline the review process and decrease the burden of these periodic reviews, distributed over several years. The Review Committee suggests that this recommendation supercede the recommendation of the 2000 NASA Chief Scientist's Review.

Response:

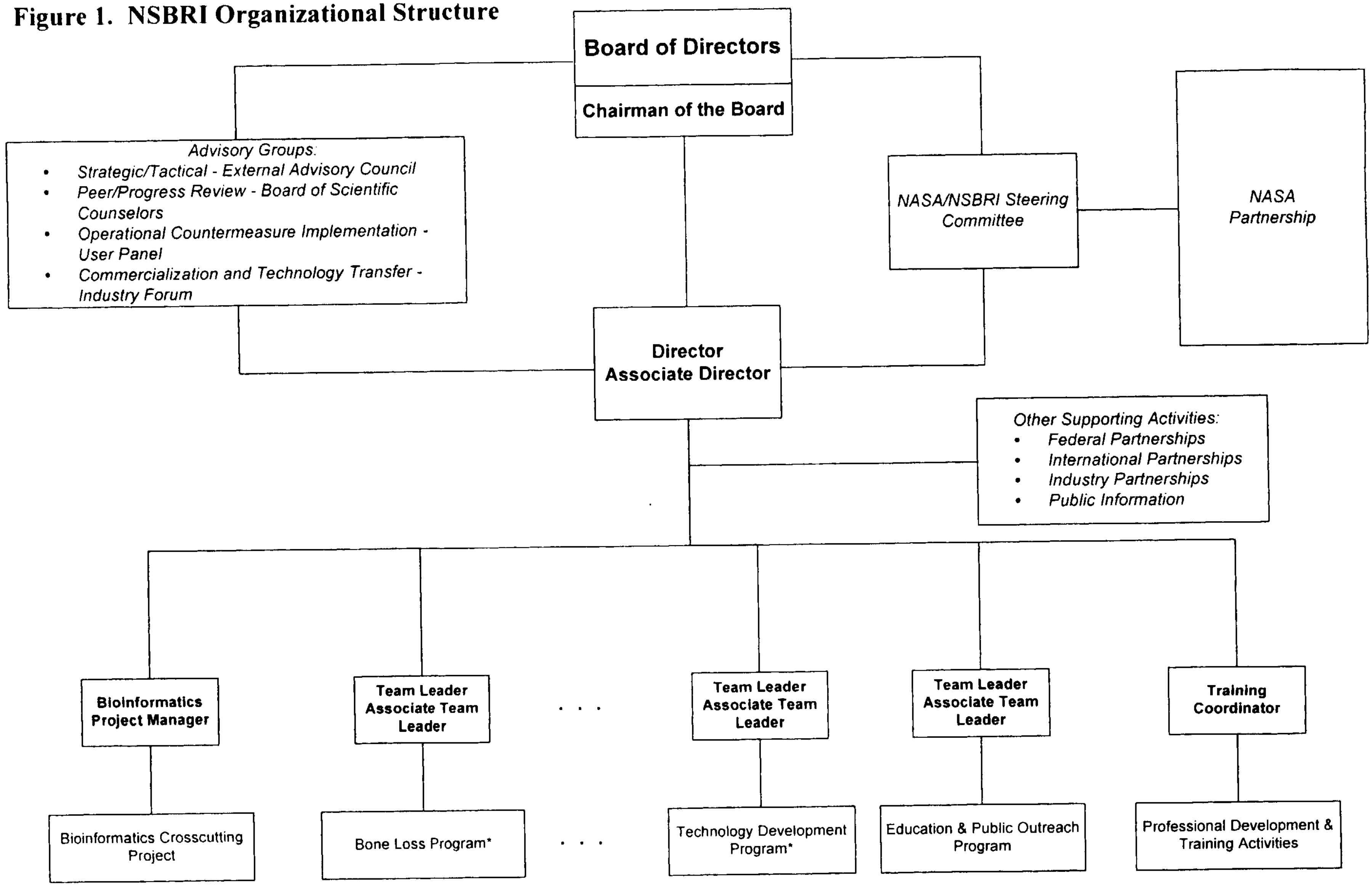
The NSBRI agrees with both recommendations. Although the roles and responsibilities of the various key personnel directly involved in managing the Institute were defined in the original proposal to establish the NSBRI, these roles and responsibilities have evolved over the first five years of the Institute's existence, and they should be clarified and strengthened. A current view of Institute management is presented in Figure 1.

In 1997, the NSBRI was established as a non-profit corporation in the State of Texas, with one member, Baylor College of Medicine (BCM), and a governing Board of Directors (Board). The Board has members representing the twelve Consortium institutions, industry, medicine, the public and the extramural scientific community. The Board, in consultation with the Director, Associate Director and NASA, sets the scientific, operational and technological priorities for the Institute. It has the ultimate authority and responsibility for the activities of the Institute, monitors and reports progress, and oversees the timely and cost-effective utilization of resources by the Institute and by participants in the Institute's programs. In addition, the Board guides the Institute's efforts in specific science and technology areas, reports Institute progress to NASA annually, encourages scientific and technological advances, and ensures that the broader research community has opportunities for strong participation in Institute activities.

Chairman of the Board. The Chairman of the Board, nominally a senior BCM official, serves as the Institute's Chief Executive Officer, is the primary interface between the Institute and BCM, and leads and coordinates the Board's activities described above. He/she represents the Institute to academic, industrial, and Government senior management and plays a major role in developing new sources of Institute support. The Chairman of the Board is appointed by BCM for a term of one year.

Underneath the Board, the NSBRI utilizes two levels of management to carry out its various programs: a central office staffed by the Director and Associate Director, and a mid-management level consisting of Team Leaders and project managers or coordinators. This simple structure is feasible only because the Institute is solidly built upon existing research management at BCM,

Figure 1. NSBRI Organizational Structure



*Similar blocks are associated with the nine other research teams.

enabling the NSBRI to utilize BCM's well-defined management infrastructure while bearing only the incremental costs necessary to enable smooth operations. Thus, BCM's capability for managing large Federal grants, contracts and consortium subcontracts, as well as its established assurance/compliance modalities required for Federal grantees, substantially reduce the administrative costs, guarantee compliance with all applicable Federal regulations, and provide administrative and fiscal oversight.

Director. The Director serves as the Chief Operating Officer of the Institute and has the ultimate responsibility for defining and carrying out the Institute's mission and achieving the Institute's objectives and aims. He/she is responsible for development and implementation of the Institute's strategic plan, for setting tactical priorities, and for assuring continued coordination among the Consortium members in education and outreach as well as research. He/she is responsible for coordinating the planning and implementation of the scientific activities of the Institute by working directly with the Team Leaders. The Director maintains an active personal research program and a position of academic leadership. The Director is nominated annually by the Board's Nominating Committee and then appointed by the Board of Directors for a term of one year. The term is renewable. The Director reports directly to the Board of Directors.

Associate Director. The Associate Director assists the Director in all aspects of management and represents the Institute in the Director's absence. He/she is responsible for Institute financial planning and management, internal coordination of Institute activities within the Consortium and scientific community and serves as the liaison with Johnson Space Center (JSC) regarding translational activities and with NASA regarding related science management activities. He/she is also responsible for development and implementation of the Institute's bioinformatics plan, interfacing with other funding agencies and with the international community, development of policies regarding operation of the Institute's programs, and management and coordination of any other supporting programs of the Institute. The Associate Director is nominated annually by the Board's Nominating Committee and then appointed by the Board of Directors for a term of one year. The term is renewable. The Associate Director reports to the Director and to the Board of Directors.

Team Leaders. Each Institute team is led by a single Team Leader and one or more Associate Team Leaders. The Team Leader is responsible for: preparing and maintaining a team research strategy that is consistent with the Institute mission, the Critical Path Roadmap and available resources; reviewing that strategy with the Institute's External Advisory Council (EAC) and Board of Scientific Counselors (BSC); implementing the approved strategy within the allocated team resources and recommending the distribution of resources among the investigators; setting priorities within the team's research area; encouraging key research scientists to develop an interest in space-related problems; requesting seed research funds for startup projects; and coordinating the activities of the investigators to maintain appropriate scientific and operational synergy. Associate Team Leaders assist the Team Leader in carrying out his/her responsibilities and represent the Team Leader in his/her absence. Team Leaders and Associate Team Leaders are appointed by the Director for a term of one year. The term is renewable. Team Leaders report to the Director. Associate Team Leaders report to their Team Leader.

Regarding individual team reviews as part of the NASA Chief Scientist's Review of the Institute: The NSBRI agrees that the team reviews should precede the Chief Scientist's Review by two to four months. This will streamline the review process and lighten its burden.

TOPIC 2: NSBRI TEAMS

Recommendations:

To optimize the team approach, NSBRI needs to pay closer attention to team management and the selection of the team leaders. NSBRI should develop a plan defining the selection, training and function of team leaders, their term of office, and their roles and responsibilities. NSBRI should consider the inclusion of NASA technical experts as potential team members. This plan should be developed in the next 6 months. Separately, NSBRI may consider evaluation of their research team approach through an independent third party to define best practices and optimize the current team approach or modify the current structure. Further, NSBRI should construct a set of simple metrics allowing them to compare team performance over time and across disciplines. (See Management of Research section below.)

These metrics may be used to determine the best allocation of resources among the teams to further the goals of the Strategic Plan.

Response:

The NSBRI agrees with this recommendation and will, within the next six months, develop a set of policies related to all aspects of team leadership, including roles and responsibilities, selection, training, evaluation and retention. Team Leaders play a pivotal role in the management and success of the Institute's research program (see the response to the recommendation related to Topic 1: Organizational Structure). Having effective Team Leaders is critical to the success of the Institute.

This topic will be discussed fully at the next meeting of the EAC (September 4-5, 2002) and the final policies will be discussed at the Board of Directors meeting on September 26, 2002. These policies will be in place by the end of 2002, well before the team-leader annual term would expire in September 2003.

The current roles and responsibilities of the Team Leaders are defined earlier in the response to the recommendations related to Topic 1. After five years of experience in managing the NSBRI research program, it is clear that this list is incomplete. Other possible roles and responsibilities include the following:

- Recruiting premier investigators to submit proposals of quality and relevance to appropriate research announcements;
- Acting as a senior spokesperson for the team and "marketing" team successes within the scientific community, NASA and the general public;
- Fostering communication within the team and between the team and the general scientific community;
- Participating actively in the NASA/NSBRI Critical Path Roadmap process to set research priorities within the team's research area;
- Delineating relative risks within the research area;
- Acting to correct problems caused by investigators losing sight of the mission of the Institute; and
- Acting as a liaison between management and the team investigators.

A clear identification of the Team Leaders' responsibilities then allows a determination of their selection criteria. These criteria might include:

- Recognition as excellent research scientists in their field;
- Possession of a broad understanding and long-term vision of appropriate and achievable goals to reduce the biomedical hazards of long-duration space missions;
- Demonstrated leadership and program/group management experience and skills;
- Ability to assist in the development of special partnerships and joint collaborations with appropriate elements of other federal agencies;
- Possession of good communication, organization and time-management skills; and
- Possession of high motivation and energy.

Past experience in dealing with management issues has demonstrated that it is an advantage for a Team Leader to be from an Institute consortium member, but this has never been a criterion and the advantage is insufficient to make it one.

Team Leader training might include the following:

- Provision of a clear summary of a Team Leader's responsibilities, including an overview of expected meetings, requirements and deadlines as far in advance as possible;
- Explanation of the overall NSBRI structure, policies and procedures and its position in NASA;
- Guidance in the complexities and demands of NASA infrastructure and operations;
- Attendance at a summer short course at Johnson Space Center to familiarize Team Leaders with the Critical Path Roadmap, NASA/NSBRI program planning and management, and operational space medicine;
- Frequent contact with other Team Leaders to share problems and solutions; and
- Education on use of electronic media to better foster communication, sharing of information and data among team members.

Currently, the Team Leader term of office is the same as the project funding term and is in cycle with the selection of projects. Discussions with the Team Leaders and with external advisors have suggested that the Team Leaders' term of office should be longer than project funding cycles and disconnected from the solicitation and selection of projects. Such a disconnection would allow a Team Leader to focus on the needs of the overall team during the normal funding cycle instead of solely on his/her own project. A five-year term of office has been suggested as the appropriate length of service, with an annual evaluation of a Team Leader's success in meeting objectives.

Evaluation of Team Leaders is an ongoing responsibility of the Institute and should be reexamined in light of possible revised responsibilities. To date, Team Leaders have been evaluated as follows, primarily in the context of project and program evaluations:

- The EAC evaluates a team's progress each time they meet, but in detail, only once every four or five years. However, if the EAC detects a problem with a Team Leader and/or team, it can move quickly to evaluate and address that problem.
- The BSC reviews both project and program (team) progress annually after years one and two of a project's lifetime and provides a rating of progress to the EAC and Institute management.
- An initial peer review provides an evaluation of a Team Leader's project and provides a certain measure of quality control.

Although all these evaluations have proven useful in identifying different kinds of weaknesses in the Institute's programs, they are not optimal for direct evaluation of Team Leaders and should be strengthened.

Direct measures of Team Leader performance (metrics) might include evaluation of:

- The Team Strategic Plan, for adherence to and focus on the NSBRI mission of countermeasure production and on the potential transfer of results for Earth benefit;
- Recruitment of quality scientists/new proposals for the team;
- The effectiveness of the Team Leader as a spokesman for the team to NASA and to the scientific community; and
- Team Leader performance by the team principal investigators and by NASA.

Additional metrics might be used to evaluate projects and teams so as to best allocate resources. These are described in the response to Topic 3: Management of Research.

TOPIC 3: MANAGEMENT OF RESEARCH

Recommendations:

The NASA and the NSBRI should develop metrics to track the development of countermeasures. The following metrics are suggested:

- *What is the distribution of tasks by CRL or TRL (Technology Readiness Level)?*
- *What is the distribution of tasks and funding by criticality (likelihood & consequences)?*
- *How many tasks are being flown to test countermeasures or develop baseline data?*

Over the next 5 years, the research program should move aggressively toward a much larger proportion of higher CRLs.

Response:

The Institute agrees that a set of metrics should be developed that track the success of NASA and the NSBRI in producing countermeasures that lower the biomedical risk of space flight and apply the limited available resources to the most important problems. Such metrics fall into two groups. The first group is descriptive, providing information about a research program. The three examples cited in the recommendation above fall into that category. In fact, these three metrics have already been applied to both the Institute's program and to NASA's Biomedical Research and Countermeasures Program. Such descriptive metrics are informative, but, unfortunately, they do not necessarily indicate the actions needed to increase team progress towards countermeasure production.

The second group of metrics is evaluative and involves the longitudinal, periodic assessment of project and team progress by an expert peer panel. As mentioned in the response to the recommendations regarding Topic 2, carrying out this evaluation is one role of the Institute's BSC. The single project evaluation criteria previously used by the BSC are:

- Are the hypotheses (where appropriate) and specific aims or objectives of the project clearly stated, and is the work proceeding in a manner that will accomplish the goals of the project?
- Is ongoing planning for this project dynamic with regard to the current state of the field, both intellectually and technically?

- Is the productivity to date for this project adequate?
- Does evidence exist for substantive collaboration between this and other projects within the research team? With other research teams within the NSBRI? Is collaborative/synergistic effort with other Institute researchers a reasonable expectation for this project?

Thus, each project has been measured against the specific aims and schedule from the original project proposal, and the project was rated as: superior, satisfactory, needs improvement or not determined (usually for very new projects).

Programs (teams) were rated by the following criteria:

- Is the program strategy for accomplishing the mission of the NSBRI clearly stated and is appropriate progress being made to effectively carry out that strategy?
- Is the scientific productivity of the research team appropriate for the (first, second) year of a three-year (generally) research program (at this level of effort)?
- Are the research projects functioning synergistically within the research program?
- Is there evidence of collaborative effort among project scientists within the research team? With other NSBRI research teams?
- Is the program research direction likely to contribute effectively to the mission of the NSBRI? Will it advance the scientific field generally?
- Is the Team Leader effective in providing leadership to the entire team? How well does the Team Leader's level of effort on behalf of the Institute match that previously promised?

Programs (teams) were rated as: superior, satisfactory or needs improvement.

We have found this method of generating metrics very useful in management decisions concerning the allocation of resources. The previously-used evaluation criteria can be strengthened. The NSBRI intends to seek the assistance of an outside panel of experts in reexamining its approach to these metrics and strengthening its set of descriptive and evaluative metrics to apply to the Institute's FY 2003 program.

TOPIC 4: RESEARCH PRIORITIES

Recommendations:

The Committee recommends that NSBRI continue to maintain Countermeasures Research as its primary research focus.

At this time, efforts in education should emphasize graduate and post-graduate support in research environments in NSBRI consortia member laboratories. As the Institute and its research programs mature, educational efforts may expand to K-12. Cooperative Research and Development, Education, Training, and Outreach should be secondary to the research focus. Some elements of Cooperative Research and Development may be incorporated into the Countermeasures Research.

Response:

The NSBRI agrees with these recommendations and will maintain Countermeasure Research as its primary focus and emphasize support for graduate and postgraduate training as its most important thrust in education. In the spirit of the last recommendation, the NSBRI intends to integrate a new program in bioinformatics into the Countermeasure Research Program (see

Figure 1). This new program includes the data archiving, modeling and systems analysis components that were formerly included in the Cooperative Research and Development area.

TOPIC 5: RADIATION HEALTH RESEARCH

Recommendations:

NASA and the NSBRI should clarify the role that the radiation effects team should play in the overall program to reduce health risks associated with exposure to space radiation.

NSBRI should consider the addition of NASA JSC technical experts on radiation to the radiation effects team.

Response:

See the separate NASA response to this recommendation.

The NSBRI agrees that NASA and the NSBRI should work together to clarify the role that the Institute's Radiation Effects Team should play in NASA's overall program and has had several preliminary discussions with NASA concerning this matter. Clearly, these discussions should continue, leading to a resolution of this issue.

The NSBRI accepts the recommendation that NASA JSC technical experts on radiation be added to the NSBRI's Radiation Effects Team. Since normal team membership involves selection of a peer-reviewed project, it is proposed that technical expertise from one of the NASA Field Centers (including JSC) be considered for *ex officio* membership in a team whenever appropriate and agreed to by NASA and NSBRI management.

TOPIC 6: BIOINFORMATICS

Recommendations:

Bioinformatics should be a prominent part of NSBRI's Strategic Plan. Tools should be developed to model and visualize data and to assess whether unexpected relationships may be present in existing databases for factors not yet identified. A comprehensive approach needs to be developed. Both NASA and the Applied Physics Laboratory at Johns Hopkins, a member of the consortium, hold world-class expertise in this area that should be tapped. The Strategic Plan should be modified to include bioinformatics as a key crosscutting set of tools essential for modern research.

Response:

The NSBRI agrees with this recommendation and will modify its strategic plan accordingly. Bioinformatics (research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, archive, analyze, or visualize such data) is essential to the Institute's ability to carry out its mission of countermeasure development. The Institute has had a program in this area since its inception, related primarily to data archiving but recently expanded to include several related modeling efforts. The Institute has proposed a modest expansion of related activities in the present strategic plan. The Institute's bioinformatics-related activities are of three types, described below.

Since 1997, an NSBRI data archiving project based at Johns Hopkins University's Applied Physics Laboratory has been developing the infrastructure to enable appropriate experimental data to be collected and disseminated to the scientific community. This Institute Data Archive System, the first bioinformatics-related activity, has been developed following a model that is based, in part, on NASA's Life Sciences Data Archive System (LSDA). Investigators are informed of the data management requirements through the research announcements. Beginning in FY 2003, investigators will be required to deliver both a data management plan and their data (as it is collected) to a central Institute data archive.

The second bioinformatics-related activity in the current strategic plan concerns the recovery of previous space-flight data not presently available to the scientific community. These data are archived in a format that is compatible with NASA's current LSDA structure. As an example, no current data archive contains the recoverable data from the Skylab missions of the 1970s. These data are the most extensive set of human data ever gathered in space.

The third activity concerns the future development of a distributed, but integrated, data management and modeling system for all research, medical and environmental space-flight data and the concurrent development of a system to allow appropriate accessing of these data by various categories of users. Included with this activity is the development of appropriate filtering systems to allow release of much of the data to the scientific community. The EAC addressed the issue of data integration and modeling in its Fall 2001 and Spring 2002 meetings, following an EAC-sponsored workshop on the topic in May 2001 (chair: F. Eugene Yates, M.D.). The workshop panel agreed with the November 2000 site-visit report that the Integrated Human Function Team should be done away with by distributing the very sound modeling projects to other teams. The panel also recommended, and the EAC agreed, that integration of data, information and modeling was an essential Institute function and should be the responsibility of a new Institute activity (part of the bioinformatics project of Figure 1). The focus of this new activity is on integrating research across the different teams and guiding the development of multi-system models for use in countermeasure research. The EAC strongly recommended that additional Institute resources be committed to carry out this responsibility and said the Institute goal of creation of a "digital human" gives the NSBRI one of its best chances for distinction.

If NASA makes appropriate funds available beginning in FY 2003, the Institute will develop a major cross-cutting initiative in the general area of bioinformatics. Planning for that initiative will begin in August 2002 with a meeting hosted by the University of Washington in Seattle.

TOPICS 7: PEER REVIEW

Recommendations:

Continue to maintain the high quality and objectivity of the Peer Review process.

Response:

The NSBRI intends to maintain its high standards of peer review.

TOPIC 8: RELATIONSHIPS WITH COMPLEMENTARY PROGRAMS

Recommendations:

Leverage NASA's investment in space travel related health risk research in collaboration with related federal research programs. Whenever possible, develop a collaboration with federal agencies on research, for example, in areas such as bone, muscle, metabolism, and health monitoring technologies. One would expect that many technologies and countermeasures developed to minimize or prevent the consequences of space travel can be adapted to have practical value in health care delivery, just as electronic developments in the formative NASA years resulted in several technologic spin-offs to society's benefit.

Response:

The NSBRI strongly agrees with this recommendation. In the original 1997 proposal to form the NSBRI, a program called the National Research Initiatives Program was proposed that would build partnership programs with federal agencies that had mutual research interests with the NSBRI. Agreement in principle to develop such a joint program was obtained with both the National Institute of Deafness and Other Communication Disorders of the NIH and the Biomedical Engineering Program in the Engineering Directorate of the National Science Foundation. In fact, a program with the former agency was established and has been operating successfully for four years. It has always been our intention to replicate this model with other federal funding agencies, but the low level of financial support for the NSBRI has precluded our doing so.

TOPIC 9: NOVEMBER 2000 EXTERNAL REVIEW

Recommendations:

None.

Response:

No response required.

TOPIC 10: PRESIDENT'S MANAGEMENT AGENDA

Recommendations:

NASA should provide stable and sufficient funding for the NSBRI (See Budget section below).

Response:

See the separate NASA response to this recommendation.

Only with stable and sufficient funding can the Institute attract and hold the high-quality investigators needed to solve the biomedical problems of space flight and accomplish its mission.

TOPIC 11: BUDGET

Recommendations:

NASA should increase and stabilize the NSBRI budget. This is essential to the success of the program and the development of the next generation of researchers. Although NSBRI funding restoration and increase is recommended, it should not be at the cost of NASA's Biomedical Research and Countermeasures Program. Without adequate funding, many talented investigators will abandon this research area and promising researchers will pursue more attractive research areas. The foregoing will preclude future safe space travel.

The Institute should consider the use of NIH-style center support mechanisms to provide an appropriate funding mechanism for more complex research queries that require a research team with complementary expertise required to develop novel research tools and technologies required by the team. A new NASA investment in 2-3 comprehensive centers of this type can lead to an integrative approach into developing countermeasures that are complex and essential and unlikely to be effectively addressed by the classic individualized R01 approach. This approach may include NASA engineers, physicists, and computer programmers working side-by-side with NSBRI investigators. The R01 mechanism remains essential for research that is hypothesis-driven and not heavily dependent on advanced technologies.

Response:

See the separate NASA response to this recommendation concerning the NSBRI budget.

The NSBRI agrees with the recommendation that an NIH-style center support mechanism would be an effective approach to certain key areas of countermeasure development. If the funding for the NSBRI increases as the review panel suggests it should, then this topic will be discussed with the EAC, NASA and the NSBRI Board of Directors. If these discussions are positive and the funding available, a plan will be developed to initiate a small number of such centers as major integrating elements of the NSBRI.

NATIONAL
SPACE BIOMEDICAL
RESEARCH INSTITUTE

CORE RESEARCH PROGRAM
YEAR 5 - FY 2002

September 10, 2002

National Space Biomedical Research Institute
Core Research Program – Year 4
FY 2002
September 10, 2002

TABLE OF CONTENTS

NSBRI RESEARCH PROGRAM
BONE LOSS

Team Leader: **Shapiro, J. R.** — **Uniformed Services University of the Health Sciences (USUHS)**

Associate Team Leaders:
Bloomfield, S. A. — **Texas A&M**
Schaffler, M. B. — **Mount Sinai**

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Susan Bloomfield, Ph.D.**
ORGANIZATION:	**Texas A&M University**
PROJECT:	**Bone and Muscle Recovery from Simulated Microgravity**

Project Executive Summary

Dramatic losses of bone mineral density (BMD) and muscle strength are two of the best-documented changes observed in humans after prolonged exposure to microgravity. Recovery of muscle upon return to a 1-G environment is well studied, however, far less is known about the rate and completeness of BMD recovery to pre-flight values. Using the mature tail-suspended adult rat model, this proposal will focus on the temporal course of recovery in tibial bone following a 28-d period of skeletal unloading. Through the study of bone density and muscle strength in the same animal, time-points during recovery from simulated microgravity will be identified when bone is at an elevated risk for fracture. These will occur due to the rapid recovery of muscle strength coupled with a slower recovery of bone, producing a significant mismatch in functional strength of these two tissues. Once the time-point of maximal mismatch is defined, various mechanical and pharmacological interventions will be tested at and around this time-point in attempt to minimize the functional difference of bone and muscle. The outcomes of this research will have high relevance for optimizing the rehabilitation of astronauts upon return to Earth, as well as upon landing on the Martian surface before assuming arduous physical tasks. Further, it will impact significantly on rehabilitation issues common to patients experiencing long periods of limb immobilization or bed rest.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Mark E. Bolander, M.D.**
ORGANIZATION:	**Mayo Clinic Rochester - Rochester**
PROJECT TITLE:	**Effect of Microgravity on Fracture Healing: Ultrasound as a Possible Countermeasure**

Project Executive Summary

The NSBRI Conference that was convened in Clear Lake, Texas, on November 16-17, 2000, identified fracture healing during space flight as an area where further information would be required to appropriately prepare for long-term space missions, and developing countermeasures to restore normal fracture healing was identified as a priority for current research. The RFA dated February 22, 2000, (NSBRI II 00-01) requested studies evaluating the effect of space flight on fracture healing and developing countermeasures. This application is submitted in response to that RFA.

Our current understanding of bone physiology suggests that fracture healing will be abnormal in the microgravity environment. This hypothesis is supported by two published studies, the first an abstract reporting abnormal healing in rats undergoing hindlimb unloading, the second a manuscript (in Russian) that describes abnormal fracture healing in five rats with fibula fractures flown on Cosmos-2044. This latter study reports that abnormalities seen in fracture healing after space flight were duplicated in the hindlimb-unloading model.

The goals of the experiments proposed in this application are 1) to confirm the previous reports that microgravity adversely affects fracture healing, and 2) to determine if ultrasound treatment, which has been shown to accelerate fracture healing in clinical studies, will reverse the impaired cellular events in fracture healing that are related to microgravity. If ultrasound does not act as an effective countermeasure we will undertake detailed evaluation of our histologic samples to identify potential targets for other countermeasures.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Carlos M. Isales, M.D.**
ORGANIZATION:	**MCG Research Institute, Inc.**
PROJECT TITLE:	**Therapeutic Modulation of Systemic Glucose-Dependent Insulintropic Peptide Levels to Counteract Microgravity-induced Bone Loss**

Project Executive Summary

Our long-term goal is to understand the molecular mechanisms of bone formation, maintenance and repair. Weight-bearing is essential for bone formation and maintenance. In the absence of load, for example, in the microgravity environment of space, bone tends to atrophy. We hypothesize that the detrimental effect of diminished gravitational load can be overcome by exploiting the hormonal cues received by bone. Our primary candidate for effecting this control is the enteric hormone, glucose-dependent insulinotropic peptide (GIP), secreted from the small intestine in direct response to nutrient intake. We propose that by therapeutically elevating GIP levels, coupled with strict dietary control, it will be possible to mitigate the impact of microgravity.

The accepted function of GIP is coupling insulin secretion to blood glucose elevations. However, our group was the first to demonstrate an additional function for GIP, namely the stimulation of bone formation(1-3). Functional GIP receptors are present on bone-forming cells *in vivo* and activation of these GIP receptors leads to an increase in bone formation and, conversely, an inhibition of bone resorption.

Thus, GIP might be an important hormonal link between nutrient ingestion and bone formation. To define GIP's role in normal bone formation we have generated transgenic mice with GIP levels up to four times normal We proposed to examine the bone phenotype in these GIP-overexpressing transgenic mice. Our hypothesis predicts that these mice will have significantly higher bone mass on the basis of both a stimulation of bone formation and inhibition of bone resorption. To define GIP's role under conditions of microgravity we propose to examine whether endogenous elevations in GIP prevent bone loss in a model of weightlessness (hindlimb suspension). Our hypothesis predicts that these mice will be protected against bone loss in the simulated microgravity environment

During the last year we have begun the characterization of the effects of GIP on the bones of the GIP overexpressing transgenic mice. The data demonstrate that these animals have denser bones than their littermates. In addition, the higher levels of GIP are protective against the bone loss associated with estrogen loss in ovariectomized mice. The higher levels of GIP do not appear to have any negative impact on the health of these mice, their weight is unchanged as is their blood sugar and lifespan. Thus, GIP would appear to have very specific beneficial effects on bone turnover. Whether GIP will be as effective in preventing bone loss associated with microgravity is not yet known. However, we are pursuing collaborations which we hope will help strengthen our findings. For example, the dynamics of GIP secretion in response to a meal are well known but the impact of microgravity on GIP secretion is not. We hope to define this by measuring levels of GIP in response to a meal under conditions of microgravity (using a bed rest study being performed by Dr. Joseph Zerwekh). We also are studying the muscle-bone interaction in these GIP overexpressing transgenic mice with the help of a NASA funded investigator of muscle atrophy (Dr. Paul McNeill). We are also trying to define GIP effects at a cellular level by examining specific genes activated by GIP which we identified using Gene Chip technology. The number of genes activated in osteoblastic-like cells by GIP are almost twice those activated by parathyroid hormone, a well described anabolic hormone for bone.

Experiments to be performed over the coming year should give us a much better understanding of GIP's effects on bone. The bones and bone markers of the GIP overexpressing mice need to be fully characterized. We do not know if the higher bone mass seen in the GIP overexpressing transgenic mice is of the same quality as normal bone, so bone strength studies need to be done. We still do not know whether GIP is protective against bone loss initiated by loss of testosterone. We do not know whether modifications in the animals diet potentiate or antagonize GIP's beneficial effects on bone mass. We do not know if other anabolic agents for bone such as PTH can synergize with GIP and give us much larger increases in bone mass. These questions need to be answered before we can begin the studies on whether GIP is protective against the bone loss associated with a microgravity environment (hind limb suspension) which we expect to begin in year three (2003) of the funding cycle.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Gerard Karsenty, M.D., Ph.D.**
ORGANIZATION:	**Baylor College of Medicine**
PROJECT TITLE:	**Leptin as a Regulator of Bone Formation in Microgravity**

Project Executive Summary

The original aims of the project are as follows:

- To determine whether leptin controls bone mass by releasing a humoral substance following its binding to its hypothalamic receptor.
- To determine whether the sympathetic nervous system is involved in mediating leptin control of bone formation.
- To determine whether a naturally occurring soluble some of the leptin receptor can prevent leptin inhibitory action on bone formation.

Several key findings were made during the previous year of funding. These can be summarized as follows:

- Leptin uses different pathways to control bone mass and body weight.
- The concentration of leptin in blood is not a good indicator of its action on bone formation
- Neurons present in the hypothalamus and controlling bone formation have been identified.
- The mediator coming out of these neurons and affecting bone formation is not present in blood.

The impact of these findings on the hypotheses, objectives and specific aims of the original proposal:

These findings confirmed largely our working hypothesis that there is a brain-derived neuronal control of bone mass. They lead us to propose new experiments to identify the mediator relaying information form the brain to the bone cells.

In the coming year we intend to use mutant mouse strains deficient in various neuromediators to identify the mediator of leptin action on bone mass. Once we will have identified this mediator we will generate an inhibitor of this mediation and we will us it in ovariectomized animals to determine whether it can be used to prevent the development of osteoporosis.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Clinton Rubin, Ph.D.**
ORGANIZATION:	**State University of New York – Stony Brook**
PROJECT TITLE:	**A Biomechanical Countermeasure for Disuse Osteopenia**

Project Executive Summary

Original aims of the project: Osteoporosis, the progressive loss of bone density and strength which cripples tens of millions on our planet, distinguishes itself as perhaps the greatest physiologic obstacle to an extended human presence in space. The principal objectives of this proposal are to establish the efficacy of a unique, biomechanical countermeasure to inhibit bone loss in an animal model of disuse osteoporosis, and correlate this regulatory influence to the expression patterns of several genes critical to bone formation and resorption. Using a ground based model of microgravity, the tail-suspended rat, we have shown that brief exposure (10 minutes) to extremely low magnitude (0.25g, engendering < 5 microstrain), high frequency (30-90 Hz) mechanical signals will inhibit the bone loss which typically parallels disuse, even though 10 minutes of full weightbearing failed to curb this loss. Longer-term experiments in sheep have shown this stimulus to be strongly anabolic, increasing bone mineral density, trabecular number and connectivity, and improving bone strength.

In a series of four specific aims, we are using several morphometric assays on the mouse model of tail-suspension to rigorously establish the efficacy of a specific mechanical signal (10 minutes at 30Hz, 0.3g; parameters being used in clinical trials to inhibit bone loss in the elderly) to inhibit and/or reverse 28 days of disuse osteopenia. In an effort to understand the mechanisms by which this signal is anabolic, we will also monitor the temporal and spatial expression of nine genes, each indicative of a specific process of bone formation or resorption. The use of the mouse will facilitate many aspects of the protocol, including comprehensive genomic profiling and expedited access to spaceflight. Considering that many flight opportunities are brief and thus do not permit long term morphologic adaptations in bone to occur, combining the molecular with the tissue level strategies will facilitate establishing countermeasure efficacy even following short term exposure to microgravity. In essence, this work represents a critical step in establishing a physiologically based, non-pharmacologic, non-invasive treatment for osteoporosis, for use on earth or in space.

Key findings of the project: Thus far, the project has demonstrated that the low-level mechanical intervention is powerfully anabolic, and can effectively inhibit the bone loss which parallels disuse. As importantly, using three distinct strains of mice, we have determined that the response of the skeleton to disuse is strongly dependent on the genomic makeup of the animal, and that the responsivity of the skeleton to the signals are dependent on the animal strain.

Impact of these findings: These findings point to a unique, non-pharmacologic, non-invasive means of controlling bone loss in a microgravity environment. This biomechanical intervention may potentially displace the need for time consuming (and relatively ineffectual) exercise regimens, or replacing the need for pharmacologic countermeasures (and the potential long-term side effects that they may cause). Importantly, promising results from preliminary clinical trials on post-menopausal women, girls with osteoporosis, and children with cerebral palsy, also indicate that this therapy may work for the 20 million people on earth who suffer from osteoporosis. This work may also contribute to identifying the genetic basis for those at greatest risk of the diseases.

Plans for the coming year: Studies will continue to identify the strain-specific sensitivity of the skeleton to disuse and/or mechanical stimulation, and efforts will begin to determine those genes that are involved in regulating the process. Work funded by NASA has begun, in the "definition" phase, to determine if this biomechanical intervention can be used effectively on astronauts in the ISS.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Mitchell B. Schaffler, Ph.D.**
ORGANIZATION:	**Mount Sinai School of Medicine**
PROJECT TITLE:	**Resorption Suppression and Bone Health in Disuse**

Project Executive Summary

Bone loss in microgravity, and the resulting bone fragility that ensues, have been identified by NASA and NSBRI as key barriers to successful long-term space flight and the recovery of normal function in astronauts upon returning to Earth's gravity. Overcoming these problems will require safe and effective countermeasures not only to prevent bone loss, but also to maintain the functional-mechanical integrity of the tissue during prolonged space flight. *A necessary prerequisite for development of those countermeasures is the identification of appropriate cellular targets for both processes. Those cellular targets have not yet been fully characterized.* We posit that 1) preventing bone loss and 2) maintaining bone health during long-duration in the absence of normal loading involve different cellular mechanisms and so will require different countermeasures. 1) Osteoclasts are clearly the agents driving bone loss due to unloading. Thus, they present an obvious countermeasure target for modulating bone loss in space flight and in other hypodynamic loading situations. Available pharmacological strategies to inhibit osteoclastic resorption have a high likelihood of success, though *definitive long-term data for remodeling suppression after unloading do not exist.* 2) Changes in osteocyte integrity result from long-term loss of normal mechanical loading. If the normal remodeling response of bone to impaired osteocytes is suppressed, as would be the case with treatment using an anti-resorptive agent, then regions of osteocytes can die, leading to the accumulation of devitalized bone. Devitalized bone becomes mechanically fragile, raising the fundamental question of whether bone loss resulting from withdrawal of normal mechanical usage can be safely prevented for the long-term, without paradoxically impairing osteocyte function, and thereby bone's ability to function mechanically in a normal load-bearing environment. The proposed experiments test the hypotheses that 1) Long-term suppression of bone remodeling in disuse will successfully maintain bone mass, microarchitecture, stiffness, and strength, but will result in compromised fracture resistance properties; and 2) Decreased mechanical usage in the presence of an antiresorptive agent results in loss of osteocyte integrity and accumulation of bone with impaired viability.

To test these hypotheses, we will undertake a series of long-term immobilization experiments in a canine model, with biphosphonate treatment to prevent bone loss. Bone health will be assessed from conservation of tissue mechanical properties and from in situ assessments of osteocyte viability. We will determine whether suppression of bone resorption superimposed in unloading leads to impaired osteocyte viability and increased brittleness of bone, and whether the extent of such alterations can be sufficient to cause significant bone fragility.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Jay R. Shapiro, M.D.**
ORGANIZATION:	**Medstar Research Institute**
PROJECT TITLE:	**Defining and Preventing Bone Loss: A Microgravity Model**

Project Executive Summary

Muscle atrophy and bone loss are major complications of spinal cord injury (SCI), chronic bed rest and exposure to microgravity. Space medicine research has amply documented the extent to which muscle and bone loss may impair strength and increase fracture risk. We propose that the SCI patient can serve as a surrogate for studying microgravity exposure. A primary objective of this research program is to limit the extent of bone loss in SCI patients by treating with a potent intravenous bisphosphonate, zoledronate for a period of one year. The zoledronate effects on bone will be measured using bone density values and femur scan structural analysis as the indicators of bone integrity. We will determine the effects of zoledronate on biomarkers of bone resorption and formation and on serum calcitropic hormone levels. To study the process of muscle atrophy when weightless, we will determine the relationships between changes in thigh muscle cross-sectional area measured by CT scan, muscle biopsy immunohistochemistry, muscle protein translation markers and markers for protein synthesis activation and protein degradation. To further understand mechanisms involved in bone loss we will determine sequential changes in femur bone geometry and structural parameters obtained from DEXA scans by established 2-D curved beam analysis methods. Using femur CT images we will measure changes in femur bone dimensions and will apply 3-D finite element analysis to estimate fracture risk. The new time-of-flight mass spectrometer will permit measuring the excretion of zoledronate in urine and plasma levels. We will compare these to radiologic measurements and bone biomarkers. The objectives of this research are: 1) to develop a regimen for minimizing bone loss in SCI subjects that may be appropriate for astronauts during extended microgravity exposure, and 2) to investigate mechanisms related to muscle and bone loss during weightlessness, and 3) to explore the SCI patient as a surrogate for the investigation of microgravity induced musculoskeletal atrophy.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Carolyn L. Smith, Ph.D.**
ORGANIZATION:	**Baylor College of Medicine**
PROJECT TITLE:	**Receptor Countermeasures to Bone Loss in Microgravity**

Project Executive Summary

The prevention of bone loss due to skeletal unloading is a complex problem and the reasons for this loss have not been elucidated. The overall goal of the bone team of NSBRI is to develop countermeasures that will not only prevent quantitative loss of bone, but also maintain bone strength. Measures that simply prevent resorption may maintain mass, but may block the necessary remodeling that ensures adequate bone strength. Studies to date suggest that good nutrition and exercise regimes will be insufficient to achieve this goal so pharmacological alternatives must be considered. The biological actions mediated by the estrogen receptor (ER) and vitamin D receptor (VDR) play key roles in the normal control of bone growth and skeletal turnover that are necessary for skeletal health. These receptors act by controlling the differentiation and/or function of osteoblasts and osteoclasts, and other cell types within the bone and bone marrow microenvironment as well as playing a role in calcium absorption (VDR). *We hypothesize that the appropriate combination of an agent that will improve calcium absorption and encourage bone formation (VDR agonist) and an agent that will reduce bone resorption (selective estrogen receptor modulators [SERM]) will achieve the goal of maintaining bone mass and bone strength.* To test this we have initiated studies to: 1. Assess the ability of novel receptor agonists of the ER and VDR, alone or in combination, to modulate osteoblastogenesis, mature osteoblast function and osteoclastogenesis *in vitro* and *in vivo* and 2. Assess the ability of novel receptor agonists of the ER and VDR, alone or in combination, to prevent bone loss in the hindlimb suspension model of skeletal unloading. Effects of unloading and the countermeasures will be assessed by: a. Measuring changes in bone mineral density, histomorphometry, mechanical strength testing and biochemical markers of bone metabolism, b. Determining the effects of these treatments on osteoblastogenesis and osteoclastogenesis and function, and c. Characterizing gene expression profiles in bone resulting from skeletal unloading and administration of the countermeasures. Our results to date indicate that ligands of both the ER and VDR possess the ability to attenuate bone loss in the rat hindlimb suspension model of skeletal unloading. Collectively, these studies will lead to a better understanding of the changes associated with skeletal unloading and will test the utility of VDR agonists and SERMS as countermeasures.

RESEARCH AREA:	**Bone Loss**
PRINCIPAL INVESTIGATOR:	**Joseph E. Zerwekh, Ph.D.**
ORGANIZATION:	**UT Southwestern Medical Center at Dallas**
PROJECT TITLE:	**Prevention of Microgravity-Induced Stone Risk by KMgCitrate**

Project Executive Summary

Ground-based studies, as well as a limited number of space flight studies, have clearly demonstrated an increased risk for stone formation as determined from the composition of the urinary environment. Increased bone resorption raises urinary calcium and the urinary state of saturation with respect to the calcium salts, calcium oxalate and brushite. However, documented changes in other urinary components such as citrate, pH, and magnesium appear to also raise the risk for the formation of not only calcium stones but also uric acid stones as well. Nutritional modifications to counter the tendency toward stone formation might include increased fluid consumption and supplementation with an appropriate countermeasure that would decrease the risk for stone formation by increasing urinary pH and the concentration of inhibitors of stone formation. Bisphosphonates reduce bone resorption and lower urinary calcium but have no effect on urinary pH or citrate. Thus, the hypothesis to be tested in this project is that KMgCit supplementation will attenuate the increased risk for stone formation and diminish microgravity-induced bone loss. This hypothesis is currently being tested during five weeks of bedrest in normal volunteers through three specific aims: 1; assess the efficacy of supplementation with potassium magnesium citrate (KMgCit) in preventing microgravity-induced increased risk of renal stone formation. 2; evaluate the effect of KMgCit supplementation in averting diminished muscle magnesium and potassium concentrations that may occur during microgravity-induced muscle atrophy and 3; assess the efficacy of supplementation with KMgCit in reducing microgravity-induced increases in bone resorption and urinary calcium losses.

A total of eight qualified normal volunteers have given informed consent to participate in this study. This study is being performed as a double blind, placebo-controlled randomized trial. This study design precludes an assessment of the treatment efficacy at this time. Results to date are summarized in Table 1 as the average for all eight subjects and in Figures 1-9 as both group averages as well as individual patient plots. Significant changes were observed for several urinary analytes and for serum immunoreactive PTH. The increase in urinary calcium and deoxypyridinoline, a marker of bone resorption, is consistent with an overall increase in bone resorption. The significant reduction in serum iPTH is also consistent with this mechanism. The other changes, such as the significant increase in urinary potassium and magnesium may reflect the response of those subjects who received the active drug. We have not observed any consistent change in the measures of urinary states of saturation for calcium oxalate or brushite. We did observe a significant reduction in the relative saturation ratio of sodium urate during the first week of bedrest. It is not possible to discern if this decrease was the result of KMgCitrate therapy or due to some other change. While this is very preliminary data, it does corroborate our earlier findings of a rapid increase in bone resorption following bedrest immobilization. Several additional analyses, including analysis of muscle biopsies for potassium and magnesium (specific aim 2), bone mineral density analyses, bone ultrasound analyses, vitamin D metabolites, and gastrointestinal absorption of calcium, are currently underway or at various stages of completion.

These preliminary findings do not deter from our original hypothesis. The small number of patients studied, combined with our double-blind study design do not permit a subgroup analysis of KMgCitrate's ability to reduce the stone-forming propensity of urine from subjects undergoing five weeks of bedrest. Such an analysis will not be possible until the study is completed. The findings do support the use of the ground-based model of bedrest to mimic the skeletal unloading experienced in the microgravity environment of space.

Research plans for the coming year call for a continuation of the current research protocol as originally described. The next two patients are scheduled to begin the protocol later this month. We fully anticipate that another 7-8 subjects will be evaluated in the coming year barring any early study termination. If we are successful in this regard, we will be on course to fulfill our pre-specified number of 20 subjects during the third year of study.

NSBRI RESEARCH PROGRAM
CARDIOVASCULAR ALTERATIONS

Team Leader: **Cohen, R. J.** **MIT**

Associate Team Leader: **Shoukas, A. A.** **Hopkins/SOM**

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Mohamed A. Bayorh, Ph.D.**
ORGANIZATION:	**Morehouse School of Medicine**
PROJECT TITLE:	**Possible Countermeasures to Post-Suspension Hypotension in the Head-Down Tilt Rat Model**

Project Executive Summary

Exposure to microgravity or simulated microgravity in humans causes cardiovascular deconditioning with orthostatic hypotension and tachycardia. Postflight orthostatic intolerance is a dramatic physiologic consequence of human adaptation to microgravity made inappropriate by a sudden return to normal gravity. Loss of appropriate cardiovascular reflexes contributes to the cardiovascular deconditioning, but the specific mechanisms remain uncertain. The endothelium is now recognized to play a critical role in the regulation of vascular resistance and blood pressure through the release of nitric oxide and/or prostacyclin. The objective of the proposed studies is to test the hypothesis that the post-suspension hypotension in rats following simulated microgravity involves elevated levels of prostacyclin and/or nitric oxide and, thus, can be attenuated by specific inhibitors of these vasodilatory factors. Using the 30^{0} tail-suspended (hindlimb-unloaded) rat model, the roles of prostacyclin and nitric oxide in post-suspension hypotension are being evaluated. For the coming year we will continue to examine gender differences in the post-suspension hypotensive response.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Donald M. Bers, Ph.D.**
ORGANIZATION:	**Loyola University Chicago**
PROJECT TITLE:	**Integrative Cardiac Myocyte Model: Ion Channels, Ca and Contraction**

Project Executive Summary

Our long-term objective is to build a detailed quantitative model of cardiac muscle, which will include electrophysiological properties, cellular Ca-regulation and contractile activation and relaxation. Aims of the project are: 1) To develop a more up-to-date electrophysiological model of cardiac myocyte dynamics; 2) to incorporate new Ca-transport data on SR Ca-uptake, release and Na/Ca exchange; 3) To extend the model to include cooperative Ca-dependent myofilaments activation, contraction and relaxation; and 4) Implement this model on highly accessible formats (one user-friendly and one computer-friendly for interfacing with other models). The rationale for our proposal stems from a lack of integration of information from the level of ion channels to Ca transients to myofilament force and shortening. We plan to develop a comprehensive quantitative model that incorporates up-to-date information on ion channels, modulation of Ca-cycling processes and myofilament activation. The approach involves a team of investigators with long-standing laboratory and modeling experience in each of these processes. Drs. Bers and Puglisi of Loyola University have extensive experience in modeling and quantitative experimental studies of regulation of Ca-cycling and membrane currents in the cardiac myocyte. Similarly, Drs. De Tombe and Solaro of the University of Illinois at Chicago have extensive experimental and modeling experience that focuses on the modulation of myocyte response to Ca. The approach involves the generation of computer models constrained by dynamic data generated in these and other laboratories. A preliminary working model LabHEART4 shows feasibility and utility of the proposed modeling format. This endeavor will provide new insights into normal physiological regulation of myocyte activity as well as providing a baseline from which altered function induced by alterations in hemodynamic loading can be readily considered. A fully integrated model of cardiac myocyte activity and regulation of myocyte activity developed here will have a broad application to acute changes in the environment as occurs in space travel and re-entry. This understanding will also have a broad significance to the understanding the effects of altered gene and protein expression associated with long-term changes in cardiac loading that occur during space travel and return to Earth.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Vincent Cassone, Ph.D.**
ORGANIZATION:	**Texas A&M University**
PROJECT TITLE:	**Microgravity and Circadian Cardiovascular Function**

Project Executive Summary

This project is directed at the physiological mechanism(s) by which the mammalian circadian clock located within the hypothalamic suprachiasmatic nuclei (SCN) regulates cardiovascular function and to what extent simulated microgravity affects circadian variation in cardiovascular function. The interaction of circadian organization and other determinative factors involved in problems associated with microgravity and cardiovascular disease will be assessed through the comparative study of circadian regulation of cardiovascular function in male vs. female rats.

It is known that astronauts suffer many disruptions to normal bodily processes while in space. The most obvious of these is the redistribution of fluids in the body. This was demonstrated as early as the Mercury era, when man first ventured into space. In the microgravity environment, fluids tend to move into the chest and head, causing facial swelling and congestion. This fluid shift also reduces circulating blood volume and plasma levels of norepinephrine as well as causing a specific increased sensitivity of beta-adrenoreceptors. These changes occur due to a rise in blood pressure as perceived by the carotid baroreceptors. In Earth-based studies, bed-rest with head oriented below the feet (HDT) is believed to simulate these effects in space. HDT causes an attenuation of blood pressure rhythmicity, causing damping out of the circadian rhythm of diastolic blood pressure. Systolic blood pressure was not affected as greatly by HDT. However, HDT did not affect the circadian variation in heart rate. However, studies monitoring heart rate while in flight show that heart rate tends to increase after several days in the microgravity environment. While the circadian period of heart rate may not change, there seems to be an increase in heart rate itself.

a) Specific Aim #1: Determination of SCN Efferents Controlling Circadian Variations of Cardiovascular Function in Long-Term, Conscious Rats: Since it is well-known that cardiovascular responses to pressors and stress are significantly different in anaesthetized vs conscious preparations, we will characterize circadian variation in cardiovascular function in conscious freely moving rats. We will then determine whether surgical blockade of SCN efferents affects the circadian variation of heart rate, cardiac output and mean arterial pressure.

b) Specific Aim #2: Role of Circadian System on Daily and Circadian Variation in Regional Blood Flow: We will determine daily and circadian variations in regional blood flow measurements using ^{85}Sr-labelled microspheres in rats whose circadian phases will be monitored independently. We will also determine whether 1) the SCN, 2) SCN efferents and 3) sympathetic innervation are required for the expression of these rhythms.

c) Specific Aim #3: Effects of Simulated Microgravity on Circadian Cardiovascular Rhythms: We will determine the effects of hind-limb unloading on the circadian variation in heart rate, regional blood flow and other cardiovascular variables. Based upon data obtained in **Specific Aims #1 and 2**, we will determine the mechanisms by which anticipated changes occur. These experiments will provide guidelines for future counter-measures in space.

d) Specific Aim #4: Effects of Gender on Circadian Changes in Cardiovascular Function and Their role in Responses to Microgravity: Because it is well-established that female and male astronauts experience a different set of cardiovascular responses to microgravity, we will also determine whether we can simulate those differences in our simulated microgravitational apparatus. If so, we will employ the information gained in **Specific Aims #1 and 2** to provide guidelines for future countermeasures.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Richard J. Cohen, M.D., Ph.D.**
ORGANIZATION:	**Massachusetts Institute of Technology**
PROJECT TITLE:	**Cardiovascular Effects of Simulated Microgravity in Man**

Project Executive Summary

This project is targeted towards studying and developing countermeasures to two of the Cardiovascular Critical Risks:

(i) Development of post-flight orthostatic intolerance
(ii) Increased susceptibility to ventricular dysrhythmias.

The development of orthostatic intolerance is a well known adverse effect of space flight on the cardiovascular system, and is a current operational problem for NASA. Astronauts post-flight may experience a drop in arterial pressure upon adopting the upright posture after flight, which may be sufficiently severe to cause presyncope or syncope. This effect is greater the longer the duration of the flight, and is more pronounced in women than in men. During space flight intravascular volume is decreased and cardiovascular reflexes are down-regulated because the cardiovascular system is no longer subjected to the stresses associated with changes in posture. Upon return to a gravitational environment, blood pools in the large veins of the lower extremities and the splanchnic circulation, leading to a drop in preload to the heart leading to a decrease in cardiac output. In addition, the reflex ability to increase heart rate and constrict arteries and veins is diminished, and there are also changes in cardiac systolic and diastolic function. Countermeasures of salt and water loading prior to re-entry and the use of G-suits are not adequate countermeasures to prevent the development of orthostatic intolerance, particularly after long duration flights. Our goal with respect to this cardiovascular risk is to better understand the detailed mechanisms leading to orthostatic intolerance and to develop and test mechanism based countermeasures.

There have been several anecdotal reports of documented episodes of self-termintaing ventricular tachycardia during space flight[1-4]. In addition it has been reported that Russian cosmonauts have suffered from ventricular arrhythmias, and two primates have suffered cardiovascular collapse after return from space flight (without ECG documentation). These data suggest that space flight may be conducive to the development of ventricular arrhythmias. However, it is not known whether or not this is in fact the case. If long duration space flight does increase the risk of potentially lethal ventricular arrhythmias then this would obviously pose an enormous problem for very long duration flights. Our goal in this project is to determine in controlled ground based experiments, whether there is evidence that simulated micro-gravity in fact alters cardiac electrical activity in a manner that may increase susceptibility to ventricular arrhythmias. If we find evidence that this is in fact the case, then we will attempt to establish mechanism and identify potential countermeasures.

In this project we analyze data from ground based human studies in which 16 day head down tilt bed rest is used to simulate microgravity. We will be studying the following groups in order to examine the effects of gender and age on these cardiovascular risks.

i. men under age 50
ii. premenopausal women
iii. men over age 50

In addition to the effects of bed rest we will also examine the effects of sleep deprivation (another condition of space flight). We will also evaluate the effects of the alpha-agonist midodrine as a countermeasure to the development of orthostatic intolerance. We may also evaluate a countermeasure to the development of ventricular arrhythmias.

The key technologies we will utilize are Cardiovascular System Identification (CSI) as a noninvasive means of assessing closed-loop cardiovascular regulation, and measurement of microvolt T-wave alternans (MTWA) as a noninvasive measurement of changes in cardiac repolarization which has been shown in clinical trials to be an accurate measure to susceptibility to ventricular arrhythmias.

To date in this project, we have found that CSI measures of autonomically mediated cardiovascular reflexes are diminished by bed rest, and that during bed rest there appears to be a shift towards increasing sympathetic/parasympathetic balance. We have found that pre-bedrest CSI measures of increased sympathetic/parasympathetic balance identify those subjects who tolerate tilt both pre-bedrest and post-bedrest. We have put considerable effort into improving CSI technology for use in these studies and for application in biomedical research and patient monitoring.

We have demonstrated that the alpha-agonist midodrine appears to be an effective countermeasure to the development of orthostatic intolerance after exposure to 16 days of simulated microgravity.

We have found that even 16 days of bed rest tends to induce sustained MTWA although not at a level that would be of immediate clinical concern. This evidence does indicate that bed rest does measurably alter cardiac repolarization processes, and raises the issue of whether long term exposure to microgravity could increase susceptibility to ventricular arrhythmias. We have also recently conducted a clinical study that demonstrates that MTWA is an accurate predictor of susceptibility to ventricular arrhythmias and sudden cardiac death in patients with heart failure and no prior history of sustained ventricular arrhythmias.

We plan to continue our ground based studies in the above identified patient groups, and evaluate the effects of sleep deprivation and midodrine countermeasures. We may also test a proposed countermeasure to the development of ventricular arrhythmias pending future results from these studies. In addition, we have submitted a flight proposal to measure CSI and MTWA pre and post flight, and to evaluate the midodrine countermeasure during flight conditions.

We plan to develop further the CSI and MTWA technologies for use on earth for biomedical research and clinical applications.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Richard J. Cohen, M.D., Ph.D.**
ORGANIZATION:	**Massachusetts Institute of Technology**
PROJECT TITLE:	**Effects of Space Flight on Cardiovascular Stability**

Project Executive Summary

Many astronauts after being weightless in space become hypotensive and presyncopal upon assuming an upright position. This phenomenon, known as orthostatic intolerance, may interfere with astronaut function during reentry and following space flight, and may limit the ability of an astronaut to exit a landed spacecraft unaided during an emergency. Orthostatic intolerance is more pronounced following long-term space flight and is a major concern with respect to the extended flights expected aboard the International Space Station and for interplanetary exploration class missions, such as a human mission to Mars. This problem has also been observed to be more pronounced among women than among men. In addition to the problem of post-flight orthostatic intolerance, a variety of heart rhythm disturbances have been observed in astronauts during and after space flight. The potential lethal arrhythmic risk for astronauts is sustained ventricular tachycardia or ventricular fibrillation, while non-sustained ventricular tachycardia could cause syncope.

In previous ground based bed rest studies sponsored by NSBRI we have applied two new techniques that we have developed to study the effects of simulated microgravity on the cardiovascular system. Cardiovascular system identification (CSI) has been used a non-invasive means of measuring alterations in closed-loop cardiovascular regulation and the measurement of microvolt level T wave alternans (TWA) has been used as a non-invasive measure of susceptibility to ventricular arrhythmias. We have also successfully tested the alpha-1 sympathetic agonist midodrine as a countermeasure to the development of orthostatic intolerance. We have found that 16 days of bed rest results in altered cardiovascular regulation. In particular, we have demonstrated alterations in baroreceptor sensitivity, altered electrical stability of the heart, and that midodrine is an effective countermeasure to the development of orthostatic intolerance.

In this proposal we plan to apply the same measurement techniques of CSI and TWA to astronauts pre- and post-flight and to test midodrine as a countermeasure to the development of orthostatic intolerance. This study will allow us to determine if the changes in cardiovascular regulation and cardiac electrical stability measured in a ground-based model also occur during actual space flight. In addition we will test for the first time a potentially highly effective countermeasure for the development of post-flight orthostatic intolerance.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**James E. Coolahan, Ph.D.**
ORGANIZATION:	**Johns Hopkins University Applied Physics Laboratory**
PROJECT TITLE:	**Distributed Simulation of Integrated Human Function**

Project Executive Summary

The project *Distributed Simulation of Integrated Human Function* is being undertaken as a part of the National Space Biomedical Research Institute (NSBRI) Integrated Human Function (IHF) team by the Johns Hopkins University (JHU), under the leadership of the Applied Physics Laboratory (APL) in collaboration with the Whitaker Biomedical Engineering Institute and the Center for Computational Medicine and Biology.

A. Review of Specific Aims

The four specific aims of the three-year project, taken from the project proposal, are as follows:

1. To develop, at JHU, an experimentally-based computational model of the human ventricular myocyte using cells isolated from tissue biopsies performed in patients; and to develop a finite-element model of the geometry and fiber structure of the human heart using diffusion-tensor imaging data to be collected at JHU, fit by a finite-element model to be developed at the University of California, San Diego (UCSD).
2. To develop a distributed simulation of human cardiac function, incorporating a simulation of the human cardiac ventricular cell resident at JHU based on the model discussed above and a simulation of coupled cardiac mechanical and electrical function resident at UCSD, with distributed simulation control based at JHU/APL;
3. Working with the NSBRI IHF team, to select other appropriate cardiovascular system models that can be represented over time using simulations, and integrate them into a distributed simulation of cardiovascular function; and
4. Again working with the NSBRI IHF team, to select bone and muscle models that can be represented over time using simulations, and integrate them into a multi-function distributed simulation representative of the full IHF simulations that will be needed for long-duration space flight.

B. Key Project Findings in the First Year

In the first year, we have made progress on the first three specific aims. On specific aim 1, in the Winslow laboratory at JHU, models of three membrane currents found in human ventricular myocytes (the transient outward current I_{to1}, the rapidly-activating outward rectifier current I_{Kr}, and the fast inward Na current) have been formulated based on electrophysiological data from cultured cells, and a model of I_{K1} has been formulated based on data from the literature. We expect to complete a first-order model of the human ventricular myocyte by early Spring, 2002.

We have also made substantial progress in developing image-based models of the canine heart, including development of a 3-D fast spin-echo diffusion imaging pulse protocol that has resulted in very substantial improvements in image signal-to-noise ratio, and are obtaining 3-D diffusion images of the canine heart at approximately 900 x 400 x 400 um resolution. We have also implemented a method for fitting finite-element models specified in prolate-spheroidal coordinates to 3-D canine heart diffusion image data on heart surfaces and fiber orientation throughout the ventricles, as well as methods for simulating conduction in 3-D models of the heart based on these finite-element models, and have generated an initial heart database containing reconstructions and models of six canine hearts. All of the techniques are in place to undertake imaging, reconstruction and modeling of the human heart, and we have obtained diffusion images of short-axis human heart sections. However, we have not yet been able to obtain freshly isolated human hearts from the JHU Pathology Department.

On specific aim 2, we have progressed along two fronts in constructing distributed simulations of cardiac function. First, as an early demonstration of the interoperable simulation capability, we constructed simplified models of cardiac electrical and mechanical activity and then integrated them into a two-computer cardiac simulation at JHU/APL using the High Level Architecture (HLA), a framework for distributed simulations developed in the Department of Defense (DoD), and now an Institute for Electrical and Electronics Engineers (IEEE) standard. The distributed simulation so constructed yielded realistic (simulated) electrocardiograms and left ventricular and systemic arterial pressure tracings with blood pressures of roughly 120/85.

Secondly, on the effort to achieve a distributed high-fidelity simulation of cardiac function via interoperation of the JHU electrical activation model and the UCSD mechanical deformation model (Continuity), we have completed most initialization and configuration steps. The JHU simulation software is installed on the IBM SP3 supercomputer at JHU. In collaboration with the NSBRI IHF team project led by Dr. Andrew McCulloch at UCSD, we have also performed three remote executions, from JHU/APL, of the mechanical simulation for a canine left ventricle on a UCSD Silicon Graphics, Inc. (SGI) platform, with visualization functions performed at JHU/APL. The near-term approach for this interoperability effort is to demonstrate a scripted automated integrated execution of one beat of a canine left ventricle model.

On specific aim 3, we have made significant progress in developing a distributed simulation of cardiovascular function. We have initiated a collaboration with members of Dr. Roger Mark's group (NSBRI Cardiovascular Alterations team) at the Massachusetts Institute of Technology (MIT), and have integrated the following two simulations using the HLA framework:

1. a medium-fidelity electrical-mechanical simulation of the left and right ventricles, called the Hybrid Cellular Automata (HCA) heart simulation, based on the ventricular model developed by A. B. Feldman, Y. B. Chernyak, and R. J. Cohen; and
2. a new cardiovascular system simulation, the Research Cardiovascular Simulator (RCVSIM), developed at MIT by R. Mukkamala, which is based on the earlier CVSIM cardiovascular simulator.

We have called the new HLA-based federated simulation the Cardiovascular – Ventricular System (CVVS) federation, which is targeted toward the cardiovascular alterations risk area in the NASA Bioastronautics Critical Path Roadmap. The simulation allows for the analysis of the static and dynamical responses of important cardiovascular variables (heart rate, blood pressure, etc.) following hypothetical perturbations of the system's parameters, such as alterations in cardiac electro-mechanical function or cardiac arrhythmias.

The CVVS federation was developed using the HLA Federation Development and Execution Process (FEDEP). The individual simulations were made compatible with the HLA by coding "wrappers" that allowed them to communicate via the HLA's Runtime Infrastructure (RTI). The federation was executed at JHU/APL over a local area network utilizing three personal computers (each with a different operating system), with the left ventricle simulation, the right ventricle simulation, and RCVSIM executing on separate computers. (For the purposes of these analyses, the coupling between the electrical and mechanical activity of the left and right ventricles was accomplished through simple execution rules.) The federation permitted 500 ms of simulated time to be executed in 234 seconds of wall clock time, in a configuration used to simulate a ventricular arrhythmia. The simulation produced representative cardiovascular system responses to the arrhythmia (although the simulation is not yet validated by clinical data).

C. Impact of Findings on Hypothesis, Objectives, and Specific Aims

The findings of the project during the first award year supported the hypothesis that interoperable simulations of human physiological functions applicable to the space flight environment, executing interactively, can produce integrated results that cannot be produced by these simulations executing independently. Specifically, the execution of the combined cardiac-cardiovascular simulation that we have called the CVVS federation was able to show reasonable cardiovascular system responses to induced ventricular arrhythmias.

This result also was a first step toward the long-term objective to demonstrate the ability to simulate integrated human function over time by providing a technical framework to permit simulations of different human physiological functions, executing in separate locations, to interact to produce synergistic results. Although the federation was executed over a local area network, the HLA provides for fully distributed operation. There are, however, network security issues in using a non-dedicated wide area network, which we will address in the second year.

Progress made in the first year described above supports three of the four stated specific aims of the project. We plan to continue work in the second year toward achieving all four original aims.

D. Proposed Research Plan for the Second Year

In the second award year of the project, we plan to continue work in the Winslow laboratory on the development of the human ventricular myocyte model, and hope to have a first-order model by the Spring of 2002. We will continue working with the JHU Pathology Department to obtain freshly isolated human hearts so that we can undertake imaging, reconstruction and modeling, in order to produce the human heart geometry needed for the full human heart model.

To demonstrate the ability to connect the high-fidelity JHU electrical activation simulation with the UCSD mechanical deformation simulation, we plan to execute early in the year a one-beat scripted run using a canine left ventricle model, utilizing the IBM SP3 computer at JHU to generate intracellular calcium concentrations and transmit them to an SGI Origin 2100 at UCSD. The interoperability approach provided by the HLA is not required for these scripted runs, and may not be the approach of choice for long run times with minimal interactions. Execution of the human heart simulation must await the completion of the human individual component models, and also the porting of the newer Continuity software to the IBM Blue Horizon supercomputer at SDSC under Dr. McCulloch's separate project.

We plan to extend the CVVS federation across three different fronts. First of all, we intend to demonstrate a distributed execution of the federation between JHU/APL and MIT, which will require resolution of network security issues. Secondly, we intend to initiate a second collaborative effort with Dr. Mark's group at MIT to explore joint development of a model of the renin-angiotensin-aldosterone system based on data obtained from the bed-rest studies being conducted by G. Williams (NSBRI Investigator) in Boston. This model will allow us to incorporate regulation of blood volume into the CVVS federation and will help facilitate analyses of effects related to longer-time-scale cardiovascular adaptations to microgravity. Thirdly, we intend to extend the CVVS federation to include, as a minimum, a simulation of human muscle via collaboration with Dr. Kushmerick's group (NSBRI IHF team). A promising application area is construction of a simulation federation to simulate exercise protocols, an idea currently being discussed among all projects of the NSBRI IHF team.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Michael D. Delp, Ph.D.**
ORGANIZATION:	**Texas A&M University**
PROJECT TITLE:	**Circulatory Remodeling with Simulated Microgravity**

Project Executive Summary

The human body is exquisitely adapted for maintaining an upright posture on Earth. However, when the force of gravity is removed during space flight, there is a cephalic fluid shift and an elimination of the head-to-foot hydrostatic pressure. This change in the fluid pressure distribution has been hypothesized to trigger adaptations within the cardiovascular system that are subsequently rendered inappropriate upon return to the Earth's gravitational environment. One of the most profound consequences of microgravity on the cardiovascular system is orthostatic intolerance. It is now becoming increasingly evident that the etiology of post-flight orthostatic intolerance is multifactorial, resulting from such factors as hypovolemia and altered regulation of the peripheral vasculature. According to Watenpaugh and Hargens (Handbook of Physiology, 1996) the primary cardiovascular adaptations that contribute to orthostatic intolerance involve the arterial, venous and lymphatic portions of the circulatory system. In order to study these phenomena on Earth, the hindlimb-unloaded (HU) rat has been used to simulate the effects of microgravity. This model induces the cephalic fluid shifts, and these animals manifest many of the adaptations that are characteristic of exposure to microgravity, such as hypovolemia, a diminished capacity to elevate peripheral vascular resistance, and orthostatic hypotension. In addition, previous work with conduit and resistance arteries indicates that hindlimb unloading alters both function and structure of the arterial circulation. Therefore, using this animal model, the general aim of this proposal is to determine the effects of simulated-microgravity on 1) the molecular mechanisms mediating structural remodeling of the arterial resistance vasculature, and 2) the functional ability of the lymphatics to generate and modulate lymph flow. More specifically, we propose to: identify early regulatory events leading to hypertrophic remodeling of cerebral arteries in response to hindlimb unloading (Aim 1); characterize signaling events leading to atrophy of resistance arteries in the soleus and gastrocnemius muscle in response to hindlimb unloading (Aim 2); and evaluate the effects of hind limb unloading on the ability of the lymphatics from different regions of the body to generate and modulate lymph flow, and thus, regulate overall body fluid homeostasis (Aim 3). Furthermore, we propose to determine the effectiveness of a lower-body negative pressure countermeasure to attenuate adaptations of the arterial and lymphatic circulation (Aim 4). These studies will provide new and important functional and mechanistic information about the etiology of microgravity-induced orthostatic intolerance.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Beverly H. Lorell, M.D.**
ORGANIZATION:	**Harvard – Beth Israel Deaconess Medical Center**
PROJECT TITLE:	**Cardiac Unloading: Biologic Mechanisms and Countermeasures for Cardiac Atrophy**

Project Executive Summary

The objective is to determine the cellular and molecular mechanisms of cardiac atrophy caused by microgravity (already demonstrated in space-flown rats and long-duration space flight in humans), determine the functional consequences on cardiac contractile reserve, and identify specific countermeasures. We will study a rodent model of cardiac unloading (heterotopic transplantation of the heart to the abdomen). Work in the current grant period showed that this model affords assessment of progressive degrees and duration of unloading as a test-bed for genes, gene products, and human-applicable hormonal interventions with the potential to protect against atrophy. Functional consequences of cardiac unloading and countermeasures will be studied by echocardiography and hemodynamic measurements, analysis of isolated myocyte contraction and intracellular ions using fluorescence microscopy, and microscopy of cell morphology. Activity of key endogenous growth regulators will be monitored by measurements of gene expression and immunohistochemical localization. We will address four Specific Aims: (1) Are ventricular myocyte contractile function and intracellular ion regulation (Ca^{2+} and Na^{+}/H^{+} exchange) modified in cardiac unloading and atrophy? (2) Does cardiac unloading stimulate myocyte cell death (apoptosis), in addition to the remodeling of cardiac geometry and muscle cell size? (3) Do hormonal and genetic countermeasures with direct trophic effects on muscle cell growth and contractility effectively blunt atrophy of the unloaded heart *in vivo*, or block the functional impairments? (4) High-throughput profiling of gene expression (by microarray studies and subtractive hybridization) will be done to identify changes in gene expression, which are unique to cardiac unloading. These studies of integrated cardiac physiology and molecular biology are an outgrowth of work in the current grant period that confirmed our hypothesis that the remodeling of the heart upon cardiac unloading *in vivo* is associated with reinduction of the fetal-hypertrophic cardiac gene program. In this project, countermeasures will focus on a-1-adrenergic pharmacological interventions. The rationale is that this approach has synergy with efforts elsewhere in the Cardiovascular Alterations Team, using the a-1-adrenergic pathway for treatment of orthostatic intolerance in humans. In addition, we have established that the pathway of RNA polymerase II signaling, which regulates the transcription machinery of the cell, is engaged by a-1-adrenergic signaling, a canonical trigger to increase cardiac mass. These studies will elucidate molecular and physiologic mechanisms of cardiac unloading which will lead to specific hypotheses and countermeasures which have the potential to be rapidly tested in the near future in human space flight missions.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Roger G. Mark, M.D., Ph.D.**
ORGANIZATION:	**Massachusetts Institute of Technology**
PROJECT TITLE:	**Computational Models of the Cardiovascular System and its Response to Microgravity and Disease**

Project Executive Summary

One of the highest priority problems in the current manned space program is orthostatic intolerance experienced by astronauts upon their return to the normal gravitational environment. This problem has been well known since the earliest days of manned spaceflight, and has been intensely investigated in in-flight studies and in many land-based simulation (bed-rest) studies. A number of countermeasures have been proposed and evaluated, but no effective and practical countermeasure has been developed to date. The number of hypotheses still under consideration and the lack of a single unifying theory of the pathophysiology of orthostatic intolerance testify to the difficulty of the problem.

Computational models of the cardiovascular system can help in this situation in that they provide a rational framework that quantitatively defines interactions among complex cardiovascular parameters and supports the clinical interpretation of experimental results and testing of hypotheses. Models also permit predictions of the impact of specific countermeasures in the context of various hypothetical cardiovascular abnormalities induced by microgravity.

These same models may also play a useful role in clinical medicine, for example, by improving the organization and interpretation of multiparameter physiologic data in intensive care units, and the tracking of a patient's status over time. The model being developed in this research, although aimed primarily at the operational problem of microgravity-induced orthostatic intolerance, therefore has important potential clinical applications.

This project will develop a general, modular model of the cardiovascular system that contains the essential features associated with the effects of gravity, and will use this model to examine the short-term hemodynamic response of the cardiovascular system to abrupt orthostatic transitions. The model will facilitate the understanding of the physiology and treatment (prevention) of OI in post-flight astronauts. We will extend the progress already made over the past 2.5 years, with the following specific aims:

- Enhance the current version of our cardiovascular simulation to better represent the short-term effects of abrupt orthostatic stress.
- Verify the model and use it to investigate and evaluate various hypotheses for OI, and to predict the effects of countermeasures. This objective will require extensive collection and archiving of experimental data from collaborators.
- Complete, document, and disseminate to other investigators a form of the model implemented in JAVA.
- Apply the cardiovascular model to the clinical problem of intelligent patient monitoring both in the context of intensive care and in tracking chronic cardiovascular disease.

Major progress has been made during the first 12 months of the program:

- We have performed extensive sensitivity analyses of the model that allow us to rank order the model parameters according to the impact they have on the transient heart rate response to orthostatic stress. The sensitivity analyses allow us to improve the computational efficiency of the parameter estimation algorithm.
- We have developed and implemented techniques that allow for automated matching of simulation output to given experimental data.
- We have enhanced the design of the simulator by extending the cardiac model to include atria. Addition of atria may improve the model's ability to track experimental stroke volume data at high heart rates.
- We have gathered, formatted, and archived in standardized form tilt and stand test data from the NSBRI bed rest studies and astronaut tilt and stand test data from the cardiovascular lab at Johnson Space Center. This data will be used for model verification and testing of hypotheses of orthostatic intolerance.
- In conjunction with the Beth Israel Deaconess Medical Center, Boston, and Philips Medical Systems (formerly Agilent Technologies) we have begun collecting large amounts of clinical (e.g., fluid input/output and medications) and physiologic (e.g., arterial blood pressure, ECG, central venous pressure) data from patients in intensive care units (ICUs). This database will form the core of a research resource to support the development and evaluation of model-based clinical decision support systems for ICU patients.

Model verification was performed by comparing the simulation output under baseline conditions and at different levels of orthostatic stress to sets of population-averaged hemodynamic data reported in the literature. The model is capable of simulating the transient response to sudden orthostatic stress as well as the steady state hemodynamic response over a wide range of orthostatic stress levels in head-up tilt (HUT) and lower body negative pressure (LBNP).
The sensitivity analyses allow us to identify the parameters of the model that contribute significantly to the transient heart rate response to HUT and to subsequently use this information to fit simulations to surrogate data and single-subject heart rate recordings. We will shortly apply the estimation algorithm to the astronaut data obtained from Johnson Space Center, Houston.

In developing an integrated approach to intelligent patient monitoring, we have started collecting large amounts of clinical and physiologic data from intensive care unit patients. Initial work in this area focused on patient de-identification, time-alignment and fusion of clinical and physiologic data, and the development of a web interface for efficient searching and indexing of the resultant database.

The research presented in this progress report is well within the time frame set forth in the original proposal and the progress made so far does not necessitate any changes to the specific aims of the proposal or the strategy with which the research is pursued.

We intend to pursue the following goals during year 2 of the funding period:

- Refine the estimation routine and start applying the algorithm to astronaut data obtained from Johnson Space Center.
- Continue to enhance the cardiovascular model by assessing the importance of vasoactive hormonal loops and adding them to the model if necessary.

- Continue to gather data from collaborators, convert the data obtained into standard format, archive the data on our central server, and incorporate the data into our analysis of the transient hemodynamic response to stand/tilt and LBNP.
- Continue to acquire clinical and physiologic data from patients in intensive care units. Develop model-based methods to detect and interpret clinically significant hemodynamic events in the multiparameter time series of physiologic signals. Develop tools for statistical analyses (data clustering techniques) and visualization of ICU data to help track the state of the cardiovascular system of patients.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Andrew D. McCulloch, Ph.D.**
ORGANIZATION:	**University of California, San Diego**
PROJECT TITLE:	**Integrated Modeling of Cardiac Mechanical and Electrical Function**

Project Executive Summary

AIMS

Aim 1: To apply our existing techniques for modeling three-dimensional cardiac mechanics and action potential propagation to develop anatomically detailed three-dimensional dynamic finite element models of regional cardiac electromechanics.

Aim 2: To bridge models and data on cardiac metabolism and cellular dynamics with systems models of coronary flow, central hemodynamics, and cardiovascular regulation.

Aim 3: To develop tools for using available wall motion data from medical imaging in man to validate the mechanoenergetic models and identify myocardial constitutive properties.

Aim 4: To apply new models of geometric and constitutive remodeling in response to chronically altered external loading conditions to develop simulations of long-term cardiac adaptation to microgravity.

Aim 5: To implement the models using modular object-oriented software engineering techniques that allow the models to be readily integrated with others through standard broker architectures for software interoperability.

Aim 6: To collaborate with other prospective projects in the Integrated Human Function Core.

KEY FINDINGS/PROGRESS

Significant progress has been made coupling cardiac electromechanical models. One new paper has been published describing a new model in which the sequence of cardiac contraction and relaxation is altered in an anatomically detailed three-dimensional model of the left and right ventricles that also includes a model of the Purkinje fiber network anatomy (Usyk TP, LeGrice IJ, McCulloch AD. Computational model of three-dimensional cardiac electromechanics. *Comput Visual Sci* 2002;4(4):249-257). In subsequent work, the model has been validated against experimental electromechanical maps during normal and ventricular paced beats showing excellent agreement with experimental data.

We have also developed and published one model that couples high energy phosphate fluxes with calcium and magnesium fluxes in the cardiac muscle cell (Michailova A, McCulloch AD. Modeling Ca2+ transients and Ca^{2+} and Mg^{2+} exchange with ATP and ADP during excitation-contraction coupling in ventricular myocytes. Biophys J 2001;81(2):614-629). In this model, ATP and ADP concentrations affected myocyte electrophysiology both through their activity as mobile buffers of calcium and magnesium and through their regulation of key ion pumps in the cell. We are presently extending this model to include a simple model of lactic acid and proton balance as a basis for pH regulation of key currents and transporters.

Model-based methods have been developed to analyze magnetic resonance imaging (MRI) data on cardiac wall motion. MRI "tagging" studies in paced canine hearts has been used to validate the results of the integrated electromechanical model developed in Aim 1.

As a result of the recent NSBRI Exercise workshop in Seattle, models of cardiac electromechanics during exercise will focus on the effects of heart rate, adrenergic stimulation and acidosis. We have developed a preliminary model of adrenergic signaling in the cardiac myocyte that couples to electrophysiology by simulating the effects of β adrenergic receptor stimulation on calcium current via phosphorylation of the L-type channel by protein kinase A.

A new object-oriented modular version of *Continuity* was recently released that has a modular client-server design, very high-level scripting language, a graphical user interface and new three-dimensional viewer.

We have engaged in productive collaborative activities with other members of the Integrated Human Function Core and begun discussions with the Cardiovascular Alterations Team.

IMPACT

These findings of the three-dimensional electromechanical model validate the original premise of the proposal that an integrated cardiac three-dimensional electromechanical model is both computational feasible and physiologically predictive. This is a fundamental advance that paves the way for the other objectives and applications. By including ATP, ADP, H^+ and P_i in the cellular models of cardiac excitation-contraction coupling, we will be in a position to simulate the physiological effects of metabolic inhibition or acidosis during stress. The new model of beta adrenergic signaling is allowing us to starting linking cell signaling mechanisms activated during exercise to altered cardiac electrical and mechanical responses.

The new software, *Continuity 6.0* provides a problem solving environment for integrative modeling that is general enough for both structurally integrated models that couple from single cell to organ system scales and functionally integrated models that couple electrophysiology, mechanics, metabolism and regulatory processes. The methods are generic and thus applicable to other systems such as soft tissues and muscle.

PROPOSED RESEARCH

We will extend the electromechanical models to include more detailed cellular biophysical models of cardiac excitation and contraction whose parameters therefore have greater physiological meaning thus making the models more inherently predictive. These cellular models are developed by our group and the group of Dr. Bers including new models of ionic currents, excitation-contraction coupling, myofilament activation and crossbridge interactions. Since these new models are more detailed and computationally complex, we will also implement more computationally efficient algorithms to solve them. We will also extend the current cellular models model to include the pH regulation of intracellular calcium handling and the regulation of cardiac electrophysiology and contraction by beta adrenergic stimulation via specific actions of protein kinase A. These developments are specifically motivated by the physiological effects of exercise. The next major release of Continuity will include improved facilities for composing and integrating cellular models and for the efficient parallel solution of large-scale whole organ models. Synergistic collaborations with other NSBRI projects will be continued and expanded.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Janice Meck, Ph.D.**
ORGANIZATION:	**NASA Johnson Space Center**
PROJECT TITLE:	**Mechanisms of Post-Space Flight Orthostatic Intolerance**

Project Executive Summary

There is still a significant number of astronauts at Johnson Space Center who suffer from post-flight orthostatic hypotension and presyncope. The mandatory use of fluid loading with salt tablets and water, anti-gravity suits, and the liquid cooling garment has not eliminated the problem. A growing body of evidence suggests that there are major physiological systems that become dysfunctional as a result of space flight. The degree of dysfunction varies from minimal to severe. Several studies have provided evidence that autonomic function is impaired during and after space flight. Additional factors such as local factors, could also be involved. An area that has not been studied in humans is the effects of space flight on nitric oxide physiology and its modulation of blood pressure. The study proposed in this application will continue the pursuit of mechanisms of autonomic dysfunction in presyncopal astronauts. In addition, it will begin to elucidate changes in nitric oxide production and the resulting effects on the cardiovascular system. This study will not have in-flight measurements. All procedures will be performed before launch, on landing day and three days after landing. The study has two specific aims: 1) to compare pre-flight to post-flight changes in responses of veins to adrenergic agonists between presyncopal and nonpresyncopal astronauts; 2) to compare pre-flight to post-flight changes in nitric oxide levels, inducible nitric oxide synthase messenger RNA and protein, cell adhesion molecules associated with endothelial activation, responses to acetylcholine with and without nitric oxide synthase inhibition, and reactive hyperemia responses in the brachial artery, the arm and the popliteal artery in the leg, between presyncopal and nonpresyncopal astronauts. Presyncopal and nonpresyncopal astronauts will be defined by their ability to complete a 10-minute upright tilt test on landing day.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Ferid Murad, M.D., Ph.D.**
ORGANIZATION:	**The University of Texas Health Science Center at Houston**
PROJECT TITLE:	**A Soluble Guanylyl Cyclase Mouse Knock-Out Model**

Project Executive Summary

Original aims of the project:

1. To resolve the genomic structure and identify promoter regions of the α_1 and β_1 subunit genes of soluble guanylyl cyclase (sGC).
2. To initiate the development of a conditional mouse knockout model of soluble guanylyl cyclase utilizing the information obtained in specific aim 1.
3. To initiate studies of transcriptional regulation of sGC genes utilizing the information obtained in specific aim 1.

The key findings of the project:

During the year of research funded by the seed money from NSBRI, progress was made in the cloning of murine α_1 sGC cDNA; resolving the genomic structures for the α_1 and β_1 murine sGC genes; subcloning and initial characterization of their promoter regions, and their chromosomal localization. The resulting research accomplishments were published in PNAS paper (see Appendix B). Utilizing the information on the genomic structure of the β_1 murine sGC gene, the Lox-β_1 sGC targeted vector was generated (see Appendix A). Employing methods established during these studies and data available through NCBI Human Genome Project, the human genomic organization for sGC genes was determined, and characterization of transcriptional regulation of human sGC genes was initiated (see Appendix A).

The impact of the findings:

Despite the fact that sGC was discovered 20 years ago and extensively biochemically characterized very little is known about the regulation of sGC gene expression. Genomic organization of mammalian sGC genes was not resolved. Also, no promoter region for any of the mammalian sGC genes have been isolated or described. Characterizing mammalian sGC genomic organization and the isolation of murine and human sGC promoter regions accomplished by our laboratory will improve understanding of the physiological events connected with regulation of sGC activity on the genomic level. Resolving genomic organization for murine genes provided necessary information and material for developing sGC gene-targeted mouse model. Developing sGC knockout model represents the unique opportunity to study the effects of sGC-cGMP signaling on the level of one gene. Presently, these studies are hampered by lack of selective pharmacological inhibitors, existence of multiple sGC isoforms and inability in most of physiological experiments to clearly separate NO-sGC-cGMP-dependent and directly NO-mediated regulatory pathways. In subsequent research, the null sGC mice will be utilized to examine the role of NO-cGMP signaling in cardiovascular alteration associated with microgravity.

Emerging data in the literature indicate that regulation of sGC transcription could be an important mechanism in the modulation of its activity. However, mechanisms of transcription can not be proven and described in detail without promoter characterization and direct experiments involving regulatory DNA regions for sGC genes. We isolated the promoter regions of the human α_1 and β_1 subunit genes of sGC and demonstrated the capacity of the isolated fragments to drive the transcription. We initiated studies on the mechanisms involved in transcriptional regulation of sGC expression and identified a cell model where we can reproduce modulating the transcriptional activity by different agents for putative promoter fragments of α_1 and β_1 sGC genes. A more precise understanding of the molecular events involved in modulation of sGC expression could have profound pathophysiological significance and could potentially help to develop novel therapeutic strategies minimizing negative side effects.

Research plan for the coming year:
To understand the sGC-cGMP regulatory pathway in cardiovascular function we will obtain an animal model with myocardium-specific and smooth muscle-specific disruption of sGC gene expression.
In order to achieve this goal:

a. β_1 sGC lox knockout mice will be generated utilizing the β_1 murine sGC gene Lox-β_1 sGC targeted vector created in our laboratory previous year;

b. β_1 sGC-lox mice will be bred with αMyHC-Cre mice containing a myocardium specific Cre-recombinase, to generate myocardium specific β_1-sGC-Cre/lox knockout mice and [SM-CreER(T2)(ki)] containing smooth muscle-specific *Cre* recombinase to generate smooth muscle-specific β_1-sGC-Cre/lox knockout mice.

Hemodynamic consequences resulting in the elimination of sGC activity in the cardiovascular system of knockout mice versus wild type will be assessed by performing following studies:

a. Embryonic development of the heart in knockout mice will be analyzed and compared to heart development in wild-type mice.

b. Postnatal development of the heart in knockout mice will also be analyzed.

c. General characterization of knockout vs wild type, including daily to recording of the general appearance, body weight, temperature, ECG, arterial blood pressure and heart rate and cardiac Doppler measurements.

Obtained knockout animals will be used subsequently to determine the role of sGC pathway deficiency in the development of orthostatic intolerance that occurs during re-adaptation to gravity. The established tail-suspended rodent model to simulate microgravity conditions will be used to study the effects of microgravity on cardiac function of knockout and wild type mice.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Chester A. Ray, Ph.D.**
ORGANIZATION:	**Pennsylvania State University**
PROJECT TITLE:	**Effect of Simulated Microgravity on the Vestibulosympathetic Reflex in Humans**

Project Executive Summary

Despite the long recognized problem of post-space-flight orthostatic intolerance (OI), the physiological mechanism(s) responsible for this condition remains unresolved. Impaired sympathetic activation is a possible factor for post-space flight OI. One possible mechanism that may be responsible for impaired sympathetic nerve activity after space flight is the vestibulosympathetic reflex. Microgravity has been demonstrated to elicit marked morphological and physiological changes to the vestibular system. Despite this information, no studies to date have examined if the vestibulosympathetic reflex is altered after space flight or its ground-based model for studying autonomic and cardiovascular function, head-down tilt bed rest. The specific aims and hypotheses of this research project are: 1) To determine muscle sympathetic nerve activity (MSNA) responses to head-down neck flexion (HDNF) before and after 1 and 7 days of 6° head-down tilt bed rest (HDBR). HDNF has been used in our laboratory to activate the vestibular system (i.e., otolith organs) in humans and has been shown to increase MSNA. We hypothesize that MSNA responses to HDNF will be attenuated after HDBR and that the attenuation of MSNA will increase as a function of HDBR duration. If this hypothesis is true, this would be the first evidence that the vestibular system may participate in regulating MSNA after HDBR and possibly space flight; and 2) To determine MSNA responses to HDNF during lower-body negative pressure before and after HDBR. We have shown that MSNA is augmented by HDNF during lower-body negative pressure. Thus in healthy adults, the vestibulosympathetic reflex can help defend against orthostatic challenges by increasing MSNA. We hypothesize that the increase in MSNA by HDNF during lower-body negative pressure will be attenuated after HDBR. Therefore, after HDBR the vestibulosympathetic reflex will be impaired and will not be able to help defend against an orthostatic challenge by increasing MSNA. This finding would give credence to the concept that alterations in the vestibulosympathetic reflex may participate importantly in post-space flight OI. These findings should have important implications in understanding the cause of OI following space flight. Moreover, these studies should provide a solid rationale for developing countermeasures involving stimulation of the vestibular system during space flights in order to minimize post-space-flight OI.

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Artin A. Shoukas, Ph.D.**
ORGANIZATION:	**Johns Hopkins University School of Medicine**
PROJECT TITLE:	**Mechanics of Cardiovascular Deconditioning**

Project Executive Summary

Changes in cardiac output result from the altered, myocardial contractility or through changes in venous filling pressure via the Frank Starling mechanism. Our laboratory has previously shown the importance of veno regulation by the carotid sinus baroreceptor reflex system on overall circulatory homeostasis, and in particular the regulation of cardiac output. Decreases in SV responses to an orthostatic challenge are the seminal patho-physiologic observation after space flight. In addition there is evidence that there is a significant degree of cardiac hypertrophy after long during space flight. The exact effects of the hypertrophy on ventricular performance is clearly unknown and could significant contribute to the ortho static intolerance after long term space flight. Our proposal aims to test our hypothesis that alterations in venous capacitance function by the carotid sinus baroreceptor reflex system is an important determinant of the cardiac output response seen in astronauts after returning to earth from long term exposure to micro gravity. In addition the physiological effects of cardiac hypertrophy on orothostatic intolerance will be determined. We will use the hind limb unweighted rat model to simulate the patho-physiological effects as they relate ` to cardiovascular deconditioning in micro-gravity. To determine mechanisms of impaired stroke volume responses integrated cardiovascular function (in vivo) and contractile reserve will be tested using miniaturized conductance micro-manometry catheters. The role of cardiac atrophy in cardiovascular deconditioning will be tested using magnetic resonance imaging to noninvasively measure cardiac mass. Since venous capacitance function and arterial resistance determine ventricular preload and after load respectively, mechanisms of impaired contractile responses in both arterial, venous, and pulmonary vascular beds will be studied. Molecular mechanisms of endothelial dependent (eg. nitric oxide), and independent (Ca^{2+} homeostasis and vascular smooth muscle myofilament Ca^{2+} sensitivity) vascular hypo responsiveness to sympathetic stimulation will be studied, using vascular contractility bioassays (in vitro), pressure-dimension analysis both (in vivo and in vitro), and intracellular Ca^{2+} measurement (fluorescence spectrophotometry). We plan to test novel, countermeasures based on mechanisms that impair both cardiac output responses and vascular hypo responsiveness in our rat model. These studies will provide important new data concerning normal capacitance vessel function in compensating for postural blood volume redistribution, test our novel hypothesis regarding the pathogenesis of orthostatic intolerance following micro-gravity exposure, and provide insights into potential countermeasures and therapies to prevent problematic postural hypotension on reentry. Our laboratory currently performs experiments from chronic instrumented animals to the cellular and molecular mechanisms involved in cardiovascular regulation and control.

KEY FINDINGS and SUMMARY OF PROGRESS

1. We have demonstrated impaired CO responses to an orthostatic challenge in rats following HLU which recovers in ~60hrs.
2. We have demonstrated that after HLU, unstressed venous vascular volume is increased following HLU and can no longer decrease in response to sympathetic stimulation. This

supports our primary hypothesis and may underlie the mechanisms leading to an exaggerated fall in stroke volume seen in astronauts.

3. Using cardiopulmonary bypass studies in which cardiac output is fixed, we have demonstrated that venous an total circulatory capacitance is increased following HLU.
4. We have demonstrated impaired alpha-1-AR and non–alpha mediated responses in large arteries (aorta) of HLU animals. We have also demonstrated that the observed vascular contractile hyporesponsiveness is reversible with time, In addition, alpha-1AR specific abnormalities in mesenteric microvessel responsiveness appear to be present.
5. We have observed a decrease in alpha-1AR specific radioligand binding in aortic vessels from HLU animals.
6. We have demonstrated both an endothelial dependent and endothelial independent component which contributes to vascular hyporesponsiveness following HLU.
7. We have demonstrated an upregulation of the regulatory subunit of myosin light chain phosphatase, a key component of the Rho kinase/Ca+ sensitivity mechanisms which regulates vascular contraction. This could contribute to the attenuated agonist induced endothelial independent contractile responses observed in vessel ring preparation.
8. We have established the technique for measurement of phosphorylated myosin light chains as a biochemical determinant of downstream contractile events.
9. We have demonstrated vascular hyporesponsiveness in the large pulmonary arteries of the HLU rats. This vascular hyporesponsiveness is obliterated with nitric oxide synthase inhibition suggesting that increased nitric oxide production may be mediating this impaired contractile response.
10. We have demonstrated an impaired heart rat and blood pressure and contractility response to a orthostatic stimulus (transient bilateral carotid occlusion) in a HLU mouse model using pressure-volume loops.
11. We have developed an external non-invasive mechanical prototype device, in conjunction with the Applied Physics Laboratory of JHU, that peristaltically pumps blood from lower extremities and abdomen towards the heart to maintain stroke volume and cardiac output during an orthostatic challenges. A notice of invention and non-disclosure has been filed with Johns Hopkins University

RESEARCH AREA:	**Cardiovascular Alterations**
PRINCIPAL INVESTIGATOR:	**Gordon H. Williams, M.D.**
ORGANIZATION:	**Harvard – Brigham and Women's Hospital**
PROJECT TITLE:	**Influence of Gender and Age on Renal and Cardio-Endocrine Responses to Simulated Microgravity**

Project Executive Summary

Orthostatic intolerance remains an operational problem following space flight, and has been observed to be more pronounced among women than among men. In addition, there is growing evidence that cardiac dysrhythmias may pose a threat to the health of space travelers.

In our previous studies we observed that subjects on a constant high dietary sodium intake during simulated weightlessness have varying degrees of sodium balance response. Furthermore, the variability in response correlated with orthostatic tolerance and subjects age. Our previous findings also are consistent with an increased basal tone of the RAAS in many subjects during simulated microgravity. These findings are even more intriguing since several subjects demonstrated changes in electrical stability of the myocardium following microgravity. Chronically increased angiotensin II, and particularly aldosterone. levels resulting from bed rest and their effects on myocardial remodeling may be at least in part responsible for these changes. It is not known whether myocardial electrical changes will occur in women or older individuals, or what role the RAAS might play. In the recent Randomized Aldactone Evaluation Study (RALES) trial of spironolactone in patients with congestive heart failure, it was shown that a low dose of spironolactone was protective against sudden cardiac death. Thus, theoretically, if microgravity increases the risk for ventricular dysrhythmias, activation of the RAAS must contribute to this increased risk. Then, a low dose of spironolactone (an aldosterone receptor blocker) may be protective against this phenomenon. Finally, in a previous study we documented that midodrine improved acute orthostatic intolerance following sixteen days of simulated microgravity

We have no data in women and only limited data in older subjects. Thus, the overall goal of this study is to assess in women (a population at increased risk for orthostatic intolerance) and in men over the age of 50 (an age range more consistent to that of astronauts than the <35 year olds involved in our previous studies) the impact of simulated microgravity on volume-regulating systems. A secondary objective is to search for any correlation between changes in these systems and changes in myocardial electrical stability. A final goal is to determine the effect of two potential countermeasures: midodrine in women and low-dose spironolactone in older men. The same methodologies we previously applied to the study of predominantly younger men will be applied in this study. This study is closely related to a companion study "Influence of Gender and Age on Cardiovascular Responses to Simulated Microgravity" by Richard J. Cohen, M.D., Ph.D., Principal Investigator. His study will investigate whether there appear to be any correlative factors between perturbations of the RAAS and effects on myocardial electrical stability.

This work has implications for the treatment and prevention of maladaptive hemodynamic responses experienced by astronauts in flight and on return to Earth. It will increase our understanding of the mechanisms by which weightlessness changes volume and sodium homeostasis, and possibly cardiac electrical stability, thereby, providing entree to develop appropriate countermeasures. Perhaps most importantly, it will broaden our database to include older individuals and women, two groups who are well represented among our population of current and future space travelers. Finally, the results of these studies may further our understanding of the pathophysiology of alterations in volume homeostatic mechanisms in cardiovascular diseases such as congestive heart failure.

NSBRI RESEARCH PROGRAM
HUMAN PERFORMANCE FACTORS

Team Leader: **Czeisler, C. A.** **Harvard**

Associate Team Leader: **Jewett, M. E.** **Harvard**

Morin, L. P.	**PI**	**SUNY**	**Circadian and Vestibular System Relationships**	**58**
Weber, E. T.	CO-I	SUNY		
Tosini, G.	**PI**	**Morehouse**	**Long-Term Exposure to Dim Light Desynchronizes the Circadian System of Rats**	**60**
Fukuhara, C.	CO-I	Morehouse		
Sonnenfeld, G.	CO-I	Morehouse		
Turek, F. W.	**PI**	**Northwestern**	**Animal Model for Sleep Loss and Circadian Disruption**	**61**
Reid, K. J.	CO-I	Northwestern		

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**George C. Brainard, Ph.D.**
ORGANIZATION:	**Jefferson Medical College of Thomas Jefferson University**
PROJECT TITLE:	**Optimizing Light Spectrum for Long Duration Space Flight**

Project Executive Summary

Risk factors for the health and safety of astronauts and NASA ground control workers include disturbed circadian rhythms and altered sleep-wake patterns. These physiological changes can result in decrements in alertness, concentration, and performance, all of which threaten the safety of personnel and the objectives of space missions. In studies of astronauts and NASA ground control workers, light treatment has been used as an effective countermeasure to provide entrainment of sleep-wake patterns and other circadian rhythms. It is important to optimize light as a countermeasure for circadian and sleep disruption in space flight missions. For civilians, light treatment is being tested for improving circadian entrainment and enhancing both performance and alertness in shift workers. A recent Congressional report estimates that 20 million full time workers in the United States are shift workers and that they have increased health problems including higher risk to cardiovascular disease, gastrointestinal distress, as well as cognitive and emotional problems. The long term goal of our research is to determine the best wavelengths of light for use as a countermeasure during long duration space flight, as well as for adjusting circadian and sleep disruption in civilians.

Towards achieving this aim, an eight wavelength action spectrum (the relative effectiveness of different wavelengths for eliciting a biological response) has been established to help identify the photoreceptor system for light regulation of melatonin in humans (Brainard et al., *J. Neuroscience* 2001). Ultimately, this action spectrum may be used as a tool for investigating the action spectrum and related photoreceptor system involved in circadian entrainment and phase-shifting. One specific aim of the current research is to extend the action spectrum for light-induced plasma melatonin suppression using monochromatic wavelengths below 440 nm and above 600 nm. These wavelengths are relevant to astronauts who have to adapt to extraterrestrial environments that have spectral characteristics different from those found on earth. As examples, there is substantially increased short wavelength light below 440 nm outside of the earth's atmosphere and Martian skylight has an abundance of long wavelengths above 600 nm. Data from the proposed studies can be used to optimize the lighting environment of astronauts on long term missions. **Specifically, these data can be used to 1) improve light treatment as a countermeasure for circadian and sleep-wake disruption in NASA space flight missions, 2) identify the best spectral transmission for space suit visors and the windows used in space vehicles and habitats, and 3) engineer the ideal spectral distribution for illumination of general living quarters during space exploration.**

The specific aims of the current NSBRI project are: 1) test the hypothesis that wavelengths below 440 nm and above 600 nm are active in regulating melatonin secretion; 2) test the hypothesis that there will be a loss of sensitivity to monochromatic light when the eyes are <u>not</u> pharmacologically dilated during the melatonin suppression trials; and 3) test the hypothesis that there will be a shift in spectral sensitivity of light regulation of melatonin when the eyes are <u>not</u> pharmacologically dilated.

For the first specific aim, a preliminary key finding is that the fluence-response relationship between 420 nm exposure and melatonin suppression is univariant with wavelengths between 440 and 600 nm. Two recent action spectra suggested that a novel vitamin A_1 retinaldehyde-based photopigment may be primarily responsible for melatonin suppression in humans (Brainard et al., *J. Neuroscience* 2001; Thapan et al., *J. Physiology* 2001). There was poor agreement between these action spectra, however, on the relative sensitivity to monochromatic light at 420-424 nm, allowing for the possibility that the action spectra could be matched to a cryptochrome absorption spectrum. These 420 nm dose-response data suggest that the melatonin action spectrum of Brainard et al. (2001) fit an absorption spectrum for a novel opsin photopigment which mediates photoreception for the human retinohypothalamic tract. **This finding has practical importance to astronauts in long duration space flight since 420 nm irradiance is greatly increased outside the earth's atmosphere (e.g. Space Shuttle and International Space Station).**

For Specific Aim 2, a preliminary key finding is that there appears to be a loss of sensitivity to 460 nm light for melatonin regulation when the pupils are free to respond to light stimuli. Further investigation is needed to specifically quantify how much loss is due to pupil regulation. **It will be important to further characterize both wavelength and intensity responses in freely constricting eyes in order to practically utilize action spectrum data in optimizing light as a countermeasure to circadian disruption during long duration space flight.** In almost all cases, astronauts' eyes will be freely reactive during long duration space flight.

Finally, additional progress that is relevant to all three specific aims involves the design and initial construction of a new Light Emitting Workstation with three times the photon output of current Light Emitting Workstations. This high output workstation is particularly important to the planned work with both short wavelength light below 440 nm and long wavelength light above 600 nm. If operational, the light output of this equipment will be so powerful that it will require a separate laboratory sequestered from the lower power workstations. The university has recently provided the needed laboratory space for this equipment along with the necessary waterlines and drains for cooling and 220 volt electrical supply for power.

Proposed Research Plan for the Coming Year

1) Complete data analysis on 420 nm dose response curve.
2) Complete pupillary project.
3) Complete building high intensity light exposure system.
4) Initiate work on a dose response curve above 600 nm.

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**Charles A. Czeisler, Ph.D., M.D.**
ORGANIZATION:	**Harvard – Brigham and Women's Hospital**
PROJECT TITLE:	**Circadian Entrainment, Sleep-Wake Regulation and Performance During Space Flight**

Project Executive Summary

Optimal human performance during space flight requires astronauts to maintain synchrony between the circadian pacemaker, which regulates the timing of sleep, endocrine function, alertness and performance, and the timing of the imposed sleep-wake schedule. Operational demands of space flight necessitate that humans live on day lengths different than the 24-h solar day of Earth (Dijk et al., 2001). Due to orbital mechanics, astronauts are commonly scheduled to the near equivalent of a shorter-than-24-hour day length in Earth orbit on space shuttle missions; moreover, they will be scheduled to the 24.65-h solar day of Mars on the planned exploration class mission to Mars.

Over the past ten years, we have successfully implemented a new technology for shuttle crewmembers involving bright light exposure during the pre-launch period to facilitate adaptation of the circadian timing system to the inversions of the sleep-wake schedule often required during dual shift missions (Czeisler et al. 1991). However for long duration space station missions it will be necessary to develop effective and attainable countermeasures that can be used chronically to optimize circadian entrainment during extended duration missions.

The purpose of this 65-day long between subjects randomized study is to test three specific hypotheses aimed at evaluating entrainment of the human circadian pacemaker to longer-than-24-hour days.
Specific aim 1: To test the hypothesis that synchronization of the human circadian pacemaker to a sleep-wake and light-dark schedule with an imposed period ~4% longer than the pacemakers intrinsic circadian period will be disturbed in men and women;
Specific aim 2: To test the hypothesis that this disturbed circadian synchronization will result in the secretion of the sleep-promoting hormone melatonin during the waking day, disturbed sleep, reduced growth hormone and cortisol secretion, and impaired performance and daytime alertness;
Specific aim 3: To test the hypothesis that two relatively brief (45 minute) daily exposures to evening bright light (~10,000 lux) will establish a normal entrained circadian phase, in subjects whose imposed sleep-wake and light-dark schedule is ~4% longer than their intrinsic period, resulting in improved sleep consolidation, undiminished endogenous growth hormone and cortisol secretion and enhanced daytime alertness and performance as compared to subjects on the same schedule with out the evening bright light exposure.

These hypotheses are based on the results of our preliminary data which indicate that: (a) the period of the human circadian pacemaker after release from entrainment to the 24-hour day is near to but on average slightly longer than-24-hours (Czeisler et al. 1999), (b) the 24.6-h day is outside the range of entrainment of the human circadian pacemaker in the presence of a weak environmental synchronizer (Wright et al., in press), and (c) intermittent exposure to bright light is a cost effective means of resetting the human circadian pacemaker with respect to power use and astronaut time compared to continuous exposure to light (Rimmer et al., 1999).

We have completed five experiments. This effort amounts to 325 subject test days in the laboratory. Originally we proposed to complete 260 subject test days per year and are thus ahead of schedule. Data collected include: Core body temperature, blood samples (melatonin), Urine samples, Sleep and waking EEG recordings, Subjective sleep quality, Actigraphy, Light intensity, neurobehavioral performance and mood. The successful collection of these data will allow us to test hypotheses 1, 2, and 3 of the project. Data analyses are currently in progress.

The plans for the near future are to continue testing subjects on the Earth and Mars day, analyze data collected, and to test as a countermeasure the ability of brief pulses of bright light to synchronize humans to a dim light-dark cycle for the Earth and Mars day lengths.

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**David F. Dinges, Ph.D.**
ORGANIZATION:	**University of Pennsylvania School of Medicine**
PROJECT TITLE:	**Countermeasures to Neurobehavioral Deficits From Partial Sleep Loss**

Project Executive Summary

This project is concerned with identifying ways to prevent neurobehavioral and physical deterioration due to inadequate sleep and sleep placed at different times across the twenty-four hour day in astronauts during long-duration manned space flight. The performance capability of astronauts during extended-duration space flight depends heavily on achieving recovery through adequate sleep. Even with appropriate circadian alignment, sleep loss can erode fundamental elements of human performance capability including vigilance, cognitive speed and accuracy, working memory, reaction time, and physiological alertness. When attempting to sleep and perform at an adverse circadian phase, the magnitude and time course of sleep loss and consequent deficits in neurobehavioural functioning are significantly affected. Adequate sleep is essential during manned space flight not only to ensure high levels of safe and effective human performance, but also as a basic regulatory biology critical to healthy human functioning.

There is now extensive objective evidence that astronaut sleep is frequently restricted in space flight to averages between 4 hr and 6.5 hr/day. Chronic sleep restriction during manned space flight can occur in response to endogenous disturbances of sleep (motion sickness, stress, circadian rhythms), environmental disruptions of sleep (noise, temperature, light), and curtailment of sleep due to the work demands and other activities that accompany extended space flight operations. The mechanism through which this risk emerges is the development of cumulative homeostatic pressure for sleep across consecutive days of inadequate sleep. Research has shown that the physiological sleepiness and performance deficits engendered by sleep debt can progressively worsen (i.e., accumulate) over consecutive days of sleep restriction, and that sleep limited to levels commonly experienced by astronauts (i.e., 4 - 6hr per night) for as little as 1 week, can result in increased lapses of attention, degradation of response times, deficits in complex problem solving, reduced learning, mood disturbance, disruption of essential neuroendocrine, metabolic, and neuroimmune responses, and in some vulnerable persons, the emergence of uncontrolled sleep attacks.

The prevention of cumulative performance deficits and neuroendocrine disruption from sleep restriction during extended duration space flight involves finding the most effective ways to obtain sleep in order to maintain the high-level cognitive and physical performance functions required for manned space flight. There is currently a critical deficiency in knowledge of the effects of how variations in sleep duration and timing relate to the most efficient return of performance per unit time invested in sleep during long-duration missions, and how the nature of sleep physiology (i.e., sleep stages, sleep electroencephalographic [EEG] power spectral analyses) change as a function of sleep restriction, the timing of sleep and performance degradation. The primary aim of this project is to meet these critical deficiencies through utilization of a response surface experimental paradigm, testing in a dose-response manner, varying combinatiôns of sleep duration and timing, for the purpose of establishing how to most effectively limit the cumulative adverse effects on human performance and physiology of chronic sleep restriction in space operations.

Although there is evidence that the less sleep obtained, the greater the waking deficits, experiments have found that for acute periods supplementing a reduced anchor sleep period with a nap has the potential to enhance performance, due to the exponential recovery of neurobehavioral functions relative to sleep duration. During the past 3 years we have been using a response surface experimental approach to systematically determine the chronic (10-day) effects of 18 sleep schedule conditions that involve restricted nocturnal anchor sleep alone and in combination with varying durations of restricted daytime naps on performance, mood, sleep, circadian physiology and hormones. The resulting preliminary response surface maps (RSMs) derived from this dose-response experiment indicate that total sleep time per 24 hours is a prime determinant of cumulative neurobehavioral deficits, and that combining a restricted nocturnal anchor sleep with a midday nap can attenuate cumulative deterioration in performance. In order to complete our understanding of how to optimize performance in the face of restricted sleep in space flight, we have reversed the circadian placement of these 18 anchor sleep + nap sleep conditions (i.e., daytime anchor sleep alone and in combination with varying durations of restricted nocturnal naps.

To develop this response surface model, 90 healthy men and women will undergo a 14-day ground-based laboratory protocol involving random assignment to one of 18 sleep-ration cells, each involving the same sleep ration for 10 consecutive days. The sleep-ration assignments involve 4 nocturnal anchor sleep durations (4.2, 5.2, 6.2, 8.2 hr) and 6 diurnal nap sleep durations (0.4, 0.8, 1.2, 1.6, 2.0, 2.4 hr) crossed to yield a total of 4 anchor-sleep-only conditions, and 14 anchor + nap sleep conditions, and spanning a dynamic range of cumulative sleep debts (i.e., from 0 to 40 hr in a 10-day period). Subjects undergo a wide range of quasi-continuous neurobehavioral performance tests and continuous physiological monitoring of waking EEG, sleep PSG, behavioral motility, and core body temperature, while living in the laboratory for 14 consecutive days. The laboratory environment is designed to simulate the low light, tight quarters, and lack of social contact with the outside world that will characterize long-duration space flight.

The data collected from N=91 subjects (i.e. 1,274 laboratory 24-hour protocols) over the past 3 years investigating restricted nocturnal anchor sleep alone and in combination with varying durations of restricted diurnal naps have been used to create RSMs for different neurobehavioural and sleep variables, including number of psychomotor vigilance task (PVT) lapses, cognitive throughput, subjective sleepiness and sleep efficiency. As data from the present study are obtained, we will (1) establish RSMs during simulated night work; and (2) by comparison with the RSMs for the study already completed, determine the role of initial circadian phase of work and sleep on the cumulative rate of impairment from chronic sleep restriction. In addition, these data will be incorporated into our original RSMs, to provide a more complete picture of the effects of restricted sleep schedules, with sleep placed at different circadian phases, on neurobehavioural functioning, sleep physiology and neuroendocrine parameters.

Sleep duration and timing are being covaried in this project at two sleep-conducive circadian phases, but counterintuitive to what would normally be expected for sleep duration: (1) anchor sleep during the daytime and (2) nap sleep during the night. Although scientific evidence strongly supports the view that the less sleep obtained, the greater the likelihood of waking deficits, both laboratory and field studies have demonstrated that a brief preplanned or preemptive nap (0.4 hr to 2.4 hr) may have the potential to sustain optimal performance capability when total sleep time is markedly curtailed. The basis for this disproportionate benefit from a relatively brief nap was recently discovered to be the result of a saturating exponential function, such that the first few hours of sleep net the greatest recovery. Thus, the disproportionate recovery potential of naps may be due to the exponential recovery of neurobehavioral performance functions in relation to sleep duration. This exponential process appears to parallel the time course of EEG slow wave activity (SWA obtained by power spectral analysis) during sleep, which is believed to manifest the physiological homeostatic drive for sleep. The data we have gathered to date in the initial experiment support the conclusion that a dual sleep period with anchor sleep placed nocturnally and an afternoon nap longer than 1 hr results in normal to high levels of physiologically deep sleep and prevention of cumulative performance deficits, even when the total time being allocated for sleep in a day is restricted to just over 6 hr. This suggests that the implementation of a brief nap may be one way in which cumulative sleep loss and waking performance deficits could be reversed or prevented. There is however a critical gap in knowledge on how a single daily nap can be most effectively used to eliminate the cumulative effects of chronic sleep restriction. This project will meet this deficiency by developing a dose-response RSM of a wide range of variations in the timing and durations of both anchor sleep and nap sleep, to establish the sleep-wake schedules that most effectively limit the cumulative adverse consequences on performance and physiology of chronic sleep restriction at the levels typically experienced in space flight. Using a wide range of experimental conditions and a two-stage regression approach, we are establishing a response surface model (RSM) of the countermeasure effectiveness of multiple combinations, timings and durations of anchor sleep and scheduled naps to test the hypothesis that such combinations can prevent the neurobehavioral performance deficits that accumulate within and across days of chronic sleep restriction. We are also systematically evaluating the relationship between sleep and circadian physiology and waking performance. Such data will help establish the extent to which homeostatic physiological processes during sleep respond to chronic sleep restriction.

To date we have completed the study of N=9 subjects in this protocol, for a total of 126 24-hour days in the Sleep and Chronobiology Laboratory. The slightly slower data acquisition rate in year 01 was necessitated by administrative, logistical and equipment issues that required resolution prior to data acquisition commencing. An aggressive data acquisition rate is planned for years 02 and 03, which will ensure a complete data set by end of year 03. We successfully managed a similar accelerated data acquisition phase in the 2nd and 3rd years of the first study, which ended with1 additional subject than was needed (i.e. N = 91) for RSMs. Analysis of the polysomnographic, neurobehavioral and neuroendocrine data is underway on the data collected from the completed subjects, so that we may integrate this data into our existing response surface models.

Prior to data collection for this protocol we acquired new physiologic recording equipment, notably the Suzanne ambulatory/ attended sleep recording system (at no cost to the project) provides enhanced ability to conduct electroencephalographic (EEG) recordings, in addition to full polysomnographic assessment for up to 24 hours, combined with real time recording ability of subjects performing at the NAB consoles, to assess for slow eye lid closures, and other physical correlates of increased sleepiness levels. In addition, we will continue using a novel non-thrombogenic catheter and blood pump device (Carmeda ConFlo blood pump system) that allows for rapid sampling (15-min. intervals) for an extended period of time. This innovative design allows us to collect blood samples for a 25-hour duration, without having to flush the vein with heparin, and thereby reducing burden on the subject.

We have continued with the development of RSMs using data collected in our initial study, looking at further neurobehavioural variables and including sleep variables (e.g. sleep efficiency), in addition to further analysis of the neuroendocrine changes associated with chronic partial sleep deprivation, and have presented this data at the national sleep conference (annual meeting of the Associated Professional Sleep Societies [APSS], June, 2001).

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**Charles A. Fuller, Ph.D.**
ORGANIZATION:	**University of California, Davis**
PROJECT TITLE:	**Primate Circadian Rhythms in the Martian Environment**

Project Executive Summary

To maintain health and homeostasis, an organism must regulate each of its physiological systems in concert with all of the others and with the external environment. The Circadian Timing System (CTS) has evolved to allow coordination of an organism's physiology and behavior both internally and with the external 24.0 hr terrestrial day. The mammalian CTS is adapted to the lighting environment found on Earth. As we move toward exploration-class space missions, we will be exposing astronauts to non-Earth environments for increasing lengths of time. Changes may include altered gravity and spectral, intensity and day-length differences. This raises the concern of whether or not humans will be able to synchronize to such an alien environment. For example, a Mars-type exploration would entail stays on Mars of one to two years. Compared with the Earth, the Martian environment has a photic spectrum shifted to the red, low illumination level, a periodicity of 24.62 hr, and a 0.38 G gravitational field. The mammalian CTS is most sensitive to light of the blue-green wavelengths and adapted to synchronize to a 24.0 hr day. In addition, light must be relatively bright to affect the CTS of primates, especially humans. Further, altered CTS function including rhythm amplitude and wave form, sensitivity to light, and CTS period, have been reported in both the microgravity environment of space flight and in hyperdynamic fields on the Earth. This program will examine the ability of primates (male and female rhesus monkeys) CTS to cope with the Martian environment. The first three experiments will examine responses to the Martian day, while the last experiment will examine the effects of G on the period of the circadian pacemaker. Experiment 1 will examine the ability of the CTS to synchronize to the Martian photic (spectrum and period) environment. We will examine long-term (4-month) physiological and behavioral responses. Experiment 2 will similarly examine long-term responses to a photic environment composed of a Martian day and Earth light spectrum. Experiment 3 will use the primate model to initiate the development of countermeasures to assure optimum entrainment of the CTS. This experiment will examine the effects of timed bright light pulses on CTS entrainment. Using the forced desynchrony protocol, experiment 4 will examine the effects of 1.0, 1.5 and 2.0 G on the period of the circadian pacemaker. We will develop a G vs. period model to predict the effect of the 0.38 G Martian environment on the period of the circadian pacemaker. This model will be used to develop countermeasure requirements to be tested in experiment 3. Thus, this program will develop a primate model to evaluate physiological and behavioral consequences of long-term exposure of male and female subjects to altered lighting and gravitational environments.

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**Megan E. Jewett, Ph.D.**
ORGANIZATION:	**Harvard – Brigham and Women's Hospital**
PROJECT TITLE:	**Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure**

Project Executive Summary

The Original Specific Aims of our Project:

Specific Aim 1: To further develop and refine our 'Dynamic Stimulus Processing' Light Model so that it can accurately predict the phase and amplitude of the human circadian system under any lighting conditions, especially those which occur in space. This will be done using data from four completed studies of the effects on the human circadian system of: *i*) three-cycles of brief bright light pulses; *ii*) three-cycles of extended bright light pulses; *iii*) three-cycles of extended low- and moderate-intensity light pulses; and *iv*) single- and double-cycles of amplitude-suppressing critically-timed extended bright light pulses.

Specific Aim 2: To validate the Light Model refined above in Specific Aim 1 using data from four other completed studies of the effects on the human circadian system of: *v*) single-cycle patterns of brief bright light pulses; *vi*) single-cycle extended bright light pulses; *vii*) single-cycle extended light pulses across a wide range of intensities; and *viii*) sleep-wake/light-dark schedules with a wide range of periods (11-h, 20-h, 23.5-h, 24-h, 24.6-h, 28-h, 42.85-h), different light intensities during wake (1, 8, or 15 lux), and with or without a single exposure to an extended bright light stimulus (in the 11-h condition only).

Specific Aim 3: To incorporate the Light Model refined and validated above in Specific Aims 1 and 2 into our mathematical Neurobehavioral Performance Model, which will then be validated against experimental performance data collected under the wide variety of lighting conditions encompassed in the eight studies described above in Specific Aims 1 and 2.

Specific Aim 4: To develop a user-friendly *Circadian Performance Simulation Software (CPSS)* package that can be used to specify appropriate light schedules as a countermeasure to the poor performance and sleep quality associated with circadian misalignment in space.

The Key Findings of the Project:

1) The current statistical models used to fit core body temperature collected during Constant Routine conditions must be modified to take into account the amplitude recovery dynamics of the human circadian pacemaker.

2) When on non-24-hour light/dark schedules, the human circadian pacemaker shows a systematic phase modulation, even when the light levels during wake are very dim (~15 lux).

3) Our Light Model can be incorporated into our Neurobehavioral Performance Model to allow us to predict performance even under unusual lighting and scheduling conditions, such as those experienced by NASA personnel.

4) Our user-friendly *Circadian Performance Simulation Software (CPSS)* package allows scientists to better design research protocols and to easily test and generate scientific hypotheses. The *CPSS* allows NASA personnel and other schedule designers to test the effects of various schedules on performance in order to enhance crew member or employee performance.

5) The Actiwatch-L tends to underestimate the amount of light exposure, but this can easily be corrected by a transformation function.

<u>The Impact of these Findings</u>:

1) The impact of finding 1 above is that we have needed to design and compare several alternative statistical models of CR core body temperature in order to determine which best encompasses the amplitude recovery dynamics of the human circadian pacemaker.

2) The impact of finding 2 above is that we need to consider whether a) there might be some non-photic cue inducing this modulation; or b) the effects of dim light might be greater than we had previously believed. Another impact is that scientists using such non-24 hour forced desynchrony protocols must be aware that there are slight day-to-day changes in period, even though the overall period is quite stable.

3) The impact of findings 3 and 4 above are that we can now offer NASA personnel, schedule designers, clinicians and scientists a tool to enhance their ability to plan the best sleep-wake and light exposure schedules for their particular needs.

4) The impact of finding 5 above is that the Actiwatch-L may prove to be an excellent method for gathering input for our Light Model, but the data it provides must be transformed prior to being input into our model.

In addition, from our interactions with NASA and NSBRI personnel about their current needs relative to using our Light and Neurobehavioral Performance Models to schedule and deliver appropriate lighting exposure for the proper entrainment of NASA crewmembers and ground crew during missions, we have learned that it is important that we also consider both how light exposure and sleep/wake data can be easily gathered and input into our models, as well as how scheduled light exposure as a countermeasure can be easily delivered to NASA personnel, both on the ground and in space. Therefore, we have added the following fifth Specific Aim to our project:

<u>Specific Aim 5</u>: To assess the applicability of currently-available portable light-measuring/actigraphy devices and light-emitting devices to be used, respectively, as inputs and implementations of the outputs of our Light and Neurobehavioral Performance Models.

<u>Proposed Research Plan for the Coming Year</u>:

<u>Specific Aim 1</u>:

1) To test six alternative statistical models of core body temperature collected under Constant Routine (CR) conditions that allow for changes in circadian amplitude in order to determine which provides the best fit to the data.

2) To fit the statistical model selected to CR data in amplitude suppression studies and use

the fitted growth rates to describe the amplitude recovery dynamics of the human circadian system.

3) To determine whether the higher-order or lower-order pacemaker model best describes the amplitude recovery dynamics.

4) To incorporate whichever is the better pacemaker model into our Light Model and to then simulate each of the four light studies listed to determine how well the model is able to predict their results.

5) To refine the Light Model as necessary so that it accurately predicts the findings of all four of the studies.

Specific Aim 2:

1) To complete the secondary analyses of the non-24-hour day studies so that we have day-by-day phase estimates throughout each of the studies.

2) To use the refined Light Model from Specific Aim 1 to simulate each of the four validation studies in order to determine whether the refined model is able to accurately predict their findings.

3) To refine the Light Model as necessary until it is able to accurately predict all eight studies listed in Specific Aims 1 and 2.

Specific Aim 3:

1) To finish the analysis of the neurobehavioral data from study *vi* in Specific Aim 1 and from study *v* and the remainder of study *viii* in Specific Aim 2.

Specific Aim 4:

1) To improve the graphical outputs of the current version of the *Circadian Performance Simulation Software* to allow the user to more easily visualize the schedule they entered and the models' predictions of circadian phase and neurobehavioral performance.

Specific Aim 5:

1) To determine the accuracy of the Actiwatch-L's light measurements in sunlight versus room lights.

2) To determine the effects of posture on the accuracy of the Actiwatch-L's light measurements.

3) To determine the extent to which using Actiwatch-L data for our model inputs improves the accuracy of our model predictions for shiftworkers.

4) To determine the actual intensity of light reaching the eye for four different light-emission devices.

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**Michael Menaker, Ph.D.**
ORGANIZATION:	**University of Virginia**
PROJECT TITLE:	**A Model of Circadian Disruption in the Space Environment**

Project Executive Summary

In order to discover countermeasures against the deleterious physiological and behavioral consequences of the inevitable disruption of normal circadian rhythmicity produced by the conditions in space, we have first to create a laboratory model of that condition (which for the sake of brevity we are calling "dysphasia"). To be successful such a model must enable us to measure the effects of simulated space conditions on multiple body functions as well as on the temporal relationships of these functions to each other and to the environment. These conditions are fulfilled in large part by our transgenic rat model in which the transcription of the clock gene *Per1* is reported in real time by luciferase. We are able to culture tissues from such rats and to measure the phase of their circadian rhythms in vitro, enabling us to infer their phase relationships in the intact animal. Our aims are first to determine how these phase relationships are disrupted by simulated space conditions, and second to devise counter measures that could in practice be employed by astronauts in space to reinstate normal temporal organization. Of necessity, to be practical, countermeasures must be compatible with the ongoing activities in space vehicles. It is therefore impractical to use the strongest known synchronizing signal, a regular 24-hour light cycle.

We have investigated an alternative synchronizing signal, precisely-timed meals, and have found that its effects are stronger than anticipated and extend deeply into the physiology of the animal. Timed meals set the phase of the circadian rhythms of gene expression in liver, stomach, colon, esophagus, lung, and also the phase of locomotor behavior. Timed meals do not influence the phase of gene expression in the suprachiasmatic nucleus (SCN) or the femoral artery. Our results suggest that timed meals may prove to be a useful partial countermeasure against dysphasia which could be combined with other signals (e.g., melatonin) that preferentially target SCN and/or the cardiovascular system. During the next year we plan to test these hypotheses on transgenic rats made dysphasic by exposure to bright constant light.

The approach outlined above depends on inferences about the behavior of tissues in intact animals based on their behavior in culture. It will be important to confirm these conclusions by direct measurement of the same rhythms in intact animals. This is a technically demanding undertaking, but we are making slow progress by recording luciferase activity with implanted light guides in awake, behaving animals. We will continue to refine this approach.

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**Lawrence P. Morin, Ph.D.**
ORGANIZATION:	**State University of New York – Stony Brook**
PROJECT TITLE:	**Circadian and Vestibular System Relationships**

Project Executive Summary

The series of studies proposed in this grant, "Circadian and Vestibular System Relationships," is entirely novel. There is no scientific literature in existence concerning the relationship between the two systems in the grant title. However, at the time the proposal was submitted, a paper had been just been published in the *Journal of Comparative Neurology* by Shiroyama and colleagues (1999) showing a direct connection between the medial vestibular nucleus and the ventral lateral geniculate nucleus. However, their data were misinterpreted and the projection is actually to a neighboring nucleus, the intergeniculate leaflet (IGL) of the circadian rhythm system. This opened a lot of possibilities that we developed into a proposal.

PROGRESS WITH RESPECT TO THE SPECIFIC AIMS:

Specific Aim 1. <u>Connections between the circadian rhythm system and the vestibular system</u>. The first objective has been completed. Using retrograde tracer applied to the IGL, we have shown neurons in the vestibular system project to a nucleus (the IGL) of the circadian rhythm system. We are presently working on two variations on the anatomical theme. One employs anterograde tracer applied to the medial vestibular nucleus to trace projections to the IGL. The other is a technique novel to this laboratory and has required significant modifications in standard operating procedure. This method uses a transynaptic viral tracer to determine whether two neurons are connected. The method has been successfully implemented in our lab and we are in the process of performing the study to determine if neurons in the medial vestibular nucleus connect to neurons in the IGL that, in turn, project to the circadian clock in the suprachiasmatic nucleus (SCN).

Specific Aim 2. <u>Functional activation of the vestibular and circadian systems by an OKN stimulus</u>. This Aim has not yet been addressed except for the fact that the machine that will deliver the light stimulus for inducing optokinetic nystagmus (OKN) has been built.

Specific Aim 3. <u>Functional activation of the vestibular and circadian systems by a non-locomotor, non-photic stimulus</u>. Functional implications of a vestibular system activating stimulus are being examined. In particular, linear acceleration/deceleration and rotational stimulation were administered to hamsters. After the stimulation, the brains were removed, fixed and processed to determine the extent and location of induction of the immediate early gene, *fos*, as indicated by the presence of FOS protein. The results show a linear relationship between rate of rotation and number of cells in the IGL (among other places) expressing FOS in response to the stimulus. The rhythm phase shift study that is part of this specific aim has not yet been addressed.

IMPACT OF THE RESULTS ON THE SPECIFIC AIMS:
There are two significant points of impact. One concerns the original set of specific aims. Were they realistic and worthy of experimental study? The answer is clearly affirmative. There are no negative changes in the specific aims. We have added rotational stimulation to the originally proposed linear acceleration/deceleration as part of work done for Specific Aim 3. The second point of impact concerns the significance of the system being studied upon health risks during space flight. The vestibular system influences has a generally pervasive influence on normal behavior. Therefore, knowledge about the routes and mechanisms through which this influence is achieved may be important. In particular, sleep and circadian rhythms may be profoundly disturbed by high level vestibular activation, or might be actually facilitated by low level vestibular activation.

RESEARCH PLAN FOR THE NEXT YEAR:
We expect to continue with the approach thus far. In particular, we will complete the anterograde tract tracing studies and the viral tracing studies. This will complete the proposed anatomical work. We will finish the study of vestibular activation on FOS protein induction. We will begin, and largely or fully complete, the study of vestibular activation and circadian rhythm phase shift. We will begin the parallel study of FOS protein induction using the OKN-inducing stimulus.

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**Gianluca Tosini, Ph.D.**
ORGANIZATION:	**Morehouse School of Medicine**
PROJECT TITLE:	**Long-Term Exposure to Dim Lighting Desynchronizes the Circadian System of Rats**

Project Executive Summary

Many biochemical, physiological and behavioral parameters exhibited by organisms show daily fluctuations and most of these daily rhythms persist in constant conditions, thus, demonstrating that they are driven by endogenous oscillators. The rhythms that persist in constant conditions with a period close to 24 hours are called circadian rhythms. One the most important aspects of space flight is the absence of geophysical 24-h cycles, which, of course, affects the overall temporal organization of the organisms. In the case of long-duration manned space flight, it is crucial to understand how the whole circadian system would react and behave in such circumstances.

We discovered that exposing rats to constant dim light for 60 days significantly affected the phase-relationship among circadian outputs in the SCN, retina and pineal, demonstrating that in these animals internal desynchronization of the circadian rhythms is occurring. We also observed that the circadian rhythm in arylalkylamine *N*-acetyltransferase (the enzyme that is responsible for the circadian rhythm in melatonin synthesis) was altered in both the retina and in the pineal gland. Our data also indicated that locomotor activity rhythm might be an unsatisfactory marker to assess the circadian status of the whole organism. Internal desynchronization has profound effects on the capability of the organisms to perform (mentally and physically) and to remain healthy. In this research proposal, we have designed a series of experiment aimed to understand the mechanisms that are responsible for the observed desynchronization. We believe that the model we have generated will be useful in to foreseeing and preventing dysfunction of the circadian system that may arise after long periods in the space environment where the normal cycle has been altered.

RESEARCH AREA:	**Human Performance Factors, Sleep and Chronobiology**
PRINCIPAL INVESTIGATOR:	**Fred W. Turek, Ph.D.**
ORGANIZATION:	**Northwestern University**
PROJECT TITLE:	**Animal Model for Sleep Loss and Circadian Disruption**

Project Executive Summary

The adverse effects associated with imposed disruptions of the normal circadian and sleep-wake cycles are particularly relevant to NASA personnel and their ability to carry out normal duties at a high level of efficiency. Many space travel situations demand that both ground-based and flight personnel engage in duty schedules that can lead to circadian rhythm disruption and sleep loss. The tasks that can be affected involve vigilance, operation and control of vehicles/aircraft, maintenance, preparation and operation of equipment, as well as command and control activities. Night operations are important for successful missions, and there is a clear need to find countermeasures that can alleviate the adverse effects of these activities on human circadian rhythms and sleep as well as on neurobehavioural capabilities and on physical performance.

Despite the high prevalence of chronic partial sleep loss and circadian disruption due to shiftwork in modern society, no animal models have previously been developed to systematically examine the effects of chronic partial sleep and circadian disruption on sleep architecture and performance. The use of a new animal model, as outlined in the original proposal, will lead to new insights into how the circadian and sleep systems are affected by the disruption of their normal phase relationship to one another, and how this temporal disorganization influences neurobehavioural capabilities and motor performance. Information gained using this novel animal model will also be important in the development of effective countermeasures to the adverse effects associated with circadian disruption and sleep loss. These countermeasures could be useful in a number of situations involving NASA personnel, particularly in extended duration space flight missions that will result in challenges to the sleep and circadian system of the flight crew and support teams. This project will also provide important insights in to the interactions between the circadian and sleep/wake systems.

There are three specific aims of the project 1) to determine the effects of 12 hours of imposed wakefulness during both normal active and inactive periods on circadian rhythms, the sleep-wake cycle and neurobehavioural and motor performance measurements 2) to test the hypothesis that treatment with either a physiological or pharmacological dose of melatonin at the beginning of the imposed period of wakefulness will alter the effects of this temporal desynchrony on the circadian clock, the sleep-wake cycle, and/or on neurobehavioural and motor performance measurements, 3) to test the hypothesis that access to a wheel (exercise) when in the home cage, will alter the effects of the imposed periods of wakefulness on the circadian clock, the sleep-wake cycle, and/or neurobehavioural and motor performance measurements.

Key findings from the first year of this program suggest that the wheel is sufficient to significantly restrict sleep and that animals employ different strategies in the recovery of sleep across successive days of sleep restriction. In addition, acute and chronic partial sleep restriction to just 4-hours per day significantly alters the hypothalamic-pituitary-adrenal axis (HPA) response to stress (Meerlo *et al*, 2002).

Progress during the past year has placed us in the position to move forward with addressing the questions posed in specific aim 1-3. Two animal rooms have been dedicated to this project, one with the capacity to record sleep in 16 animals and activity and core body temperature in 28. The second adjacent room is equipped for behavioural testing. Studies carried out during year one of the project have indicated that chronic partial sleep deprivation has a significant impact on not only performance but also other physiological systems (HPA axis). It is also clear that there are strain differences in some of our measures at baseline and that this will have a significant impact on our results during the forced wakefulness protocol. Sleep recording during recovery periods following 8 days of chronic partial sleep deprivation has provided important information. We will use this information to aid in determining which days of recovery will be the focus of our analysis in order to detect important changes in sleep recovery on successive days of imposed wakefulness.

During the coming year ongoing experiments will be investigating both strain and light level differences on the impact of 12 hours of imposed wakefulness during both the normal active and inactive periods on circadian rhythms (activity and core body temperature), the sleep-wake cycle and neurobehavioural and motor performance measurements. Once the initial experiments outlined in specific aim one are completed and a baseline is established we will begin testing countermeasures as outlined in specific aims two and three. The current animal model will provide the opportunity to test novel countermeasures developed to alleviate the impact of circadian disruption and sleep loss.

NSBRI RESEARCH PROGRAM
IMMUNOLOGY, INFECTION AND HEMATOLOGY

Team Leader:	**Shearer, W. T.**	**Baylor**
Associate Team Leaders:	**Butel, J. S.**	**Baylor**
	Sonnenfeld, G.	**Morehouse**

RESEARCH AREA:	**Immunology, Infection and Hematology**
PRINCIPAL INVESTIGATOR:	**Janet S. Butel, Ph.D.**
ORGANIZATION:	**Baylor College of Medicine**
PROJECT TITLE:	**Viral Infections and Mucosal Immunity**

Project Executive Summary

Space flight has been found to affect immune responses, and alterations in a normal immune response could have a major impact on the host's ability to control infections. An important question being explored is whether infectious diseases will pose an unacceptable medical risk to the success of long-duration space journeys. All humans are infected for life with latent and persistent viruses, and it is well-known that suppression of the immune system allows latent viruses to reactivate and multiply, which may cause disease in the person undergoing reactivation or in contacts to whom the virus is transmitted. The general hypothesis being addressed is that conditions of long-duration space flight will alter human immune responses, leading to reactivation of latent viruses, increased viral infections and viral disease, and possible development of malignancies, and to altered mucosal immunity, an important host defense against microbial infections. We are focusing on reactivation and shedding of human herpesvirus EBV and human polyomaviruses, agents known to establish persistent infections and to undergo reactivation and cause disease, including cancer, when the host immune system is compromised. Animal models are being used to study radiation effects on host responses to infections, with the suspended mouse model being used for mucosal immunity studies.

There are several ground-based human models that mimic certain aspects of space flight (but not microgravity). One is wintering-over for 8–12 months in Antarctica and another is a closed chamber study in which individuals are confined within space-craft-like chambers on the ground. Both these conditions mimic, but do not precisely duplicate the stress, confinement, isolation, and microbial contamination expected to be encountered during actual space flight. To these we added HIV-infected individuals, a medical condition in which patients suffer immunosuppression due to infection with HIV, the AIDS virus. They are an effective model of medical problems that arise due to damage to the immune system and, by studying patients in various stages of HIV-related disease, different degrees of immune damage can be modeled. Long-term studies of virus reactivation in the three ground-based human models of space flight had been planned and initiated in previous grant years, and sample acquisition and viral assays came to fruition during this current grant year. We completed first a year-long study of reactivation and shedding patterns of herpesviruses and polyomaviruses in 30 normal, healthy individuals in Houston so that results of virus reactivation studies in ground-based analogs of space flight could be meaningfully interpreted in the context of normal, baseline reactivation patterns. Data analyses (including statistical analyses) are ongoing. The general approach was that DNAs were extracted from peripheral blood mononuclear cells, urine cell pellets, and saliva and were tested for the presence of viral DNAs by polymerase chain reaction.

The study involving the Antarctic expeditioners began in late 1998, with specimens received by us in mid-2000. Difficulties were encountered due to the harsh, isolated Antarctica environment and the quality of samples returned from different outposts varied significantly. We also added a new control group of normal volunteers in Australia, as the Antarctic expeditioners were all Australian. The study population involved 63 polar expeditioners and 50 controls. Data to date suggest that the stress or other effects of isolation in Antarctica may lead to an alteration in the host-pathogen status, as reflected in increased polyomavirus reactivation and shedding by younger individuals. We participated in a 240-day closed chamber study (SFINCSS-99) in Moscow, Russia in collaboration with the Institute for Biomedical Problems. Four crew members were confined in the chamber for the duration of the study and were visited by two 4-person crews, each for 110 days, modeling future crew interactions in the International Space Station. The chamber closed in July 1999 and specimens were hand-transported to Houston in Fall 2000. Specimen analysis is ongoing. Upon completion, this will be the first long-duration chamber isolation experience to yield integrated immunological and virological studies. In the HIV infection study involving 70 HIV-infected individuals and 68 uninfected controls, we found that shedding of both polyomavirus and EBV was elevated in the HIV-positive cohort. Using the CD4 cell count as a surrogate marker for immune status, we found that even modest depressions in immune function correlated with virus reactivation in both HIV-positive and HIV-negative groups. This emphasizes the importance of understanding the effect of long-duration space flight on the host immune system. Next, we examined the possible transmission of microbial agents within space analog environments by monitoring infection by *Helicobacter pylori*. This bacterium is causally related to chronic gastritis and peptic ulcer disease and indirectly related to gastric cancer. Transmission is believed to occur person-to-person by the fecal-oral route under conditions of poor sanitation; acquisition of infection has been associated with crowded living conditions. *H. pylori* antibodies were measured using a sensitive and specific ELISA test in plasma specimens from volunteers in the Antarctic winter-over and in the Russian chamber study. There was no evidence for transmission of bacterial infection under these isolation conditions, but a major caveat to this conclusion is that the sample sizes of study volunteers may have been too small to detect transmission of this organism. These studies have involved collaborations with Drs. I. Larina (Russia), D. J. Lugg (Australia/ANARE), D. L. Pierson (NASA/JSC), J. A. Lednicky (Loyola University, Chicago), and D. Y. Graham, W. A. Keitel, and W. T. Shearer (all of Baylor).

A major risk to long-duration space missions is chronic exposure to ionizing radiation. The hypothesis being tested is that space radiation will lead to reactivation of viruses, increased viral infections, and the development of virus-associated malignancies. We are testing this hypothesis with mouse models using the murine gammaherpesvirus 68 and the murine polyomavirus as mouse equivalents of human EBV and of human polyomaviruses, respectively. These studies are being performed in a three-way collaboration with Dr. W.T. Shearer and his "Space Flight Immunodeficiency" project, and Dr. D. S. Gridley at Loma Linda University in California. This project suffered delays due to the flooding of the Baylor animal facility this past summer, but we anticipate that we will soon be fully operational. Another goal of the mouse model studies is to define changes in both the mucosal and systemic immune systems under simulated space flight conditions, to determine whether any observed changes would pose significant risks to crew members and to gain basic information necessary for future design and testing of appropriate countermeasures to abrogate detrimental immunologic changes. These studies utilize a ground-based anti-orthostatic suspension mouse model. The approach is to catalog global changes in the immune system (cell distributions, cytokine production, gene expression) under simulated space flight conditions, and then to determine any additive effects of concomitant virus infection and/or proton irradiation on those patterns. This comprehensive approach will provide new insights into mucosal and systemic host immune functions.

RESEARCH AREA:	**Immunology, Infection and Hematology**
PRINCIPAL INVESTIGATOR:	**George E. Fox, Ph.D.**
ORGANIZATION:	**University of Houston**
PROJECT TITLE:	**Microorganisms in the Spacecraft Environment**

Project Executive Summary

Significant progress has been made in the past year as documented by three peer review papers that have been published or are in press, one that has been accepted pending revision and one that has been submitted. In addition, a book chapter is in press. We are continuing to develop a hybridization array assay for water quality. Several of the previously designed probes have been placed on glass slides and successfully used to capture target 16S rRNAs. It appears that an array assay using a modest number of probes will work better if long capture probes are used in conjunction with the established smaller group specific probes as detectors in a sandwich assay. Three longer oligonucleotides (40, 52 and 65 mers) were designed and initial tests indicate that this format will be preferable for modest arrays. The conditions for this sandwich hybridization assay are currently being optimized.

We are also continuing to examine possible solution formats, which would simplify sample preparation. We have shown that molecular beacons work well with 5S rRNAs, even in the presence of large excesses of very similar non-target RNA. However, they have been problematic with 16S rRNA due to inability of the probes to reach the target sequences. We therefore are developing a controlled fragmentation system for 16S rRNA by using limited ribonuclease digestion in magnesium buffer in order to improve target accessibility of probe target regions. Irrespective of the results with 16S rRNA an assay that targets 5S rRNA has considerable merit. Molecular beacons targeting this RNA can be readily designed to be specific species. We have in the last year developed a greatly simplified procedure in which the 5S rRNA target leaks out of cells after their membrane is damaged. This very simple assay will work with most Gram-negative species. Molecular beacons may not be the most useful detection system however. We have been able to detect as little as 0.1 picomole of 5S rRNA using an immunohybridization assay in which hybrids between the probes and the target RNA are captured on a solid surface. This approach has now been successfully implemented with probes targeting *Vibrio proteolyticus* 16S rRNA. Future tests will focus on other organisms that will be targeted in the water assay.

Significant progress has been made in the identification of oligonucleotide signature sequences that might be used as the basis of an assay to identify problematic organisms whether their presence was expected or not. In a publication that is in press, we show that large numbers of these signature oligonucleotides exist and present an algorithm for finding them. Ongoing work is focused on developing a more effective database of such signature sequences so that we can develop a better understanding of where they occur and what type of groupings, will be easy or hard to identify by this approach. Finally, we have begun to establish protocols for mRNA purification, arranged appropriate collaborations and hired new personnel as a prelude to studying the effects of simulated microgravity on bacterial gene expression.

RESEARCH AREA:	**Immunology, Infection and Hematology**
PRINCIPAL INVESTIGATOR:	**Alan M. Gewirtz, M.D.**
ORGANIZATION:	**University of Pennsylvania School of Medicine**
PROJECT TITLE:	**Effect of Deep Space Radiation on Human Hematopoietic Stem Cells**

Project Executive Summary

Astronauts on long-term missions in deep space will be placed at risk from a variety of hazards. Some of these are known while others may be anticipated. Damage to hematopoietic stem cells as a result of radiation exposure is as an example of the latter. Our long-term goal is to identify and quantitate the risks of deep space radiation to the human hematopoietic system, with particular emphasis on the hematopoietic stem cell. Stem cells are the ultimate source of both the blood and immune systems and damage to these cells could have grave immediate and long-term consequences. At the same time, because these cells can be readily removed from the body, manipulated, and stored, they are also unique candidates for countermeasures that might obviate, or totally negate, damage incurred to them. Accordingly, this project will have three specific aims that support our long-term goals. These are to: 1) *Investigate the cellular consequences of exposing human hematopoietic stem cells to an environment which simulates the radiation environment of deep space.* While much is known about the effects of "conventional" radiation on hematopoietic cells, virtually nothing is known about the effects of deep space, high LET radiation on human hematopoietic stem (HSC) and progenitor (HPC) cells. 2) *Examine the molecular consequences of exposing human hematopoietic stem cells to an environment which simulates the radiation environment of deep space.* This aim has two purposes. If radiation leads to degradation of hematopoietic cell function it will clearly be of interest to look for the molecular lesions potentially responsible for such damage. Alternatively, more long-term, but initially occult damage may also be induced. The consequences of such damage could lead either to a complete failure of hematopoiesis (aplastic anemia) or the development of hematological malignancies. Identification of such damage is therefore important. 3) *Design potential countermeasures to obviate or negate cellular and molecular damage discerned during the course of carrying out Aims 1 and 2.* We propose both simple and more complex solutions to problems that might be identified during the course of this study. We suggest that prophylactic (pre-flight) harvest and storage of astronaut stem cells might be a safe, effective, and relatively inexpensive mechanism for countering long-term damage to cells of the hematopoietic systems. Countermeasures that might prove effective in combating damage encountered during flight will also be developed and explored for their utility.

RESEARCH AREA:	**Immunology, Infection, and Hematology**
PRINCIPAL INVESTIGATOR:	**William T. Shearer, M.D., Ph.D.**
ORGANIZATION:	**Baylor College of Medicine**
PROJECT TITLE:	**Space Flight Immunodeficiency**

Project Executive Summary

Original Aims

There are two specific aims to this project concerning Space Flight Immunodeficiency that can be summarized as follows:

A. **Specific Aim 1.** Using human blood specimens collected in the Australian National

Antarctic Research Expedition (ANARE) winter-over, assess the effects of extreme weather climates, isolation, containment, sleep disturbance, and possible microbial contamination on immune function.

Hypothesis for Specific Aim 1. The ground-based space-equivalent model of the Antarctic winter-over will provide an assessment of some of the conditions of space flight that may have a negative impact upon human immune function.

Objective for Specific Aim 1. Using ANARE plasma samples collected every month from ANARE study subjects stationed in the Antarctic and from control subjects stationed on Macquarie Island, determine whether there are differences in concentrations of cytokines and their soluble receptors, possibly due to the isolation of study subjects.

B. **Specific Aim 2.** Assess the effects of deep-space radiation and latent viral infection on immune function of experimental animals and determine whether depressed immunity in these animals leads to a state of chronic infection and development of tumors.

Hypothesis for Specific Aim 2. Radiation and virus infection in a murine model will demonstrate a synergistic and permanent depression of immunity, leading to conditions of chronic viral infection and malignancy.

Objective for Specific Aim 2. Using sublethal doses of proton and gamma radiation, reduce immune function in study animals to determine if activation of a latent murine virus induces chronic infection and cancer.

Key Findings of Project

A. Plasma Cytokines and Cytokine Receptor Antagonists in ANARE Subjects

Based in part upon our previous NSBRI-supported human sleep deprivation studies published in 2001, we have extended these studies of plasma cytokines and soluble cytokine receptor antagonists to the space model of the Antarctic winter-over. Australian volunteers were taken by boat from the mainland in October/November 1999 to one of three destinations, two in Antarctica and one on Macquarie Island. The study subjects were those stationed in the two

Antarctic locations (Casey, N=10, Davis, N=11, total N=21), and the control subjects (N=7) were those stationed on Macquarie Island (still had access to the mainland during winter). A period of total isolation for the Antarctic study subjects began in late March/early April, when access to the mainland was prevented by the enlarging ice mass. Monthly plasma specimens were obtained and frozen at −70°C, beginning in January 2000 and ending in September of the same year. After transport of the frozen (dry ice) specimens to Houston, cytokine and cytokine receptor assays were performed with quality-assured ELISA assays. Analysis of the large amount of data is continuing, but several preliminary statements can be made. There appeared to be progressive time-dependent increases in plasma interleukin-12 (IL-12) and interferon-gamma (IFN-γ) levels and time-dependent progressive decreases in plasma levels of interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1RA) in the Antarctic study cohorts, as compared to the Macquarie Island control cohorts. IL-12 and IFN-γ cytokines are important in the activation of cytotoxic T-cells, such as those that might be activated in response to a viral infection – possibly a latent infection that becomes active due to the severe conditions of the Antarctic winter-over. Also, the progressive decrease of IL-10 and IL-1RA levels in the plasma of study subjects in total isolation is a sign of the immune system turning off its anti-inflammatory response, as reflected in the concentrations of IL-10, known to be an anti-inflammatory cytokine and in IL-1RA, a pro-inflammatory receptor antagonist. All of these findings are consistent with the Antarctic volunteers undergoing T-cell activation, possibly due to viral infection.

B. Radiation and Virus Infection in a Murine Model

The co-investigators met in Houston on June 19, 2001 for the team retreat. Dr. Daila Gridley was an invited guest and presented the results of her current work with proton and gamma radiation in mice, demonstrating profound and some lasting deficits of immune function. The following plans were made with regard to collaborative immunology-radiation biology studies. Selected strains of mice (e.g., BALB/c C57 black) will be exposed to proton and gamma ray radiation and subsequently to murine viruses (e.g., gamma 68, polyomavirus) in an attempt to determine the combined effects of space radiation and latent virus infection on the immune function of study animals. This first approach will examine the simultaneous effects of radiation and infection and will then be followed by a sequential approach of infection first and radiation second, the likely scenario for human space travelers to Mars. The dose of radiation that will be utilized initially (3Gy, the estimate of radiation received by astronauts on a Mars Mission) will be that used by Dr. Gridley and her colleagues, who have demonstrated rapid and profound alterations in immune cells and immune responses in murine subjects. Replicate and controlled experiments will be performed by both the Loma Linda University (LLU) site and the Baylor site to insure that the same methods are followed at both sites and that the results of the experiments at Baylor confirm those of LLU. If gamma radiation proves to be equivalent to proton radiation, in terms of effects upon the immune system (e.g., spleen cell T-cell response to non-specific stimuli and specific antigen stimulation; plasma antibody formation to neoantigen; spleen lymphocyte subset distribution), it may be possible to avoid transfer of mice between institutions, as Baylor has a source of gamma radiation. In addition to examination of the effects of radiation and latent virus infection on immune cells and immune responses, study animals will be evaluated for the development of tumors and blood malignancies. This will be carried out with the assistance of Dr. Cory Brayton, a veterinary pathologist at Baylor who has agreed to collaborate on this project.

Because of the complete loss of the vivarium at Baylor College of Medicine, due to Tropical Storm Allison flooding the Texas Medical Center, these small animal studies have had to be postponed. However, the veterinarians at Baylor and LLU have been preparing for these collaborative studies with the submission of documents to the Animal Welfare Committees of both institutions. The Baylor vivarium is now operating at a ten percent capacity, and soon it will be possible to proceed with the research on Specific Aim 2.

Impact of Findings on Hypothesis, Objectives, and Specific Aims of Original Proposal

A. Plasma Cytokines and Cytokine Receptor Antagonists in ANARE Winter-Over Subjects

The findings of this study strongly support the hypothesis that the immune systems of humans exposed to the long and severe isolation of the Antarctic winter-over become activated by a recurrence of latent virus infection. Therefore, this model of space flight has (to the extent of the present findings) been validated, suggesting that viral infections in space travel will become activated – possibly leading to a state of profound immunodeficiency. These data need further exploration with additional objectives, such as the functional assessment of cellular immunity. Lymphocyte proliferation to specific antigens or the secretion of cytokines in response to specific antigen challenge, or the measurement of T-cell cytotoxicity to virus-infected target cells would be objectives for the next phase of this work. The specific aim would remain the same. It is of considerable interest that these same subjects did not demonstrate defects of B-cell mediated immunity, as assessed with their specific antibody responses to the T-cell-dependent neoantigen, phi-X174 bacteriophage (Shearer, et al., 2001). It is possible that the alterations achieved in T-cell immunity are reflective of T-cell activation only and that immunosuppression did not occur during the one winter-over period. Additional human experiments in this and other models of space flight are warranted.

B. Radiation and Virus Infections in a Murine Model

The difficulties encountered with the Baylor College of Medicine vivarium due to the great flood of 2001 are likely not to be repeated and as more space within the vivarium becomes operational, experiments will get underway. The specific aim and objective remain the same to test the original hypothesis.

Proposed Research Plan for the Coming Year

A. Plasma Cytokines and Cytokine Receptor Antagonists in ANARE Subjects

A complete analysis of the data will be made, and a manuscript will be written for peer-reviewed publication. Plans will be made for additional ANARE experiments in collaboration with Dr. Desmond Lugg. These would include the possibility of performing real time assays of immune function in the Antarctic for the ANARE 2003 expedition. The experience with using frozen specimens delivered from the Antarctic from ANARE 1999 was that too few cells remained viable for analysis of immune function. If the postponed NASA Isolation Capsule Study at the Johnson Space Center in Houston is restarted, it would be possible to perform these cytokine analyses along with the functional assessment of T-cell activation.

B. Radiation and Virus Infections in a Murine Model

See Impact of Findings, B above.

RESEARCH AREA:	**Immunology, Infection and Hematology**
PRINCIPAL INVESTIGATOR:	**Yufang Shi, D.V.M., Ph.D.**
ORGANIZATION:	**University of Medicine and Dentistry of New Jersey Robert Woods Johnson Medical School**
PROJECT TITLE:	**Effects of Antiorthostatic Suspension on the Immune System**

Project Executive Summary

Space flight has profound effects on the immune system of humans, monkeys and rodents. Several factors including microgravity, lack of load bearing, stress, acceleration forces, and irradiation have been proposed to contribute to the changes of the immune system, however, the exact mechanisms by which these factors affect the immune system remain to be established. Simulations of some of these factors with ground animal models, as hindlimb suspension in rodents, have replicated such changes in the immune system. Our recent studies have shown that opioids could induce Fas expression. In addition, restraint stress in mice induces Fas-mediated apoptosis in splenocytes in an endogenous opioid-dependent manner. Since space flight conditions resemble both physical and psychological stress to humans and animals, we hypothesize that immunosuppression during space flight is a result of the expression of Fas, induced by increased production of endogenous opioids.

We propose the following aims to test this hypothesis: 1) Investigate the modulation of the Th1 and Th2 responses in mice upon subjection to antiorthostatic suspension. Recent studies have clearly demonstrated that stress-induced immunosuppression is not simply due to an overall downregulation of the immune system. Rather, Th1 responses are suppressed while at the same time Th2 responses are enhanced. We hypothesize that antiorthostatic suspension could increase Th2 while at the same time decrease Th1 responses.

Aim 2) will explore the mechanisms of antiorthostatic suspension-induced thymus involution. It has been shown that space flight and antiorthostatic suspension could induce significant thymus involution in animals. This reduction could decrease the peripheral repopulation capacity, especially when a large proportion of peripheral lymphocytes also undergoing cell death under such conditions. Our hypothesis is that thymus involution induced by antiorthostatic suspension is mediated either by glucocorticoid or by endogenous opioids.

And, aim 3) will examine the role of RANKL in the communication between the immune and skeletal systems during antiorthostatic suspension. Space flight and antiorthostatic suspension causes significant bone loss. Recent studies have shown that OPG could inhibit bone alteration in antiorthostatically suspended mice, indicating the importance of RANKL in this process. We have recently shown that RANKL could be induced by activation and dexamethasone in T cells and thymocytes. We hypothesize that antiorthostatic suspension induced glucocorticoids could promote lymphocytes to express RANKL, which causes bone loss.

These studies will further investigate the molecular mechanisms by which antiorthostatic suspension induces immune alteration. Furthermore, we will also test our novel hypothesis that the immune system contributes to bone loss under weightless conditions. It is expected that our studies will provide information for the development of novel countermeasures to overcome the deleterious effects of space flight.

RESEARCH AREA:	**Immunology, Infection and Hematology**
PRINCIPAL INVESTIGATOR:	**Gerald Sonnenfeld, Ph.D.**
ORGANIZATION:	**Morehouse School of Medicine**
PROJECT TITLE:	**Suspension, the HPA Axis and Resistance to Infection**

Project Executive Summary

The hypothesis bring tested is: antiorthostatic (AOH or hindlimb) suspension of mice, a model for some of the effects of space flight on the immune system, results in altered resistance to infection with pathogens. Testing of this hypothesis will provide data to allow development of future studies to determine if space flight affects resistance to infection and if countermeasures can be developed to prevent any detrimental effects.

The specific aims of the study are:

A) to expand the range of infections altered by AOH suspension. We have already shown that resistance to some infections that are not likely to be risks during space flight has been altered by AOH suspension and we now wish to determine if infections that could be a risk during space flight are affected by the suspension model.

B) to determine the mechanism of alteration of resistance to infection induced by AOH suspension. Although previous studies have shown that immune responses are altered by space flight, we now wish to extend these studies to determine the role of neuroendocrine system in regulating infections. This will be carried out using two approaches. The data obtained from experiments using both approaches will be integrated to allow for development of a model for the mechanism(s) of the effects of hindlimb suspension on resistance to infections.

We have begun studies to expand the range of infections shown to be altered by AOH suspension. We have completed an LD50 study for Klebsiella pneumoniae in Swiss/Webster mice. We have carried out a study to determine the effects of AOH suspension on resistance to infection with K. pneumoniae. In a preliminary experiment, have shown that mortality was 50% for control mice that were normally caged and housed and received 1 LD50 of K. pneumoniae. Mortality was 43% for control mice that were orthostatically restrained and received 1 LD50 of K. pneumoniae. Mortality was 86% for experimental mice that were anitorthostatically suspended and received 1 LD50 of K. pneumoniae. We have carried out additional mechanistic studies that show that the bacteria spreads to the blood and organs after infection of all animals. However, in the restrained and normally housed control animals, the bacteria were cleared from the blood and organs. The suspended animals could not clear the infection from the blood or organs and this led to their death.

We have completed initial studies to determine the effects of catecholamines on the growth of potentially pathogenic bacteria that would be encountered during space flight. Supplementation of minimal medium inoculated with bacteria cultures with norepinephrine, epinephrine, dopamine, or isoproterenol resulted in marked increases in growth compared to controls. Norepinephrine and dopamine had the greatest enhancing effects on growth of cultures of Pseudomonas aeruginosa and Klebsiella pneumoniae, while epinephrine and isoproterenol also enhanced growth to a lesser extent. The growth of Escherichia coli in the presence of norepinephrine was greater than growth in the presence of the three other neurochemicals used in the study. Growth of Staphylococcus aureus was also enhanced in the presence of norepinephrine, but not to the same degree as was the growth of gram negative bacteria. Addition of culture supernatants from E. coli cultures that had been grown in the presence of norepinephrine was able to enhance the growth of K. pneumoniae. Addition of the culture supernatant fluid culture from E. coli cultures that had been grown in the presence of norepinephrine did not enhance growth of P. aeruginosa or S. aureus. Culture supernatant fluids from bacteria other than E. coli grown in the presence of norepinephrine were not able to enhance the growth of any bacteria tested. The results suggest that catecholamines can enhance growth of pathogenic bacteria, which may contribute to development of pathogenesis; however, there is no uniform effect of catecholamines on bacterial growth.

The results of the current research are very much inline with the proposed studies described in the original proposal. We will continue in the next year with the work as outlined in the original proposal.

We will, in the next year, expand our studies with suspension to include other potential pathogens and to study effects on immune and hormonal responses. We will also expand our hormonal studies to determine the effects of catecholamines on growth and virulence of additional bacterial and viral pathogens. We also hope to begin synergism projects utilizing array analysis to determine what specific proteins are affected by exposing pathogenic bacteria to catecholamines.

NSBRI RESEARCH PROGRAM
MUSCLE ALTERATIONS AND ATROPHY

Team Leader: **Baldwin, K. M.** **UC, Irvine**

Associate Team Leader: **Goldberg, A. L.** **Harvard**

Sinha, S.	**PI**	**UCLA**	**In Vivo Stress-Strain Dynamics in Human Muscle**	**86**
Edgerton, V. R.	CO-I	UCLA		
Lai, A.	CO-I	UCLA		
Hodgson, J. A.	CO-I	UCLA		
Roy, R. R.	CO-I	UCLA		
Elashoff, R. M.	CO-I	UCLA		
Wiseman, R. W.	**PI**	**Michigan State**	**Ca^{+2} Homeostasis and Muscle Phenotype: Role of Cellular Energetics**	**87**
Jeneson, J. A. L.	CO-I	Washington		

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Parker B. Antin, Ph.D.**
ORGANIZATION:	**University of Arizona**
PROJECT TITLE:	**Calpains in Simulated Microgravity-Induced Muscle Atrophy**

Project Executive Summary

The overall goal of this proposal is to test the hypothesis that inhibition of calpain activity in skeletal muscles can reduce myofibril degradation and muscle atrophy. Muscle wasting is an important impediment to extended space travel, and studies have shown that muscle size is regulated by the balance between myofibrillar protein synthesis and degradation. Calpain is the major calcium activated protease in animal cells and plays a primary role in regulating the rate of muscle protein accumulation. Considerable evidence suggests that increasing the levels of calpastatin, a protein inhibitor of calpains, enhances muscle protein accumulation. Inhibition of calpain activity, either by increasing calpastatin levels or by expression of dominant negative forms of calpain, may therefore reduce or inhibit muscle atrophy. Research in this proposal will explore these possibilities and has the following specific aims: 1) investigate whether targeted over expression of calpastatin will reduce skeletal muscle atrophy in transgenic mice using the hindlimb unweighting model; and 2) investigate the use of dominant negative forms of calpains to inhibit calpain activity and reduce skeletal muscle protein degradation and atrophy. Studies will use either the muscle creatine kinase promoter or a fully characterized tetracycline inducible system to express calpastatin or mutated calpains in muscles of transgenic mice or in cultured L8 muscle cells. Muscles will be analyzed for changes in overall size, nucleus/cytoplasm ratio, fiber type, total protein accumulation and degradation rates, and accumulation of individual myofibrillar proteins. Information gained is expected to broaden our understanding of muscle growth and may suggest approaches for alleviating muscle atrophy in space and on Earth.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Kenneth M. Baldwin, Ph.D.**
ORGANIZATION:	**University of California, Irvine**
PROJECT TITLE:	**Role of Muscle Loading on Mechanisms of Protein Translation and the Impact on Unloading-Induced Atrophy**

Project Executive Summary

Project Goals As Defined in the Original Proposal:

1. To determine how changes in mechanical loading impact fundamental signaling pathways and regulatory processes that control protein translation capacity/efficiency in the context of skeletal atrophy and hypertrophy.

2. To systematically develop a rodent resistance training program designed to attenuate the atrophy process and blunt slow to fast transitions in contractile protein phenotype.

3. To determine the potential interaction of amino acid (leucine and cysteine) therapy and resistance training as a countermeasure.

Objectives For the Current Funding Period:

1. Initiate experiments to identify mechanisms responsible for muscle atrophy when the target skeletal muscles are induced to become totally inactive via the intervention of the model of spinal isolation.

2. Identify regulatory mechanisms for muscle hypertrophy using an approach that places continuous mechanical stress on the target muscles via the model of functional overload.

3. Initiate experiments to ascertain if chronically altered loading of human skeletal muscle induces adaptations similar to that seen in animal models.

Progress To Date:

In FY 2000-2001 three projects were initiated in order to establish cellular/molecular profiles in skeletal muscle reflecting anabolic/catabolic states based on net protein balance in skeletal muscle using models that cause either marked atrophy or hypertrophy.

Project #1 examined changes in rodent slow and fast skeletal muscle in response to complete muscle inactivity, as induced by the novel technique of spinal isolation (SI) in which the spinal cord is severed; and all afferent input into the motor pathways to the muscles are inactivated or silenced.

Project #2 examined adaptive hypertrophy responses to the intervention of chronic functional overload (FO) in which the target muscles (soleus and plantaris) were induced to increase their weight bearing activities by the surgical elimination of gastrocnemius synergist.

Project #3 examined cellular/molecular markers of anabolic/catabolic processes in human skeletal muscles of subjects that were exposed to either unilateral lower limb suspension (ULLS) alone, resistance training (RT) alone, or the combination f ULLS plus RT. This latter project was performed in collaboration with Dr. Per Tesch of the Karolinska Research Institute in Stockholm, Sweden.

Key Findings:

The SI model induces marked atrophy by 40 –50% in both slow and fast rodent muscle (figure 1, appendix A). The atrophy response is brought about by marked decrease in transcriptional activity of sarcomeric genes (myosin heavy chain and actin), which lowers the amount of mRNA (Figures 6 and 7, appendix A) available for translation (figures 11 and 12, appendix A). Total RNA concentration and content, of which the majority is ribosomal, is markedly reduced (Figure 4, appendix A). Although the activity of enzyme systems involved in protein translation remain activated in the inactive muscles (figures 13 and 14, appendix A), it appears that the decrease in transcription and the increased expression of enzyme systems involved in protein degradation (enzymes of the ubiquitin proteasome and calcium activated calpains) (figures 15 and 16, Appendix A) are up-regulated to create net protein loss. These findings clearly point to the importance of maintaining transcriptional activity in order to generate sufficient substrate for protein translation in models of marked atrophy.

With functional overload, the opposite occurs in that transcriptional activity of sarcomeric proteins is increased. Also, enzyme systems and activation of proteins involved in protein initiation processes in translation are increased relative to control states (Figures 21-26, Appendix B). Further, there is increased expression of muscle growth factors such as IGF-1 and myogenic growth factor and their associated binding proteins (Figures 13,14, 15, 16, appendix B), which are thought to increase signaling for protein translation. Preliminary studies suggest that there is either no change or decreased expression of the proteins involved in protein degradation (Figures 21 and 22, appendix B). Thus, in this robust model of hypertrophy there is net positive protein balance by increasing the transcriptional/translational events while exerting less impact degradation processes. One of the interesting observations in this overload model involves the transient reduction in the concentration of the myofibril fraction in both fast and slow overloaded muscle during the initial stages of the overload stimulus (3, 4, 7,8,9,10,11,12, appendix B). Thus, in the hypertrophying response, there may be an initial protein reduction in the contractile apparatus that precedes the anabolic stage of the muscle. More research is needed to determine if this is a common response to different paradigms of muscle growth and hypertrophy.

Finally, in humans undergoing muscle atrophy, the patterns of change of mRNA for both myosin heavy chain and actin are reduced, which is consistent with the type of changes observed in rodent models of muscle atrophy. This observation suggests that human and animal muscle may respond to altered loading via similar mechanisms. Resistance training, either alone or in combination with lower limb unlading, consisting of a combination of concentric/eccentric contraction creates the opposite responses compared to that seen with the unloading state on the molecular markers of muscle homeostasis.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**P. Bryant Chase, Ph.D.**
ORGANIZATION:	**Florida State University**
PROJECT TITLE:	**Cell and Molecular Biomechanics: Cardiac and Skeletal Muscle**

Project Executive Summary

This proposal is targeted to the National Space Biomedical Research Institute's Integrated Human Function Team (primary) with a secondary target as the existing Muscle Team. The overall goal of this proposal is to produce a muscle cell model (digital cell) that will: explain biomechanical adaptations that occur with alterations in muscle protein isoforms due to changes in activity level; predict bioenegetic changes associated with changes in activity level; and be integrated into computational models of human limb and heart. The essential molecular and subcellular components of the model will be identified and algorithms constructed based on experimental data obtained in a controlled environment. The cell model will be tested against published biomechanical and bioenergetic data obtained under a broad spectrum of environmental conditions. Our muscle cell model will be one of the main building blocks for constructing a model of integrated human function because the cell is the basic unit of physiological organization; the musculoskeletal system is ~80% of body mass and thus is a major determinant of energy consumption, as well as being responsible for movement and cardiovascular function. To accomplish our goal of constructing a digital muscle cell, we will: (1) identify contractile protein composition of skeletal and cardiac muscles from high- and low-activity rats; (2) characterize contractile properties (phenotype) of selected muscles containing unique mixtures of protein isoforms, as identified in Aim 1; and (3) develop the "digital" cell biomechanical model.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Alfred L. Goldberg, Ph.D.**
ORGANIZATION:	**Harvard Medical School**
PROJECT TITLE:	**The Activation of Protein Breakdown in Muscle Upon Unloading and Possible Countermeasures**

Project Executive Summary

The marked loss of muscle mass that occurs in astronauts in space due to muscle unloading and also in many systemic diseases results primarily from accelerated degradation of muscle proteins, especially myofibrillar components. We have shown that the enhancement of protein breakdown in these various types of muscle atrophy results mainly from activation of the ubiquitin-proteasome system and that one pair of ubiquitination enzymes ($E2_{14K}$ and $E3\alpha$), which comprise the "N-end rule" pathway, plays a particularly important role in atrophying muscles. Our major goals now are to clarify the basis for the activation of this ubiquitination pathway in the unloaded muscles and to develop pharmacological inhibitors of the ubiquitin-proteasome pathway that may retard muscle wasting. We shall attempt to identify more potent, selective inhibitors of $E3\alpha$ and to use genetic models to examine the consequences of blocking the "N-end rule" pathway *in vivo*. Proteasome inhibitors are promising new agents for treating human disease, and based on recent findings about proteasome function, we hope to synthesize new types of inhibitors that act allosterically to reduce proteolysis partially and thus should be safer and more appropriate for use against muscle wasting.

To obtain a more complete picture of the changes in gene expression leading to the loss of muscle mass and functional capacity, we are also undertaking a gene microarray analysis to identify systematically the transcriptional changes that occur during atrophy of rat muscles induced by hind-limb suspension or glucocorticoid treatment, as well as in human muscle biopsies obtained during prolonged bed rest. This approach should help to identify novel targets for inhibitor development and useful markers to monitor muscle wasting and efficacy of countermeasures.

To explore how atrophy may be prevented by nonpharmacological approaches, we also plan to analyze animal muscles from certain unusual physiological states, black bears during winter and rats upon dietary protein restriction, both of which suppress proteolysis and preserve muscle mass, despite reduced caloric intake and disuse.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Marc T. Hamilton, Ph.D.**
ORGANIZATION:	**University of Missouri**
PROJECT TITLE:	**Genomics of Human Skeletal Muscle During Bed Rest and Exercise**

Project Executive Summary

Reduced use of weight-bearing skeletal muscles during microgravity and sedentary life on Earth causes unhealthy and potentially dangerous consequences. For example, leg muscles atrophy, and also have a profound reduction of lipoprotein lipase activity (an enzyme in the blood vessels of muscles with a protective effect against lipoprotein risk factors for coronary heart disease). It is likely that an unbiased determination of the global expression pattern of the human genome with microarrays will reveal many muscle mRNAs increasing and decreasing, including mRNAs that heretofore have never even been hypothesized to contribute to the "microgravity or sedentary phenotype." Additionally, large scale genomic studies are likely to begin to reveal clusters of related mRNAs that provide clues as to the sets of genes orchestrating some of the cellular signaling, transcriptional changes, cellular growth, and metabolism. This project will build upon recent experience established from microarray studies of hindlimb suspension, endurance exercise, and muscle fiber type that support the statements described above. The effects of bed rest and one-leg exercise (as a countermeasure to attenuate the effects of inactivity) on the soleus muscle of 6 men and 6 women will be studied. Using state-of-the-art microarray methodologies, this project will measure the expression of ~12,000 full-length sequence verified mRNAs and ~3,000 of the most abundant muscle ESTs. This project is being proposed by a laboratory already using microarrays in the study of muscle physiology, in collaboration with a bioinformatics laboratory, a physical therapy laboratory focused on muscle function, a physician-scientist studying muscle diseases, and a core laboratory for microarray development. This study is likely to discover novel candidate genes and clusters of related genes potentially responsible for the unhealthy responses to reduced muscle use during physical inactivity.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Susan C. Kandarian, Ph.D.**
ORGANIZATION:	**Boston University**
PROJECT TITLE:	**Gene Expression Profiling of Unloaded Skeletal Muscle**

Project Executive Summary

Prolonged periods of biomechanical unloading due to space travel or physical inactivity are marked by significant decreases in the size and functional capacity of skeletal muscle. The overall aim of the proposed work is to delineate cellular mechanisms involved in unloading-induced skeletal muscle atrophy. In the face of overall muscle wasting, some subsets of genes are actually upregulated indicating the complexity of the biological processes underlying atrophy and the need for characterization at a molecular level. As a first step in elucidating these mechanisms we will analyze global gene expression patterns in rat soleus muscles using Affymetrix GeneChips at 1, 4, 7, 14 days of biomechanical unloading. Temporal analysis of the parallel expression of ~7,000 full-length genes and several thousand expressed sequence tags will serve as a window into the signaling networks that underlie the atrophy process. Microarray data analysis software will be used to segregate gene expression changes based on involvement in known functional groups, regulatory and signaling pathways. Clustering algorithms will be used to elucidate sets of genes with known or unknown functions that have similar temporal expression patterns. These types of analyses will be used to illuminate gene associations and candidate players in pathways that may be involved in the progression of muscle atrophy. Further investigation of candidate players will be performed using more quantitative and conventional techniques such as northern blot, western blot, activity assays, and immunolocalization studies. Sequence alignment algorithms such as AlignACE will be used to identify regulatory sequence conserved among genes that are co-regulated. This type of analysis will expedite attempts to determine unloading-sensitive regulatory sequences and will facilitate a better understanding of how activity patterns regulate transcriptional machinery. Protein-DNA binding assays using these conserved regulatory motifs will complement the computational analysis. By characterizing atrophy at this level we will be in a better position to design effective countermeasures to mitigate the deleterious changes in muscle function, which not only has applications for life in space but also for the quality of life on this planet.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Martin J. Kushmerick, M.D., Ph.D.**
ORGANIZATION:	**University of Washington**
PROJECT TITLE:	**Integrating Human Muscle Energetics and Mechanics**

Project Executive Summary

We propose a novel combination of ^{31}P NMR spectroscopies, ultrasound functional images, biomechanical analyses and multi-level modeling for analysis leading to an integration of human limb muscle function. We will integrate macroscopic properties in terms of molecular mechanisms. Human limb muscle will provide an exemplar for the integrated human function team: the analysis and modeling of different cell types and tissues in the limb as a functional organ will provide enabling concepts and technology for larger scale modeling of the "digital human" and guide strategies for database and global computer system development. We believe the current best strategy to develop milestones and to make progress on the ambitious goal of the "digital human" is to commence work on one body part that includes important pieces of NASA's critical path analysis. An understanding of limb muscle function is crucial to the planning of training exercises and to selecting personnel for the most strenuous activities with optimal efficiency and minimal risk. The science of this proposal evaluates the mechanisms responsible for transient and steady state performance of limb muscle. This analysis requires the specification of: 1) the mechanical power output by specific muscles during limb functions; 2) the analysis of the properties of different muscles in the same individual and of the same muscles in different individuals; 3) the quantification of energy demand by mechanical output; 4) the division of energy supply between glycolytic and oxidative processes and analysis of their inter-related controls; and 5) analysis of the response of these components with integrated models of the system. The information obtained through these experimental approaches is crucial to develop a model-based approach to the study of *in vivo* muscle energy balance in humans for two reasons: 1) the relevant data is not available; and 2) more importantly, the conceptual basis for integrating the component mechanisms can only be evolved from these new observations. We will show that the tissues in the limb have ideal properties and components that render hierarchical modeling feasible. Many properties of these processes are known and characterized *in vitro* but *in vivo* they form an integrated system, the characteristics and regulation of which is largely unknown. We will expand a mathematical model for intracellular energetics to include mechanics and blood flow. The goal is a hierarchical and mechanistic model of these crucial components of limb muscle function which can be extended to include additional metabolic and cellular features developed by other investigators, bone mechanical properties and, eventually, cardiovascular and respiratory analyses currently under development in other teams. We expect the intermediate milestone of the limb functional model will be a powerful tool for analyzing altered physiological responses to space environment and for testing efficacy of countermeasures.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Michael B. Reid, Ph.D.**
ORGANIZATION:	**Baylor College of Medicine**
PROJECT TITLE:	**Redox Modulation of Muscle Function in Microgravity**

Project Executive Summary

Exercise-induced fatigue and muscle atrophy are mediated in part by reactive oxygen species (ROS), a stimulus that may be exaggerated by radiation during spaceflight. The current project is assessing the roles of ROS signaling and radiation on muscle fatigue and atrophy and is testing antioxidants as possible countermeasures. Progress was hindered by severe damage to our institution by Tropical Storm Allison in June, 2002, but these losses have been resolved and are making rapid progress as outlined below:

Aim 1. To determine if oxidative stress contributes to muscle fatigue during handgrip exercise. Fatigue of hand and forearm muscles may limit crew performance during extravehicular activity (EVA). N-acetylcysteine (NAC) is an antioxidant that inhibits muscle fatigue in humans. We are testing the capacity of NAC to inhibit muscle fatigue and oxidative stress in humans during handgrip exercise. Working with Dr. Jeff Jones, Flight Surgeon at NASA Johnson Space Center, we are using equipment and test procedures designed for use on the International Space Station. Pilot data indicate these methods are reproducible so we plan to begin NAC experiments early in Year 2.

Aim 2. To determine whether ionizing radiation accelerates ROS production and fatigue in skeletal muscle. The radiation absorbed during EVA is predicted to increase tissue ROS levels and accelerate fatigue. We plan to test these postulates by studying rodent limb muscles in a proton radiation field that mimics EVA conditions. Ongoing collaborations with Dr. Carlos Gonzalez, Director of the cyclotron at the University of Texas Medical School, were disrupted when Tropical Storm Allison destroyed the cyclotron facility. We now are developing an alternative plan using the cyclotron at Texas A&M University in collaboration with Dr. Henry Clark, Director of the A&M facility. Experiments are expected to begin in Year 2.

Aim 3. To evaluate oxidative stress as a mediator of muscle atrophy caused by gravitational unloading. Muscle atrophy is a primary cause of muscle dysfunction during prolonged spaceflight. We are evaluating oxidative stress as a cause of atrophy in mouse soleus during 12-days of hindlimb unloading. Unloading increases oxidant levels in soleus muscle fibers. Antioxidant (NAC, allopurinol) administration decreases muscle oxidant levels and blunts contractile dysfunction but does not inhibit atrophy. In Year 2, we plan to complete these studies and test vitamin E effects. Related studies have identified a novel ubiquitin conjugating enzyme, UbcH2/$E2_{20k}$, that is highly expressed in skeletal muscle and mediates ubiquitin conjugation to muscle proteins. We are now testing the role of UbcH2/$E2_{20k}$ in atrophy of unloaded muscle.

Aim 4. To determine if radiation stimulates atrophic signaling in muscle. ROS accelerate protein loss in differentiated muscle cells by activating nuclear factor-6B (NF-6B), a transcription factor that influences expression of regulatory proteins in the ubiquitin/proteasome pathway. We postulate radiation-derived ROS will stimulate this pathway. Planned experiments will measure activity of this signal transduction pathway in muscle following proton radiation exposure. Due to destruction of the Medical Center cyclotron, experiments have been delayed until Year 2 and will use the A&M facility. In a related project, we have begun collaborating with Drs. Butel, Conner, and Gridley of the NSBRI Immunology, Infection, and Hematology Team. We have obtained muscle from gamma-irradiated animals at various times following radiation exposure and are analyzing the tissue for signaling events linked to muscle catabolism.

RESEARCH AREA:	**Muscle Alterations & Atrophy**
PRINCIPAL INVESTIGATOR:	**Shantanu Sinha, Ph.D.**
ORGANIZATION:	**University of California, Los Angeles**
PROJECT TITLE:	**In-Vivo Stress-Strain Dynamics in Human Muscle**

Project Executive Summary

Muscle atrophy is a complication of prolonged exposure to microgravity and likely involves an alteration in the strain properties of the muscle-tendon unit. Such alterations in biomechanical properties are likely to predispose muscle to strain injury as well as create errors in motor function, both in the microgravity environment and upon return to Earth-based activities. Quantifying the magnitude and distribution of the stress-strain properties of muscle during both the atrophic and recovering state is a specific aim of this project. Preliminary evidence shows that the strain distribution within muscle is highly heterogeneous but closely linked to the anatomical architecture of the muscle. Reduced levels of mechanical load likely plays a significant role in the development of muscle atrophy through alteration of the strain characteristics of muscle, (magnitude and the strain distribution). In our experimental design, a group of subjects (n=12) will undergo unilateral lower limb suspension (ULLS) for 6 weeks to induce muscle atrophy of the triceps surae muscle complex (TSMC) in one extremity. Strain magnitude and distribution within the muscle will be measured by velocity encoded cine-phase contrast MRI during an *in vivo* isometric contraction of the TSMC with maximal effort. Static muscle volumes of individual muscles of the TSMC, peak muscle velocity, and torque at that point of time will also be quantified. A custom designed force transducer apparatus will measure torque. The scanning and testing sessions for the ULLS group will be at 2 weeks and 1 day prior to suspension, last day of a 6-week suspension period and 2, 4, and 6 weeks post suspension. The muscle stress-strain dynamics will demonstrate the regions of muscle most affected by visualization and quantification of atrophy and the corresponding susceptibility to strain injury. Development of the MRI technology used in this study should be useful in future studies to test the efficacy of a wide range of exercise countermeasures by providing an objective measure of changes in stress-strain properties and recovery of these parameters following muscle atrophy.

RESEARCH AREA:	**Muscle Alterations and Atrophy**
PRINCIPAL INVESTIGATOR:	**Robert W. Wiseman, Ph.D.**
ORGANIZATION:	**Michigan State University**
PROJECT TITLE:	**Ca^{+2} Homeostatis and Muscle Phenotype: Role of Cellular Energetics**

Project Executive Summary

Exposure of skeletal muscle to space flight results in a significant loss of mass and a shift in the phenotype from slow to fast muscle isoforms. To a limited extent, astronauts are able to ameliorate this remodeling of muscle tissue through exercise. If the mechanistic link between physiologic function and phenotype were better understood, design of countermeasures using combinations of exercise protocols and pharmaceuticals could be employed to increase the efficacy of training while on space missions. We propose that altered physiologic function signals the initiation of the remodeling process through Ca^{+2} sensitive transcription factors (CSTFs) which are activated through changes in two homeostatic processes; mitochondrial ATP synthesis and sarcoplasmic reticulum (SR) ATPase Ca^{+2} handling. It is our assertion that alterations in phenotype in response to changes in load bearing or any other metabolic stress involves processing information from the physiology in the form of feedback from these two homeostatic processes. We use an integrative approach to study this problem in isolated superfused skeletal muscles using a combination of non-invasive techniques (^{31}P-NMR and fluorescence spectroscopy and mechanics) and molecular techniques. In the first Aim we determine the sensitivity of cytosolic Ca^{+2} handling to metabolic loads induced by electrical pacing and metabolic inhibitors. In the second aim we test the response of CSTFs to alterations in Ca^{+2} homeostasis using ionophores, SR ATPase inhibitors as well as the metabolic stresses we develop in Aim 1. We believe once the mechanistic link is established that we may be able to design countermeasures to mask the loss of mechanical loading by direct manipulation of cytosolic Ca^{+2} and more effectively stave off the changes occurring in limb musculature.

NSBRI RESEARCH PROGRAM
NEUROBEHAVIORAL AND PSYCHOSOCIAL FACTORS

Team Leader: **Dinges, D. F.** **Penn**

Associate Team Leader: **Wood, J.** **Baylor**

Lieberman, P.	**PI**	**Brown**	**Speech Monitoring Cognitive and Personality Alterations**	**100**
Friedman, J. H.	CO-I	Brown		
Mertus, J. A.	CO-I	Brown		
Tabin, G. C.	CO-I	U of Vermont		
Orasanu, J. M.	**PI**	**NASA Ames**	**Distributed Team Decision Making in Exploration Missions**	**101**
Fischer, U. M.	CO-I	Georgia Tech		
Wood, J.	**PI**	**Baylor**	**Individuals and Cultures in Social Isolation**	**104**
Helmreich, R. L.	CO-I	UT-Austin		
Phillips, T. M.	CO-I	NIH		
Lugg, D. J.	CO-I	Australian Antarctic Div.		

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**Gary Aston-Jones, Ph.D.**
ORGANIZATION:	**University of Pennsylvania School of Medicine**
PROJECT TITLE:	**Stress, Performance and Locus Coeruleus**

Project Executive Summary

Original Aims – The original aims of this project were: 1. Analyze the activity of brain stem noradrenergic locus coeruleus (LC) neurons during a continuous performance task, 2. Determine the effects of acute and repeated stress on changes in LC function and performance, and 3. Identify pharmacological countermeasures to mitigate stress effects on LC activity and attentional function.

Key Findings –

1. *Development of a continuous performance task for the rat.* We developed a target detection continuous performance task that rats can learn rapidly. This task mimics many of the attributes of the target detection task in our previous studies in monkeys in which LC activity appears to play a major role. Rats initiate each trial by pressing one lever, and then must discriminate between two signal lights to determine if the one illuminated is a target or non-target. If the target signal light is illuminated the rat must press a second lever to obtain food reward. If the nontarget is illuminated he must withhold responding with no reward and await the next trial. Targets occur randomly on 20% of the trials. This task will be the means by which we measure performance abilities and changes therein induced by stress and pharmacologic treatments.

2. *Effects of stress on performance in the target detection task.* To date we have tested only acute noise stress on performance of this task. Results indicate that white noise during task performance at 90 db significantly increased responding to the non-target stimulus (false alarm (FA) errors) in this task. Interestingly, this effect habituated rapidly, so that subsequent administration of 105 db did not influence performance. Chronic stress (planned for this year) may be needed to see continued performance deficits. The alpha2 adrenoceptor agonist clonidine (which decreases LC-NE neurotransmission) at 8 mg/kg reduced the FA error rate seen with 90 db noise stress. Higher doses of clonidine (25 mg/kg) produced sedation. These preliminary experiments require confirmation with additional studies, but they suggest that the NE system may be involved in stress effects on performance in this task.

3. *Effects of idazoxan on performance in the target detection task.* The alpha2 adrenoceptor antagonist idazoxan increases firing of LC neurons and release of NE from LC terminals. Our view of LC's role in performance predicts that this agent should worsen performance on this task, with increased FA errors (as observed in monkey LC neurons during periods of high tonic LC activity). Systemic idazoxan had no effect on two rats that were performing marginally in the task (i.e. a 30% false alarm rate). However, this compound markedly increased false alarms in both of the rats that were performing exceptionally well and had low baseline false alarm rates in the absence of the drug. Although preliminary, these results are consistent with the view that moderate levels of tonic LC activity are critical for maintaining focused attentiveness to task stimuli and performing optimally, and that behavioral performance declines when tonic LC firing rates are increased. We speculate that the lack of an effect of idazoxan in rats with marginal

baseline performance reflects the inverted U relationship described by the PI for the relationship between LC activity and performance on such a task. Thus, in these rats the poor performance pre-drug may have been due to a high level of baseline tonic LC activity, placing them at the right of the inverted U relationship. This pre-existing heightened LC activity could have created a ceiling effect that prevented idazoxan from further increasing LC firing rates and disrupting responses.

4. Role of the LC in circadian regulation of sleep and waking. We expanded our program to include analysis of the role of LC in effects of sleep deprivation on performance. We took this step because sleep deprivation is one of the largest stresses affecting the astronaut, and there are well-established effects of sleep deprivation on performance. For this, considerable technological development has occurred. We implemented a telemetry system for recording EEG, EMG, body temperature and locomotor activity in freely moving, untethered rats. This system produces robust sleep measures over long periods of time. We have also developed a mechanism for producing sleep deprivation, consisting of a slowly rotating wheel that the rat is within. This device allows access to food and water and also contains levers and stimuli to allow task performance during the sleep deprivation period. We will use this system to deprive rats of sleep at different times of their circadian rhythm and examine effects on performance. We will then analyze effects of manipulating the LC system on the performance deficits produced by sleep deprivation.

<u>Impact of these findings</u> – The development of a target detection task for the rat now allows us to test the effects of stressors on a type of performance important in space missions. This model will also allow analysis of the effects of manipulations of the brain NE system of the LC in these stress effects to facilitate development of countermeasures that should facilitate performance in the face of stress. We found that acute stress increases FA errors in this task, and that decreasing neurotransmission in the LC system with clonidine may offset this effect. Accordingly, we also found that increased NE neurotransmission (with idazoxan) in non-stressed animals worsens performance on this task by producing the same type of errors (FAs). These results indicate that the LC-NE system may be a valid target for development of countermeasures to the effects of stress on performance. Finally, we have developed a device to sleep-deprive rats and measure effects on performance in this task. This will allow analysis of this important stressor on performance, and the ability of manipulations of the LC system to offset such stress effects on performance.

<u>Proposed research plan for next year</u> – Studies will continue in the areas described above to confirm findings to date. In addition, new studies will be undertaken to examine the effects of chronic noise stress, as well as sleep deprivation stress, on performance. The ability of manipulations of the LC-NE system to offset these stress effects on performance will be determined.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**Joseph Brady, Ph.D.**
ORGANIZATION:	**Johns Hopkins University School of Medicine**
PROJECT TITLE:	**Psychosocial Performance Factors in Space Dwelling Groups**

Project Executive Summary

The original aims of the project were the development and laboratory testing of a simulation approach to providing an automated means for research analysis of performances in space-dwelling groups as well as monitoring electronically the effects of varying experimental conditions that influence psychosocial interactions. The significance and relevance of the research resides in the potential for conceptual and methodological advances that not only promote psychosocial and ecological stability in small isolated space-dwelling groups but may as well ultimately benefit larger societal units, including those that remain Earth-bound, by enhancing educational and training technologies that facilitate communication of an expanded generalizeable knowledge base.

With the shift in focus to long-duration manned spaceflight missions, planning strategies and tactics as they relate to the behavioral biology science and technology support base require reorientation and an essential change in emphasis. Whereas screening, selection, and training have been the hallmarks of demonstrably successful short-term manned space flight initiatives to date, the integration of behavioral and environmental programming systems "in flight" over extended mission durations must clearly be a priority concern in future spaceflight operations. Virtually all human life support functions (e.g., sleep and wakefulness, nutrition and fluid balance, work and emergency performances, organizational functions, social and recreational activities, etc.) will require operational definition in terms of behavioral interactions between organism and environment under conditions involving time series changes over both short and long duration intervals. A science-based technology for systems management, monitoring, and program control of such behavior/environment interactions is as essential to insure the success of long-duration manned spaceflight missions as is the hardware and softwear technologies that make such initiatives possible.

Simulations are at best approximations and all essential features of the operational setting cannot be replicated. Superordinate objectives and ultimate aversive consequences are, of necessity, less compelling under laboratory circumstances, and many organizational and sociopolitical issues of critical concern in considering the needs of projected long-term space-dwelling groups must await more advanced phases of such an investigative endeavor. But the obvious benefits of obtaining valid and reliable answers to at least some of the operational questions of critical concern in planning and carrying out projected extended manned space missions (e.g., command structure and functions, group performance effectiveness, work and social interactions, etc.) far outweigh the proportional costs when the magnitude of the resource investment required for these initiatives is taken into account. And even if these extended duration human operations in space were to be postponed well into the future, the lead time to get our ducks in a row on these behavioral biology requirements clearly emphasizes the need for long-term human studies under experimentally controlled laboratory environmental conditions.

Research progress during this first award year has focused upon the development of the programming softwear for the initial three-person crew simulation of the planetary exploration mission involving an Orbiter/Lander/Rover model. Progress to date on this initial critical phase of the research project includes completion and installation of both the communication software and expeditionary simulation softwear on the networked simulated crew stations. In addition, the computer hardware architecture has been delivered and assembled to permit interactive communication and expeditionary system pre-testing between the functional networked crew stations.

Construction of a specially designed laboratory facility for the NSBRI Psychosocial Performance Factors research project at the Institute for Behavior Resources Headquarters Building in Baltimore City in the vicinity of the Johns Hopkins University Homewood Campus has also been completed. The laboratory provides for three acoustically controlled workstations plus an additional separate 'Mission Control' station for operational implementation of the simulated Orbiter, Lander, Rover expedition for planetary surface exploration missions.

Progress has also been made in the recruitment and training of essential professional and technical support personnel for computer system maintenance and troubleshooting as well as the personality testing and evaluation phases of the project. In addition, preliminary testing has begun to calibrate the scenario difficulty, pretest the speed of solutions by typical groups, troubleshoot the instructions and the task effectiveness questionnaires, and assess the inherent variability of the group decision processes. During these pretests, the scenario is undergoing modification as necessary and finalization, the reliability and validity of measurements is being verified, and the performance rates that characterize group participants' approach are determining the kind and extent of scheduled pretraining required before the start of an experiment. The effects of the time pressure stressor that involves interruption of the on-going task (e.g., to perform a radiation protection drill to avoid a hazardous event) are also being pretested. These preliminary tests will determine the range of task interruption times that represent low and high levels of stress. It is anticipated that four to six groups will be required for this preliminary testing involving twelve to eighteen participants before formal enrollment of experimental subjects for the six to twelve research groups to be studied during the coming year.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**Lane J. Brunner, Ph.D.**
ORGANIZATION:	**The University of Texas at Austin**
PROJECT TITLE:	**Effect of Space Flight on the Pharmacokinetics of Psychotherapeutic Agents**

Project Executive Summary

The physiological changes that have been shown to occur during space flight may potentially alter the pharmacokinetics and pharmacodynamics of drugs administered to crewmembers. The rate and extent of drug absorption from the gastrointestinal tract following oral administration depend upon gastric emptying, gastrointestinal fluid volume, interaction with components of the gastrointestinal tract and mixing. The extent to which a drug distributes proteins, red blood cells or other blood components (dependent upon both drug and component concentration), binding to tissue proteins, and the actual perfusion of tissues by the blood. Drug elimination is dependent upon organ perfusion, primarily the kidney and liver, as well as binding to various blood components. While these pharmacokinetic characteristics of drugs have been well studied under normal conditions and the influence of disease states, age, sex, etc., investigated, the effects of space flight and zero gravity on such parameters are unknown. Since the therapeutic effect of a drug is related to its absorption, distribution and elimination, knowledge of the effects of space flight on these parameters is essential for rational use of therapeutic agents during space flight. This issue will be of particular importance during long-term space flights where the likelihood of medication use for such illnesses as depression, anxiety, and other psychogenic disorders will greatly increase.

A long-term objective of these studies is to determine the effect of space flight on drug pharmacokinetics and pharmacodynamics and the underlying physiologic processes. The present proposal will investigate the effect of space flight on gastric motility and drug absorption through the examination of the absorption profile of the anti-anxiety drug, lorazepam before, during, and after space flight to estimate alterations in gastric emptying rate. In addition, lorazepam pharmacokinetics will be examined following both oral and intravenous dosing. The absorption, distribution, metabolism, and elimination profile of the anti-depressant, venlafaxine, before, during, and after space flight will also be studied to determine the effect of zero gravity on the pharmacokinetics of this model compound. These data together will address the effect of space flight on the disposition of these therapeutic agents and how future dosing regimens of these and other agents should be determined during actual space flight to maximize effectiveness and minimize toxicity.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**James Carter, Ph.D.**
ORGANIZATION:	**Dartmouth College**
PROJECT TITLE:	**Designing a Smart Medical System for Psychosocial Support**

Project Executive Summary

Psychosocial problems in the Russian and American space programs have led to poor productivity, interpersonal tension and even mission termination. Both depression and interpersonal conflicts have been significant problems in isolated settings in space. Diagnosing, treating, and preventing these problems is challenging, since psychological services are unavailable on most space missions. Additionally, acknowledging psychosocial problems can stigmatize the crew and confidentiality is difficult to maintain. Recent work has demonstrated that computer-based systems can be used for self-diagnosis and treatment of psychosocial problems. Recent studies show that mental health patients respond more openly to questions posed by a computer system than by mental health professionals and that, for minor depression and anxiety, computer-based treatment can have efficacy comparable to live treatment. We propose to develop a Smart Medical System for Psychosocial Support (SMS-PS) prototype, including the systems infrastructure and basic functions of 3 modules, including self-diagnosis of psychological problems, treatment of depression, and conflict management. The SMS-PS could subsequently be expanded to include numerous additional modules for diagnosis, treatment, patient management, and prevention of any possible psychosocial problems that might arise on space missions. The prototype would apply IML's Virtual Practicum model, creating an immersive, welcoming environment in which to seek assistance for psychosocial problems. The interface of the system would be flexible, depending on crew's needs. For crewmembers seeking assistance, the Interactive Media Lab's (IML's) "Virtual Practicum" model could be applied, presenting a realistic, immersive environment, such as a "Virtual Space Station," with a warm, "human" feel crewmembers seeking rapid access to guidance or information the SMS-PS could take the form of an easily-searchable, cataloged database. Evaluation of the program will guide the expansion and complete development of the SMS-PS.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**David Dinges, Ph.D.**
ORGANIZATION:	**University of Pennsylvania School of Medicine**
PROJECT TITLE:	**Optical Computer Recognition of Behavioral Stress**

Project Executive Summary

The goal of this project is to develop and test an optically based computer recognition algorithm of the face to reliably detect the presence of stress during performance demands. Manned space flights of increasingly longer durations are being planned. There is evidence from U.S. and Russian space missions that astronauts and cosmonauts have experienced operational stressors that adversely affected subjective well-being, physiology, and performance capability. In order to provide countermeasures for stressor-induced impairments in astronauts, objective, unobtrusive measures of the presence of stress reactions are needed. This project seeks to achieve such a measure, through a collaboration between two established laboratories at the University of Pennsylvania—one with expertise in the evaluation of behavioral and physiological responses under stressful and non-stressful conditions (Prof. D. Dinges, Department of Psychiatry, Unit for Experimental Psychiatry), and the other with expertise in optical computer recognition of human subjects' facial expressions and gestures (Prof. D. Metaxas, Department of Computer Science, Vision Analysis and Simulation Technologies).

Astronauts aboard extended-duration space missions will endure the harsh space environment and the effects of various stressors (e.g., microgravity, perceived risks, work requirements, habitability constraints, radiation, restricted communication with Earth) to a much greater degree than have been experienced previously. Maintaining individual neurobehavioral functioning of astronauts will be vital to assuring mission success. However, in order to provide countermeasures for stressor-induced, physical and functional impairments in astronauts, objective measures of the presence of heightened stress reactions are needed. The earlier that stress reactions (regardless of their operational, psychosocial, or neurobiological source) can be detected, the greater the probability that an appropriate countermeasure strategy can be implemented (e.g., rest, pharmacology, behavior). In the absence of objective detection of developing stress reactions, it is unlikely that countermeasures for stress impairment of astronauts can be managed. Many techniques for monitoring stress reactivity in space flight are impractical (e.g., cortisol measurement), unreliable (e.g., self-report), or obtrusive. However, unobtrusive, continuous video monitoring of the human face during neurobehavioral tasks, offers a potential solution to these problems. Consequently, this project will provide the first scientific test of the use of optically based computer recognition of the face to unobtrusively and reliably detect the presence of stress during laboratory performance demands.

The proposed computer-based optical recognition system will build on the research of Prof. Metaxas by utilizing automatic optical tracking of human subjects' anatomical and motoric changes in facial expressions during non-verbal performance tests. Video input to the system will be provided from experiments performed in the laboratory of Prof. Dinges, in which healthy adults (males and females of different ethnic backgrounds) will be exposed to behavioral stressors to increase the likelihood of developing a sensitive algorithm.

The aim of the protocol is to experimentally establish whether an optical computer recognition algorithm based on facial expression can be developed that can objectively, independently and reliably discriminate when subjects are undergoing behavioral stressors, and whether a high degree of accurate categorization can be achieved for both male and female subjects; for both younger (22-32 years) and older (33-45 years) subjects; and for subjects of different ethnic backgrounds. Further, in exploratory and heuristic analyses, we will evaluate the effects of behavioral stressors on physiological responses of cortisol secretion and heart rate, on psychological responses of self-report ratings of stress and mood, and on neurobehavioral performance responses; and explore the extent to which the magnitude of the stress response as assessed by these measures relates to the accuracy of the optically based computer recognition algorithm of the face.

A single-blind, repeated-measures cross-over, controlled trial will be used to achieve these aims and to provide the data required to test the hypothesis that an objective, unobtrusive, optically based computer recognition algorithm of the face can be developed to reliably detect the presence of high stress (and of low stress) during performance. A total of 60 healthy adults will be studied in the Unit for Experimental Psychiatry laboratory (Dr. Dinges) during three sessions: I—screening session; II—training session for development of the optical computer recognition algorithm; and III—prospective test session of the predictive utility of the optical recognition algorithm to discriminate high versus low stressed states associated with behavioral stressors. Stress reactions will be tracked during both control (low stress) and high stress conditions in sessions II and III, by measurement of salivary cortisol, heart rate, subjective mood/stress responses, and neurobehavioral performance. Videos of subjects' faces in the low and high stress conditions of session II will be used by the Vision Analysis and Simulation Technologies laboratory (Dr. Metaxas) to develop a predictive optical algorithm that will be tested blind to stressor level (i.e., high vs. low) in the behavioral stressor conditions of session III.

The experiment is designed to test the <u>hypothesis</u> that an optical computer recognition algorithm can be used to discriminate when subjects are undergoing behavioral stressors, as defined by established stress-related changes in cortisol secretion, heart rate, subjective reports, and performance.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**Nick Kanas, M.D.**
ORGANIZATION:	**Northern California Institute for Research and Education**
PROJECT TITLE:	**Psychosocial Education (PSE) Training for ISS Missions**

Project Executive Summary

Previous studies suggest that changes occur in the interpersonal environments of crewmembers and mission control personnel during long-duration space missions that influence performance and well being. The objective of this proposal will be to evaluate the effectiveness of our new Psychosocial Education (PSE) training program, which is aimed at optimizing crew and ground safety, well being, and performance. It will consist of two parts: a 5-hour PSE pre-launch training session and two 30-minute PSE Post-launch training sessions.

Five ISS crews and their associated mission control personnel will receive the PSE training. Following their missions, these subjects are expected to exhibit: 1) less overall tension, 2) more overall cohesion, 3) more leader support, 4) less displacement of group tension and dysphoria to outside personnel, 5) less negative interpersonal impact from cultural effects, 6) less tendency toward 2nd half increases in tension and decreases in cohesion and leadership support, and 7) more expressiveness and personal growth relative to the subject responses from our previous Shuttle/Mir and ISS investigations.

All subjects will complete standard mood and interpersonal group climate questionnaires, a critical incident log, and a culture and language questionnaire. The culture and language questionnaire will be administered once before each mission. The other measures will be completed on a weekly basis before, during, and after each mission; will take 15-20 minutes to fill out; and will already be in use onboard the ISS. In addition, the subjects will be given a semi-structured interview within a month of their return evaluating the usefulness and effectiveness of the PSE training. The effectiveness of the PSE training also will be evaluated descriptively by comparing the interpersonal environment of these crews with the group climate reported in our previous Shuttle/Mir and current ISS studies.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**Stephen Kosslyn, Ph.D.**
ORGANIZATION:	**Harvard College**
PROJECT TITLE:	**Quick Assessment of Basic Cognitive Function: Blood Pressure Cuffs for the Mind**

Project Executive Summary

It is unclear what effects prolonged microgravity will have on human cognitive function. Moreover, it is unclear how such effects will interact with other variables that affect our cognitive abilities, such as the lack of sleep. The present proposal is aimed at developing a new set of tools, which are analogous to "blood pressure cuffs" for the mind. The general goal is to develop tasks that can be self-administered very quickly to obtain an objective assessment of the state of basic cognitive processes. The specific goal is to develop two kinds of tasks. The first will be computerized versions of 12 "standard" tasks from cognitive psychology, which tap a range of basic cognitive abilities. The second will be very short versions or variants of these tasks. Our aim is to design short, easy-to-administer variants that best capture the processing differences indicated by the scores on the standard tasks.

We will administer both sets of tasks to 50 subjects. After this is accomplished, we will correlate performance on the two versions, and redesign all short version tasks that correlate less than r=.80 with the standard version. A new group of 50 subjects will be tested on the redesigned short versions and corresponding standard versions. This process will be repeated until criterion is reached for all tasks. We will then perform factor analysis, multidimensional scaling, and hierarchical cluster analysis on the data from both versions separately; the purpose of these analyses is to validate that the tasks do in fact tap different underlying processes, and that the short versions tap the same underlying processing as the long versions.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**Philip Lieberman, Ph.D.**
ORGANIZATION:	**Brown University**
PROJECT TITLE:	**Speech Monitoring Cognitive and Personality Alterations**

Project Executive Summary

Our long-term goal is a system that will detect cognitive deficits, changes in personality and emotional disturbances occurring during prolonged space flight by means of acoustic measures of a person's speech. The system that we propose would monitor the flow of normal conversation, deriving relevant acoustic parameters using automated computer-implemented procedures that we will develop and verify in the study that we now propose. We will study the speech and behavior of individuals in a "space-analog," as well as patients suffering neurodegenerative diseases. These populations, to different degrees, exhibit degraded neural processes regulating these behaviors, that may also be compromised in space.

Our previous studies demonstrate that certain cognitive deficits can be monitored by means of objective acoustic measures of speech (Lieberman et. al., 1992, 1994, 1995; Pickett, 1998; Pickett et al., 1998; Lieberman, 2000). Other studies suggest that speech measures may provide indices of personality alterations. Advances in neuroscience show these dependencies reflect the neural architecture of the human brain. Dopaminergic, subcortical basal ganglia structures regulating speech motor control also support cortico-striatal neural circuits regulating cognition. Altered activity in these circuits can result in apathy, irritability, disinhibition, mood changes and obsessive-compulsive behavior (Alexander et al., 1986; Laplane et. al., 1989; Cummings, 1993; Marsden and Obeso, 1994). Given the possibility of cosmic ray damage to cerebral dopamine pathways during long space missions, noninvasive, unobtrusive monitoring of space crews by means of speech analysis may be prudent and useful. We propose a two track approach to achieve timely development of an operational system.

We will obtain data using the "space-analog" studied in our previous NASA sponsored project, climbers ascending Mount Everest. The expeditions members selected will be a reasonable match to space-flight crews: extremely fit, highly motivated, and intelligent. It would be difficult to otherwise ethically reproduce the hypoxic insult, high levels of stress resulting from a life-threatening environment, and the resulting group interactions that occur on Mount Everest. Prolonged exposure to extreme altitudes during the Everest climb produces speech production and cognitive deficits (Lieberman et. al., 1994, 1995) similar in nature to those occurring in Parkinson's Disease, which degrades dopaminergic cortico-striatal circuits (globus pallidus, the principal basal ganglia output structure, is sensitive to oxygen deprivation). Whereas our 1993 study focused on one acoustic parameter derived from isolated test words, we propose to develop and verify techniques that will allow us to analyze conversational speech. Moreover, we will derive additional acoustic parameters that have been associated with cognitive-linguistic deficits in our subsequent studies (Pickett et al. 1998; Lieberman, 2000). We also will assess changes in mood and personality and speech measures that may track these changes. In addition, we propose to study a population having more extreme compromised dopaminergic circuit function similar in nature to that which may occur in space, Parkinson's Disease patients.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**Judith Orasanu, Ph.D.**
ORGANIZATION:	**NASA Ames Research Center**
PROJECT TITLE:	**Distributed Team Decision Making in Exploration Missions**

Project Executive Summary

Background and Project Goals

Successful long-duration space missions will depend on the ability of team members (both space crews and ground controllers) to respond to unanticipated problems and to collaborate effectively under highly stressful conditions. In addition to environmental threats (radiation, microgravity) and task-related stressors (time pressure, danger, workload, and fatigue), crews are subjected to psychosocial stressors such as confinement with the same small group of people, lack of privacy and personal space, isolation from family, and restricted or delayed communication with Earth. During prolonged space missions, these psychosocial stressors could well threaten the psychological well-being of the individual astronaut and limit crew effectiveness. While crewmembers are highly selected and technically skilled, "the history of space explorations has seen many instances of poor interpersonal relations and faulty decision making" (Committee on Space Biology and Medicine, NRC, 1998). As a result, NASA has concluded that interpersonal difficulties could well threaten the success of long-duration space missions (NASA Critical Path Analysis, [*http://criticalpath.jsc.nasa.gov*], NSBRI-99-02). Interpersonal relationships are of particular concern as crewmembers become more diverse in terms of culture, gender and professional backgrounds. Tensions are likely to result from miscommunications and misunderstandings based on differing cultural norms and expectations.

The goal of our project is to understand how team problem solving and decision making are affected by task-related and psychosocial stressors similar to those that may be encountered in space. Results of the study will yield a basis for (a) designing or revising procedures, training practices, and technologies to support effective team performance, and (b) developing technologies for monitoring and predicting breakdown of team interactions so that countermeasures may be introduced before team dynamics deteriorate to the point of threatening mission success. Five specific questions will be addressed in our studies: (1) What is the impact of task-related and psychosocial stressors on decision making and interactional behaviors in team problem solving situations? (2) What task and team strategies are most effective in performing collaborative work? (3) How do gender and cultural background influence decision making strategies and team interactions? (4) Are there physiological and biomedical indicators that predict individual stress and deteriorating team interactions? (5) Are these measures robust across gender and national group?

Approach

A set of experiments will be conducted to answer these questions. Teams of four participants will work together on a computer-based dynamic decision making task. While participants are working on the task, we will monitor their physiological responses and facial expressions for signs of mental and emotional stress. Participants' physiological arousal levels and facial affect will subsequently be correlated with individual and team performance in the decision making task. The distributed decision making task used in our studies involves a simulated search and rescue mission in Antarctica. The simulation presents graphical displays of evolving problem scenarios and supports communication among team members via e-mail messages. The simulated mission will enable us to examine collaborative behaviors among team members in two phases of the task: (a) during *planning* of how to go about locating the lost party, and (b) during *executing* the search task under a variety of task constraints such as time limitations, unexpected obstacles, and unreliable information. The software will also permit manipulation of a variety of potential stressors in two categories: *Task Difficulty* and *Team Conflict*.

Accomplishments and Key Findings - Year One

Scenario Developed for the simulated search and rescue mission. Aptima Inc. developed a prototype scenario for the search and rescue task. This prototype was tested in our lab for usability and software problems. A number of changes concerning the display and the search and rescue task have been requested of Aptima and are currently being incorporated. The first scenario in its four versions is expected to be completed and delivered to NASA Ames by the end of August. Two versions of the scenario will be designed to induce cooperation between team members and will vary in task difficulty (moderate and high). The other two versions will include variables to induce team conflict (again, one of moderate and the other of high task difficulty). Two additional scenarios (four versions of each) will be developed and delivered by September 30, 2002.

Laboratory Established. All the computer and video equipment necessary for our research has been purchased and set up. Four individual work stations have been connected through a local area network to enable team members' cooperation during the simulated search and rescue task. Physiological monitoring devices (Biologs developed by UFI) available at NASA Ames Research Center have been adapted for use in our experiments. Equipment and software required to time-stamp and coordinate the recording of dependent measures from various sources (i.e., behavioral, physiological and facial affect measurements) have been acquired and are currently being tested.

Physiological Measures. The biomedical literature was reviewed to identify physiological measurements that might be useful for analyzing mental and emotional stress. Seven candidate measurements were selected and included in a preliminary study to determine which of them were most sensitive to low levels of emotional and mental stress and thus best suited for early detection of stress. We also sought to reduce the number of measurements from seven to four in order to minimize subject discomfort. A final issue was whether physiological measurements taken at alternate locations on the body would provide meaningful data while allowing subjects maximum movement and comfort.

Physiological data were collected while participants, four healthy adults aged 21-39, engaged in a commercially available active video game intended to activate the sympathetic nervous system. Each trial began with five minutes of relaxation time, followed by 60 minutes of playing the video game. Upon completion of the game, the subjects were again given five minutes of relaxation time. In order to maximize movement and comfort and to receive stronger signals, the PPG electrodes were moved from fingers to earlobe, EMG electrodes were moved from the lower arm to the neck muscles, and SCL electrodes were moved from the hand to the foot.

Analyses of the sensitivity of the physiological measures while crews engaged in a stressful task compared to rest periods indicated that ECG (R-R interval, Heart Rate), EMG (frequency power spectra and the amplitude within the band width of 10-25 Hz), respiration (frequency and amplitude), temperature and SCL (trend measurements) proved to be the most useful measurements for assessing mental and emotional stress at a low level.

Implications

• Findings on the effects of stressors on team performance in a dynamic challenging task will extend the research base on stress and behavior. Types of performance that may be affected include problem solving task performance, communication, and cooperative behaviors.

• The combination of selected physiological measures and facial affect measurements (described below) may yield a powerful instrument for assessment of low level mental and emotional stress. If successful, this tool could lead to early introduction of countermeasures, and thus prevent development of high levels of stress and deterioration of team performance.

• Positive stress-coping behaviors in a distributed problem solving task will be extracted from our findings. These will serve as a basis for developing interactional and strategic behaviors for managing challenging team tasks. These will include communication, team support, cooperative and self-monitoring behaviors that can serve as the basis for countermeasure training.

• We anticipate testing laboratory-based task and stress-management techniques in non-laboratory conditions, such as simulations of long-duration missions involving multi-cultural crews (e.g., NASDA or ESA studies). Our goal is to adapt the tools so that they can be used by crews as self-monitoring and management systems.

Proposed Activities for Year Two

Facial Affect Coding. Our next research steps will include the synchronization of the selected physiological measurements with video recordings of facial expressions. We plan to focus on facial actions related to typical expressions of basic emotions. While each national culture has a different body language and behavior, facial expressions are relatively stable across cultures. For example, researchers at the Japanese Space Agency have successfully used the facial action coding system (FACS) developed by Paul Ekman (1971) to examine facial expression during long-term missions in the ISS. Based on experts' recommendations, we plan to use Ekman's emotional facial action coding system (EMFACS) as a basis for our analyses.

Data Collection. During the fall and early winter 2002, we will test the effectiveness of the task difficulty and the crew conflict manipulations, the reliability and validity of performance measures, and of our physiological and behavioral monitoring tools. These tests will be done with homogenous teams made up of US participants.

Full-scale data collection will begin once the tools, tasks, and manipulations have been tested and found to meet our requirements. Data collection will begin in the winter, 2002.

- The first study will address the effects of task manipulations on team performance using culturally homogenous teams. Teams will consist of all male subjects born in the US. Task difficulty and team conflict will be the independent variables in this study. Task difficulty will vary within team, while team conflict will vary between teams.
- Cultural diversity in teams will be examined in the second set of studies. Participants will be sought who are from countries that will participate in the ISS: Russians, Japanese, Canadians, Europeans and Americans. Only male subjects with technical training similar to mission specialists will be used. Teams will be configured as either culturally homogeneous or culturally diverse.
- Gender variation will be introduced in the third set of studies expected to begin at the end of year two.

RESEARCH AREA:	**Neurobehavioral and Psychosocial Factors**
PRINCIPAL INVESTIGATOR:	**JoAnna Wood, Ph.D.**
ORGANIZATION:	**Baylor College of Medicine**
PROJECT TITLE:	**Individuals and Cultures in Social Isolation**

Project Executive Summary

The proposed research is designed to study the roles of personality, culture, and group influences on behavior, performance, and health outcomes in winter-over Antarctic research stations. These remote and isolated habitations provide an environment analogous to long duration space missions, such as those planned for the International Space Station and eventually a piloted expedition to the planet Mars. The ultimate objectives of this project are to:

1. Increase our understanding of the effects of personality, culture, and group characteristics on both individual and group performance in extreme environments.
2. Identify those elements of leadership that maximize crew functioning in extreme environments.
3. To understand how individual and group factors affect physical health under prolonged stress.

We will examine changes in weekly self-assessment of individual and group adaptation, monthly levels of several neuropeptides, and other health outcomes, as a function of individual (personality, demographic, personal history) and group characteristics (leader traits, culture mix, group tensions) and local events. This study will use Hierarchical Linear Modeling to partition variance in our dependent variables among relevant individual, group, and time factors.

NSBRI RESEARCH PROGRAM
NEUROVESTIBULAR ADAPTATION

Team Leader:	**Oman, C. M.**	**MIT**
Associate Team Leaders:	**Cohen, B.**	**Mount Sinai**
	Wall, C. C.	**Harvard**

Shelhamer, M. J.	**PI**	**Hopkins/SOM**	**Context-Specificity and Other Approaches to Neurovestibular Adaptation**	**116**
Minor, L. B.	CO-I	Hopkins/SOM		
Zee, D. S.	CO-I	Hopkins/SOM		
Angelaki, D.	CO-I	Wash. Univ.		
Snyder, L. H.	CO-I	Wash. Univ.		
Zhou, W.	CO-I	U of Miss.		
Wall, C. C.	**PI**	**Harvard**	**Advanced Techniques to Assess and Counter Gait Ataxia**	**120**
Bloomberg, J. J.	CO-I	NASA JSC		
Oddsson, L.	CO-I	Boston University		
Raphan, T.	CO-I	Mount Sinai		
Young, L. R.	**PI**	**MIT**	**Neuro-Vestibular Aspects of Artificial Gravity Created by Short-Radius Centrifugation**	**122**
Hecht, H.	CO-I	MIT		
Oman, C. M.	CO-I	MIT		
Mast, F.	CO-I	Harvard/MIT		
Dizio, P.	CO-I	Brandeis		
Lackner, J.	CO-I	Brandeis		
Paloski, W. H.	CO-I	NASA JSC		
Cohen, B.	CO-I	Mount Sinai		
Dai, M.	CO-I	Mount Sinai		
Cohen, M.	CO-I	NASA Ames		
Welch, R.	CO-I	NASA Ames		
Stone, L.	CO-I	NASA Ames		

RESEARCH AREA:	**Neurovestibular Adaptation**
PRINCIPAL INVESTIGATOR:	**Jacob J. Bloomberg, Ph.D.**
ORGANIZATION:	**NASA Johnson Space Center**
PROJECT TITLE:	**Understanding Full-Body Gaze Control During Locomotion**

Project Executive Summary

Locomotion is a complex task, demanding coordination of the eye-head, head-trunk and the lower limb locomotor apparatus. During locomotion the performer must satisfy two performance criteria: maintain stable forward translation and stabilize gaze (the direction of the eye with respect to space). Fulfilling both criteria places substantial demands on multiple sensorimotor subsystems for precise coordination. After space fight astronauts experience locomotor dysfunction because these multiple subsystems are altered. Traditionally, gaze stabilization has been studied almost exclusively as a problem of eye-head or eye-head-trunk coordination. However, coordination among the eye, head and trunk may not be the only mechanism aiding gaze stabilization during locomotion. Another important factor is the regulation of energy flow or shock wave transmission through the body at high impact phases with the support surface like that which occurs at heel-strike. Allowing these excessive transmissions of energy to the head may compromise gaze stability, leading to oscillopsia and decreased dynamic visual acuity. Specific coordinated actions at the lower limb may contribute to attenuation of the shock wave to the head. Thus, stabilized gaze during natural body movement results from full-body coordination of the eye-head and head-trunk systems combined with the lower limb apparatus. From this point of view, the whole body is an *integrated* gaze stabilization system, with several subsystems contributing to gaze stabilization during body motion. For this investigation, we propose to systematically alter each gaze stabilization subsystem (eye-head, head-trunk and lower limb apparatus) to determine how they interact to preserve visual acuity during locomotion. In this manner, we can observe the emergent full-body coordination patterns resulting in appropriate gaze stabilization during locomotion.

Therefore, the goal of this study is to determine how the multiple, interdependent full-body sensorimotor subsystems aiding gaze stabilization during locomotion are functionally coordinated. Subjects will perform a gaze stabilization task during treadmill locomotion under the following conditions: 1) before and after exposure to minifying and magnifying lenses to adaptively modify vestibulo-ocular reflex gain; 2) while wearing a neck brace that will induce a head-trunk "strapped down" strategy, and 3) while wearing a knee brace that will result in an increase in the shock-wave transmitted to the head during the high impact phases of the gait cycle.

This information will enable a better understanding of the different aspects of full-body coordination which function to preserve gaze stabilization during locomotion. This information will lead to improved tests of post flight locomotion dysfunction that will enable the effective evaluation of the efficacy of sensorimotor countermeasures used to mitigate the deleterious effects of space flight on locomotor control.

RESEARCH AREA:	**Neurovestibular Adaptation**
PRINCIPAL INVESTIGATOR:	**John L. Dornhoffer, M.D.**
ORGANIZATION:	**University of Arkansas for Medical Sciences**
PROJECT TITLE:	**Pharmacological Countermeasures for Space Motion Sickness**

Project Executive Summary

AIMS OF STUDY

Space motion sickness (SMS) is a problem during the first 72 hours of spaceflight and during transitions from different gravity environments. To date, there are no effective drug countermeasures that are able to combat SMS while allowing the individual to retain cognitive integrity. This creates a dilemma for astronauts as full cognition is particularly important during gravity transitions, such as take-off and landing. SMS is generally believed to be caused by a sensory conflict due to unweighting of the otolithic organs; in other words, vestibular cues indicate the head is stable while visual cues indicate the head is moving. Vertigo, on the other hand, is due to under- or overstimulation of the semicircular canals. We hypothesized that the vestibular dysfunction due to overstimulation of the semicircular canals by the rotary chair can serve as a paradigm for SMS, thus enabling us to effectively test drug countermeasures while using test batteries to determine the effect of these countermeasures on cognition. This study addresses one of the main exploration-mission risk areas set forth by NASA in the Critical Path Roadmap and represents a countermeasure readiness level of 6. Our aims are to:

Specific Aim 1. Determine the effects of 4 drug countermeasures (lorazepam, meclizine, promethazine, and scopolamine) in alleviating motion sickness induced by vestibular stimulation with a rotary chair. These countermeasures were selected based on our extensive clinical experience with pharmacologic interventions for vertigo. **Specific Aim 2.** Determine the effects of these countermeasures on cognitive performance and in counteracting the effects of rotation (our SMS paradigm) using an Operant Test Battery (OTB) to assess effects on short-term memory, learning, and time perception, and measures of the P50 potential to assess effects on arousal and distractibility (ability to filter out extraneous information, or sensory gating). **Specific Aim 3.** Use 3D oculography and unilateral otolith testing to determine the extent of correlation between vestibular dysfunction induced by the rotary chair and unloading of otolithic organs due to 0 G. Studies are conducted at the Vestibular Function Laboratory in Antwerp.

KEY FINDINGS

Preliminary results indicate a rank order of efficacy of scopolamine > promethazine > lorazepam ≈ meclizine ≈ placebo, based on increase in duration of rotation post-treatment. Scopolamine appeared to significantly increase both rotation time and time to onset of symptoms whereas promethazine did not increase rotation time significantly but did result in a significant delay in onset of symptoms.

P50 potential studies indicate that rotation does not affect level of arousal but does cause a deficit in sensory gating. Thus, an individual will exhibit increased distractibility from being spun in the rotary chair, our paradigm for SMS. None of the drug countermeasures affected arousal (P50 potential), and only meclizine was able to reduce the deficit in sensory gating produced by rotation. However, more data is needed before these results are conclusive.

The Operant Test Battery (OTB) indicates the Delayed Matching-to-Sample (DMTS) task, or short-term memory and attention task, to be the most sensitive. This showed that meclizine had no adverse effects. Lorazepam caused a decrease in accuracy when combined with rotation but did not appear to elicit an effect on accuracy by itself; however, this countermeasure caused a decrease in response speed that was exacerbated by rotation. Promethazine showed accuracy to be decreased, but this effect was not made worse by spinning. Scopolamine showed accuracy was not decreased by drug treatment alone, but when combined with rotation, accuracy at the longer recall delays was decreased (this effect was the only statistically significant finding noted so far); however, scopolamine had no effect on response speed. Thus, all of the noted countermeasure/rotation effects for scopolamine were observed in the accuracy measures for the longer recall delays, suggesting a relatively specific effect on short-term/working memory.

Studies at the Antwerp site suggest the landmark finding that the reaction on medication is not necessarily the same for the different parts of the vestibular system (the semi-circular canals versus the otolith organs). Promethazine led to a suppression of utricular function, a declined responsiveness of the horizontal semicircular canals, and to central inhibition whereas scopolamine and meclizine did not reduce utricular sensitivity but did provoke a central inhibition and a significant decline in horizontal semicircular canal function. Further experiments are needed to corroborate these findings.

In addition to these results, several off-shoot studies have been carried out which have presented some intriguing findings to augment the present NSBRI study. We are currently using the Psychomotor Vigilance Task (PVT) in a subset of NSBRI subjects to determine the degree to which it is associated with our other measures of cognitive function. Based on results in these subjects, we plan to add the PVT to our NSBRI protocol as a measure of behavioral alertness in order to further validate our OTB findings and P50 results and to test for any learned behaviors. We have also attempted to assess the individual otolith organs (utricle and saccule) using a new clinical paradigm involving off-axis rotation and measurement of the subjective visual vertical (SVV), the ability of an individual in darkness to adjust a luminous line to true vertical at rest and during rotation. Clinical assessment of otolith organs is important to space medicine research due to the involvement of the utricle and saccule in SMS. Results of this protocol in 20 healthy adult subjects revealed that certain subjects have a mild asymmetry (dominance) of the otolith organs. Some of these subjects with dominant otolith organs were able to spin in the chair 2.5 to 3 times longer than those without ear dominance, indicating less susceptibility to motion sickness. This finding is intriguing as it offers a potential screening tool for determining susceptibility to SMS. This concept is now being pursued using the SVV/rotation protocol and the same study subjects enrolled on the NSBRI protocol. We hope to find that those subjects who could spin the longest pre-medication on the NSBRI protocol exhibit ear dominance.

IMPACT

Our project addresses one of the major space neurovestibular risk areas identified through the Critical Path Roadmap: Impaired cognitive and/or physical performance due to motion sickness symptoms or treatments, especially during/after G-level changes (Risk Type III, Risk Rank 3). We are addressing the critical question 9.12: How effective are other drugs in providing fast relief in mission critical situations and does the drug have unacceptable side effects, particularly the short term effects on cognitive function? **(Aims 1 and 2)**. With a countermeasure readiness level of 6, the results of our study will lead to new countermeasures for SMS that are ready for countermeasure demonstration (levels 7 and 8). In addition, through the completion of this study, we will have standardized measures of oculomotor function, postural stability, and cognitive performance **(Aims 1, 2, and 3)**. These standards are crucial for establishing the effectiveness and quantifying the side effects of potential drug countermeasures.

As our preliminary results indicate scopolamine may be the countermeasure of choice, with the highest mean percent increases in duration of rotation (32.77%) and delay to symptom onset (34.73%), future research will focus on optimizing delivery routes and offsetting any cognitive deficits. We hope to collaborate with Dr. Lakshmi Putcha of the Johnson Space Center to develop the concept of intranasal delivery of this countermeasure.

If our off-axis work reveals a correlation between inner ear dominance and resistance to SMS, future work will also focus on developing a reliable screening paradigm for astronauts using off-axis rotation. This would tie in nicely with future scopolamine work as studies have revealed that scopolamine is better as a preventive rather than as a rescue countermeasure. Thus, the SVV/rotational paradigm could be used to determine those individuals who would be most susceptible to SMS, and they would receive scopolamine pre-flight.

The results of our study will also advance earth medical research by determining the extent of correlation between rotary-induced motion sickness (i.e., vertigo) and SMS and developing a testable model that integrates our current knowledge of both conditions. This may ultimately help physicians treat patients with balance disorders related to inner ear dysfunction. Our findings at the Antwerp site strongly suggest that there is a distinct difference in reaction to medication between the semi-circular canals and the utricular system. This can have a great impact on the pharmaceutical treatment of dizziness and vertigo since different management might be necessary depending on the site (canal related or otolith related) of the vestibular lesion.

In addition, the SVV/rotational paradigm is already being utilized to diagnose inner ear problems of patients on Earth. One patient seen by the research team in an effort to diagnose her problems with dizziness was enrolled on the off-axis protocol. Testing revealed a problem with her left ear, leading to a diagnosis of crisis of tumarkin, an inner ear condition in which patients suffer drop attacks. This condition, which eluded previous physicians, was documented in the patient's otolith organs using off-axis rotation and the SVV/rotational paradigm.

Finally, demonstrating links between vestibular dysfunction and cognitive difficulties would be an important discovery by allowing clinicians to better educate patients about how vestibular pathology may affect their ability to concentrate and retain information. We would be better able to educate people with jobs that require mental sharpness, in that they could be alerted to expect difficulties as a result of their vestibular dysfunction. Our findings could also lead to future research into different treatment modalities. Current treatment for peripheral vestibular dysfunction includes the use of vestibular suppressants. Our findings may indicate that research is also needed in the area of treating patients' cognitive difficulties, possibly via CNS stimulants.

PROPOSED RESEARCH PLAN

Over the next project year, we plan to conclude our enrollment and testing to give a total of 75 subjects for which data will be available. We plan to add the Psychomotor Vigilance Task (PVT) to our NSBRI protocol as a measure of basic attentional processes (behavioral alertness) in order to further validate our OTB findings and P50 results and to test for any learned behaviors. This test is the gold standard for measuring pre-attentional mechanisms rapidly and efficiently in a number of military applications. The effects of rotation-induced motion sickness on PVT performance will be compared and correlated with P50 potential and OTB measures, seeking to validate the entire battery of tests, and determining which pharmacological countermeasure is optimal for decreasing symptom severity while not impairing performance. This also will make our findings using the P50 potential (to assess arousal and pre-attentional status) and the OTB (to assess higher cognitive function) more compatible with currently used measures of mission performance, such as the PVT. We also plan to continue off-axis testing of the NSBRI study subjects in an effort to show a correlation between otolith symmetry and susceptibility to SMS. At the Antwerp study site, patient enrolment will continue and further testing will be done to confirm or modify the preliminary findings, which suggest that the different parts of the vestibular system (semicircular canals versus otolith organs) do not necessarily react the same to medication.

RESEARCH AREA:	**Neurovestibular Adaptation**
PRINCIPAL INVESTIGATOR:	**Charles M. Oman, Ph.D.**
ORGANIZATION:	**Massachusetts Institute of Technology**
PROJECT TITLE:	**Visual Orientation and Spatial Memory: Mechanisms and Countermeasures**

Project Executive Summary

When astronauts enter weightlessness, there is no sensation of falling, and normal simple head movements do not elicit disorientation and oscillopsia the way they often do in vestibular patients on Earth. However some astronauts experience persistent "inversion illusions", and most crewmembers occasionally experience startling "visual reorientation illusions" when they leave their seats and float sideways or upside down, or simply even watch another person doing this. The illusion results from a sudden realignment of the cognitive reference frame used for spatial orientation, and a disorienting change in the subjective identity of interior surfaces (e.g. ceilings seem like floors). As a result, crewmembers make reaching errors, and can even become momentarily lost within the vehicle. These illusions – which crewmembers often call "the downs" - are known to trigger space motion sickness. Zero-G disorientation is among the primary biomedical risks of spaceflight as defined by NASA's Critical Path Roadmap.

The goal of this multi-institutional, multi-investigator NSBRI neurovestibular research project is to better understand the process of visual orientation and spatial memory in 1-G and 0-g, and to develop countermeasures for these inflight problems. Our research also pertains to human health on Earth, for example disorientation, spatial memory and navigation problems in vestibular patients, Alzheimer's patients, and in the elderly. Our specific aims are to study:

Human visual orientation. To better understand static and dynamic visual orientation illusions in 0-G by quantifying them in 1-G. To determine how visual frame, polarity, motion and gravireceptor cues influence the direction of the subjective vertical, the response of the oculomotor and motor control systems, stability of the visual world (oscillopsia), and how viewing one's own body, environmental brightness and color cues determine the subjective vertical. (I. Howard, et al, York University)

Three-dimensional spatial memory and learning. To understand why astronauts have difficulty making spatial judgments between modules with different visual verticals, by quantifying how humans use visual cues in 1-G to establish "spatial frameworks" within and between adjacent visual environments. To develop a computerized technique for teaching generic 3-D spatial orientation and memory skills. To investigate and evaluate ISS allocentric coordinate marking systems, and to develop a "virtual porthole" display so trainees can learn to visualize the spatial relationships of ISS modules and potential escape routes in three dimensions. (C. Oman, et al, MIT/W. Shebilske, et al, Wright State)

Neural coding of spatial orientation in an animal model. To define how the preferred direction of limbic system head direction cell depends on visual, vestibular, gravireceptive, proprioceptive and motoric cues in a rat animal model during three-dimensional locomotion. To understand how the vestibular system contributes to these head direction cell responses. Ultimately, to develop a neurophysiological understanding of visual reorientation illusions and spatial cognition in astronauts. (J. Taube, et al, Dartmouth).

Over a three year period, we plan 17 research activities spanning these three aims, and NASA Countermeasures Readiness levels 1-6. Some address the basic mechanisms underlying visual orientation in humans and animals. Others resolve more applied questions directly related to development of specific countermeasures. Recent findings and their implications:

Human visual orientation: We previously reported that the majority of gravitationally supine subjects viewing the interior a furnished room which has been experimentally tilted 90 degrees so that the visual frame and polarity cues align with their body axis experience a visual reorientation illusion and feel subjectively upright, and if the hands are extended they feel weightless. This year we found that if the subject is rotated (rolled) about the gravitational axis, the movement increases the number of subjects who experience this levitation illusion. If left in this visually tilted position, subjects feel tilted from the vertical, but underestimate the angle of the rotation of their body axis with respect to the room by about fifty percent. This effect may be another manifestation of the "idiotropic" tendency which is believed to cause Aubert illusion on Earth, and contribute to Visual Reorientation Illusions in weightlessness. The method could ultimately prove useful in understanding and predicting idiotropic effects in astronauts. Using a mirror bed device, we also demonstrated that visual polarity cues presented in the foreground are less effective in reorienting the direction of the subjective vertical than similar cues in the background.

Three-dimensional spatial memory and learning: Our previous studies of human spatial memory and learning demonstrated that most of our subjects could quickly learn to remember the identity of landmarks on six surrounding walls of a virtual environment and when shown any two of them with the environment rotated to an arbitrary orientation could correctly indicate the direction to a third object. Ability was correlated with conventional measures of mental rotation ability. Subjects "learn how to learn" to some degree, since they learn a second environment more quickly. Ability was retained for at least a month. Experiments completed this year have shown the importance of vestibular and haptic cues in maintaining spatial memory, and the advantages of randomized rather than blocked presentations during training sequences. Preliminary results also suggest that subjects trained using a viewpoint within an environment retain their ability when the viewpoint is moved outside.

Neural coding of spatial orientation: In recent years we have been developing an animal model for limbic coding of head direction information to help us understand the mechanisms of spatial memory and visual reorientation illusions in humans. Head direction (HD) cells in the anterodorsal thalamus of the rat normally are tuned to respond in a gravitationally horizontal plane, independent of head pitch or roll up to 90 degrees. What happens when animals locomote on the walls or ceiling of a 1-g test chamber ? In a 0-G or hypergravic environment ? This year we completed two studies showing that HD cells frequently – but not always- lose their directional tuning when the animal crawls upside down on the ceiling. In 1-G, some cells discharge in the same preferred direction as on the floor, suggesting the animals maintained a consistent exocentric (allocentric) reference frame. HD cells continue to show normal spatial tuning in 0-g parabolic flight when the animal locomotes on the floor or wall of the test chamber, but usually loose their tuning when on the ceiling, or occasionally shift their preferred direction across the axis of symmetry of the cage, as if the animal had experienced a VRI. In other studies completed this year, we showed how angular head velocity cells in rat dorsal tegmental nucleus update HD cells in lateral mammilary nucleus, and the importance of motor efference copy signals vs. vestibular and optic flow in stabilizing the preferred direction of HD cell firing.

Our research team is an interdisciplinary group of psychologists, physiologists, and engineers, with background in visual, vestibular and motor psychology and physiology, human and animal navigation and VR technology. We coordinate research through bimonthly teleconferences and inter-laboratory visits, and actively collaborate with other colleagues at NSBRI and NASA Johnson Space Center. Facilities include unique tumbling rooms at York University, animal research facilities at Dartmouth, and several types of immersive virtual reality facilities at MIT, York, and Wright State University.

Our role is to do the critical experiments that provide a rationale and methodology for scientifically based countermeasures against spatial disorientation in astronauts. Our objective is to develop strong scientific hypotheses, evidence and pedagogy to define a program of preflight visual orientation training of astronauts, as well as various devices, operational techniques, medical procedures and human factors standards to prevent and treat spatial disorientation and spatial memory problems both inflight and postflight. Our work is far enough along in several areas that within the next three years, we expect to propose the transfer of several types of VR based spatial memory training techniques and devices to NASA, and suggest scientifically based human factors standards for use of visual polarity, architectural symmetry, brightness, color, escape path, and allocentric visual landmark systems.

RESEARCH AREA:	**Neurovestibular Adaptation**
PRINCIPAL INVESTIGATOR:	**Millard F. Reschke, Ph.D.**
ORGANIZATION:	**NASA Johnson Space Center**
PROJECT TITLE:	**Modification of Eccentric Gaze-Holding**

Project Executive Summary

Clear vision is a prerequisite for reliable performance of motor tasks. Space flight confronts the crewmember with a stimulus rearrangement that requires adaptation to function effectively with the new requirements of altered spatial orientation and motor coordination. Adaptation and motor learning driven by the effects of cerebellar disorders may share some of the same demands that face our astronauts. One measure of spatial localization shared by the astronauts and those suffering from cerebellar disorders that is easily quantified, and for which a neurobiological substrate has been identified, is the control of the angle of gaze (the "line of sight"). The disturbances of gaze control that have been documented to occur in astronauts, both in-flight and post-flight, can be directly related to changes in the extrinsic gravitational environment and intrinsic proprioceptive mechanisms thus, lending themselves to description by mathematical models. The basic models can be formulated using normal, non-astronaut test subjects and subsequently extended using centrifugation techniques to alter the gravitational and proprioceptive environment of these subjects. Further tests and extensions of the models can be made by studying abnormalities of gaze control in patients with cerebellar disease. Finally, tests of astronaut subjects during and after exposure to space flight, in association with the corresponding sensory-motor adaptations, will allow us to evaluate and extend our developed understanding of adaptation in the control of eccentric gaze-holding. The specific aims of this study are: (1) To investigate the mechanisms of gaze-holding in normal, non-astronaut subjects, with the head held in various orientations with respect to gravity and the head held in various orientations relative to both gravity and the trunk. This will involve characterizing the *time constant of centripetal gaze drift*, the rate in which the eyes naturally drift back toward the null position following an eccentric eye movement. (2) To investigate the mechanisms that adaptively compensate for gaze-holding failure, especially the "rebound nystagmus" phenomenon, which decreases the rate of centripetal drift of the eyes. We will study the time course of rebound nystagmus in normal, non-astronaut subjects. (3) To investigate the stimulus rearrangement and adaptation resulting from exposure to gravitoinertial environments *greater* than 1 G using prolonged exposure to centrifugation. (4) To study mechanisms that adaptively compensate for gaze-holding failure in patients with vestibular cerebellar disease who show impaired gaze-holding ability. We will compare gaze-holding defects and rebound nystagmus in patients with that obtained in our normal subjects. (5) To compare the gaze-holding abilities of astronaut subjects prior to, during, and immediately following space flight with specific predictions made as a consequence of the ground-based research. Tests similar to those performed upon normal, non-astronaut subjects will be conducted to quantify changes in the time constant of centripetal drift of the eyes in relation to changes in the gaze-holding induced as a result of the stimulus rearrangement of space flight. (6) To measure the stability of gaze, during all phases of flight, with the eye at the central position in astronauts to investigate the occurrence of saccadic intrusions known as "square wave jerks" (SWJ), and to relate SWJ mechanisms common to the failure of gaze-holding.

RESEARCH AREA:	**Neurovestibular Adaptation**
PRINCIPAL INVESTIGATOR:	**Mark J. Shelhamer, Sc.D.**
ORGANIZATION:	**Johns Hopkins University School of Medicine**
PROJECT TITLE:	**Context-Specificity and Other Approaches to Neurovestibular Adaptation**

Project Executive Summary

There are several operational issues involved with altered human performance during and immediately after space flight. These issues have implications for human safety and effectiveness. Our planned experiments are designed to give us the information needed to develop and assess appropriate countermeasures (pre-flight or in-flight activities) for the vestibular deconditioning that occurs during flight (and often persists upon return to a planetary environment). Whenever g-transitions occur, there is a very real possibility of disruptions in perceptual and sensorimotor processing and reflex calibrations. These can have serious consequences in a dynamic environment such as shuttle re-entry or Mars landing.

We propose context-specific adaptation (CSA) as a countermeasure to some of the deleterious neurovestibular effects of space flight. By CSA we mean the ability of an organism to 1) maintain two different adapted states for a response (such as two different saccade gains), 2) have each state associated with a specific context (such as g level), and 3) switch between the adapted states immediately upon a change in context (i.e., without de-adaptation and re-adaptation upon each transition). This phenomenon can be useful during phases of space flight that require transitions between different g environments (e.g., in and out of artificial gravity, from orbital flight to planetary landing). A related theme is the determination of effective adaptation procedures and effective context cues. The role of the cerebellum, and its possible disruption during flight, is another central issue, as is transfer of adaptation between motor systems.

Outline of sub-projects in this proposal
Our project consists of an integrated set of experiments that have as their overall goal the design of a spaceflight countermeasure based on forms of vestibular adaptation. Briefly, the experiments include three main investigations at Johns Hopkins: 1) studies on the effects of torsional misalignment, and the use of saccade adaptation and cyclovergence adaptation as countermeasures (Shelhamer/Zee, aims 1-3), 2) studies on the relationship between the LVOR and smooth pursuit and the role of the cerebellum on adaptation of these responses (Zee/Minor/Shelhamer, aims 4-6), and 3) a study on context cues in the human LVOR (Shelhamer, aim 9). Another set of experiments will be conducted at Washington University (St. Louis) to study how CSA might transfer between eye movements and limb movements (Angelaki/Snyder, aim 7), and experiments at the University of Mississippi Medical Center will investigate adaptation of the LVOR with transient accelerations (Zhou, aim 8).

Complementarity of human and animal studies
Some of the sub-projects proposed here include experiments with animals. Eventually, for a successful transition from lab research to countermeasure, most if not all of our work must be demonstrated in humans. Nevertheless, there are significant research questions which at this stage can only be practically addressed with animal models. This approach builds on the strengths of the individual investigators and their ongoing work, and allows for natural connections between different sub-projects; for example, work on cerebellar effects on pursuit

and the LVOR (Zee/Minor/Shelhamer) can be related, in later years, to work on transfer of adaptation from eye movements to limb movements (Angelaki/Snyder) by using monkeys with cerebellar lesions for the latter study, after effects of lesions on the basic responses and their adaptation have been fully characterized in the former. Our goal will always be to connect our animal and human work (e.g., as in our work on LVOR and pursuit in normal humans, cerebellar patients, and normal and cerebellar-lesioned monkeys). Aim 8 (Zhou/King) is an example of an effect (rapid LVOR adaptation) first established in monkeys (under joint NIH/NSBRI support), and now being verified and extended in humans.

To some extent our monkey work is basic science aimed at localizing the neuroanatomical site of context-specific learning. Use might be made of this information, however, in the design of human countermeasures, by helping to determine to what extent such behavior is reflexive (learning presumably mediated by the cerebellum) and to what extent it is cognitive (cortically mediated). Adaptation and training strategies could be tailored depending on this information. People exhibit a range of adaptive alterations; for example, we see a range of adaptive strategies in the LVOR where some subjects use saccadic tracking rather than an increase in smooth component gain to increase overall gain. With lesion experiments, if adaptation is mediated by the cerebellum, then we can determine what adaptive strategies are used when cerebellar function is disrupted. Cerebellar lesions in humans seem to have a detrimental effect on the low-frequency translational LVOR, while possibly sparing the torsional tilt response. If otolith-ocular adaptation is mediated by the cerebellum, then tilt or translation adaptation can be selectively targeted in humans, depending on any negative effects of 0g on cerebellar function. Since the specific role of the cerebellum in the LVOR is unknown, this aspect of the animal work is directly pertinent.

Specific Aims

1. To determine if static torsional eye position (induced by a visual display or by parabolic flight) can be used as a context cue for the adaptation of saccade metrics. Previous work implies that torsional changes in flight may affect saccades and other spatially-oriented behaviors. We will attempt to demonstrate that saccades can be made veridical in two different torsional states.

2. To see if CSA can be more readily acquired by allowing consolidation of adaptation to take place before changing contexts. We will allow for consolidation of each adapted state to occur by inserting a rest interval between the two context states during the CSA procedure..

3. To develop cyclovergence adaptation as a countermeasure to torsional offsets during changes in gravity. A visual stimulus can be used to induce torsional misalignment (cyclovergence). We will design an effective cyclotorsion adaptation stimulus in lab experiments, and use it to maintain the usual (1g-based) torsional alignment during parabolic flight, and see if otherwise inappropriate responses (saccades) in flight are evoked correctly if torsion is "corrected" to its normal (1g) state.

4. To compare horizontal and vertical pursuit and LVOR deficits over a wide range of frequencies, in cerebellar patients and in monkeys with vestibulocerebellar lesions.

5. To study in normal humans, and in monkeys before and after vestibulocerebellar lesions, pursuit and LVOR adaptation and their transfer over a wide range of frequencies.

6. To study in normal humans, and in monkeys before and after vestibulocerebellar lesions, CSA of the LVOR and in particular the ability to use pursuit stimuli with different g cues as a stimulus for learning multiple LVOR gains as a function of the g state.

7. To determine if CSA learned in one behavior (eye movements) will transfer to a different behavior (arm movements) in rhesus monkeys. We will use static head tilt as a context cue to adapt either the horizontal AVOR or horizontal saccades. Then we will investigate whether this context-specific adaptation is also present in memory-guided saccades and reaching. Experiments will be performed in intact animals and in animals with cerebellar lesions.

8. To use the transient linear vestibulo-ocular reflex (LVOR) to study context-specific otolith-ocular adaptation in human subjects. Our goal is to find the most effective procedure for adaptation of the transient LVOR, in anticipation of its possible use as part of a space flight countermeasure. (a) Systematically characterize task-specific LVOR adaptation in human subjects. (b) Identify the most effective training protocols to induce context-specific adaptation in human subjects. (c) Test for the ability of visual cues to substitute for vestibular cues in context-specific LVOR adaptation in human subjects.

9. To study CSA in the naso-occipital LVOR as for the inter-aural LVOR, and to determine what context cues are effective in each case.

Key findings and their impact

1. Context-switching (in saccades) is more effective if the context cue includes a motor (as opposed to purely sensory) component. This has implications for the design of CSA paradigms which might depend on gravity as a context cue, and suggests that gravity-sensing alone may not be a sufficiently powerful cue for context-switching.

2. Demonstration of dual-increase and dual-decrease CSA (for saccades) confirms that CSA does not require gain-increase versus gain-decrease conditions in order to be effective. This extends the range of behaviors which might be subject to context-switching.

3. Findings in cerebellar patients and lesioned monkeys include abnormalities of torsion during pursuit, OKN, and brief high-acceleration rotations of the head. This suggests a role for the cerebellum in the binocular control of the rotation axis of the VOR. Abnormalities of the modulation of the LVOR with near viewing in cerebellar patients, but with sparing of the first 25-30 ms of response, suggests an important role for the cerebellum in the LVOR. If the cerebellum is affected by space flight (anecdotal evidence suggests that it may be), then sensorimotor responses and adaptations which rely on the cerebellum may be problematic.

4. Context-specific adaptation of pursuit (in monkey) suggests a role for pursuit adaptation in modifying otolith-ocular reflexes such as the LVOR in response to translational motion.

5. Demonstration of LVOR adaptation without retinal slip has implications for the design of effective adaptation paradigms. Lack of adaptation transfer between LVOR and AVOR (and specificity of adaptation to motion direction) suggest that ultimately countermeasures based on CSA procedures must include a wide range of adaptation stimulus parameters.

6. Initial verification of the presence and adaptability of the naso-occipital LVOR lays the groundwork for work on otolith-mediated responses along the fore-aft axis and in the pitch plane.

Research plan for year 2

The overall plan for year 2 remains unchanged from that originally outlined. We will perform our delayed parabolic flight experiments on torsion and saccades, and begin work on consolidation of adaptation. Experiments on cerebellar function in humans and animals will continue, with studies on pursuit and the LVOR and, in particular, their context-specific adaptation. LVOR adaptation using transient accelerations will be extended to human subjects. Experiments on transfer of CSA between eye and limb movements will commence, and adaptation of the naso-occipital LVOR will begin in earnest.

RESEARCH AREA:	**Neurovestibular Adaptation**
PRINCIPAL INVESTIGATOR:	**Conrad Wall III, Ph.D.**
ORGANIZATION:	**Harvard – Massachusetts Eye and Ear Infirmary**
PROJECT TITLE:	**Advanced Techniques to Assess and Counter Gait Ataxia**

Project Executive Summary

The overall goals of this project are to develop "countermeasure assessment criteria" to evaluate recovery from disturbances, and during turning, circular walking and ascending and descending stairs. We also consider countermeasures using a balance prosthesis and dynamic exercises designed to challenge and increase subjects' balance. We will determine the sensitivity of the countermeasure assessment criteria in evaluating effects the prosthesis and the exercises on postural stability and locomotion. Using human subjects, the specific aims of this project are to: 1. Study body and head movements during precise perturbations of gait during continuous straight locomotion. 2. Study body, head and eye movements during continuous straight or circular locomotion on a circular treadmill. 3. Study body, head and eye movements during ascending and descending a staircase. 4. Study body, head and eye movements during standing, linear walking and treadmill walking with a balance prosthesis designed as a countermeasure for vestibular adaptation. 5. Study the effect of dynamic balance exercises for vestibulopathic subjects upon their ability to stand quietly and to recover from mild perturbations.

Key findings of the project

We have developed an experimental protocol that introduces a calibrated disturbance to the foot during the support phase of normal locomotion. This provides a means for the objective quantification of locomotor response dynamics that are known to be altered in astronauts upon return from exposure to microgravity but for which no current test exists. Returning astronauts whose orientation mechanism has been distorted and patients having balance disorders (vestibulopathies) that may well affect their orientation mechanism was expected to have different recovery trajectories than healthy normals. This is has now been demonstrated for vestibulopathic subjects. A simplified version of our research device is now being developed for use in evaluating the functional mobility of astronauts by scientists at the Johnson Space Center.

One of our working hypothesis was that profound impairments of posture, gaze and locomotion stability are caused by alterations in compensatory and orientation mechanisms that are generated in the central vestibular system from motion inputs. During exposure to altered gravity, the motion inputs from the otolith organs are "distorted" compared to the on-earth conditions. These distortions, in turn, cause both inappropriate body head and eye movements and an altered sense of orientation, which degrades stability during locomotion. We compared motions of the body during walking along a straight line with body motions while walking along a curved path. In the latter condition subjects accelerate in toward the direction of the curve, which introduces an inertial component which may or may not effect measures of their body orientation in space. Our results show that compensatory eye, head and body movements stabilize gaze during straight walking, while orienting mechanisms direct the eyes, head and body to tilts of the resultant of gravitational and centripetal acceleration in space during turning. This finding in normal subjects can now be compared to subjects with known impairments in their balance system or to returning astronauts to determine whether or not such individuals can successfully align parts of their bodies in an appropriate way while turning.

We have developed the simplified precursor to a balance aid. It uses body mounted motion sensors to estimate the tilt of the subject. This estimated tilt is coded and fed back to the subject using an array of small, non-invasive tactile vibrators mounted on the skin. The application of vibrotactile display of body tilt demonstrates for the first time (to our knowledge) that tilt estimates derived from body-mounted motion-sensing instruments can actually be used to reduce sway in subjects who have documented deficits in their balance (vestibular) function. The single most important finding was that subjects who repeatedly fell under challenging balance conditions were able to stand with the use of this aid.

Impact of these findings on the hypotheses or requirements (technology), objectives and specific aims of the original proposal and the proposed research plan for the coming year

These findings indicate that the overall objectives of the project are being met. The research plan for the coming year will remain as originally planned.

RESEARCH AREA:	**Neurovestibular Adaptation**
PRINCIPAL INVESTIGATOR:	**Laurence R. Young, Sc.D.**
ORGANIZATION:	**Massachusetts Institute of Technology**
PROJECT TITLE:	**Neuro-Vestibular Aspects of Artificial Gravity Created by Short-Radius Centrifugation**

Project Executive Summary

Traditional countermeasures against the adverse effects of prolonged weightlessness, such as exercise, resistive garments and lower-body negative pressure, appear to be insufficient in practice and are often too inconvenient for astronauts. Artificial Gravity (AG) represents a potential countermeasure that is unique. It promises salutary effects on bone, muscle, cardiovascular and vestibular function. Rather than alleviating the symptoms, it attempts to remove their cause. Spacecraft size dictates that any AG centrifuge tested in the foreseeable future be of limited radius (on the order of 1-5 m). In order to achieve sufficient centrifugal forces equivalent to 1-g, rotation rates will have to be rather high (between 10 and 30 rpm). Unfortunately, at these rates a number of unpleasant side effects, including motion sickness, reflexive eye movements, and sensory illusions occur. Fortunately, people seem to adapt to such sensory rearrangement changes. The matter is further complicated because our senses and motor system still need to function in 0-g and 1-g as well as in AG. Thus, the astronaut must adapt to function effectively in at least two environments, centrifugation and 0-g. Dual or multiple context-specific adaptation is required.

<u>The goal of the present research project is to gain insights into how the motor and perceptual systems are able to adapt in this context-specific manner and to use these insights to develop practical AG countermeasure protocols</u>. To meet this goal, we pursue 8 Specific Aims forming a unified research program that consists of two categories. The first attempts to understand the basic mechanisms underlying context-specific adaptation. The second involves applied questions related to optimizing the conditions for adaptation. During the first year of funding we have made progress in both categories.

For the first time, we have established that human subjects can adapt to single-axis head movements in the rotating environment of a horizontal short-radius centrifuge (SRC) rotating at 23 rpm. Inappropriate eye movements, motion sickness and illusory body tilt are all reduced after several adaptation periods of head movements in the light. Two forthcoming publications (in Acta Astronautica and Journal of Vestibular Research) have been completed within the last 12 months. In addition, we have completed the data collection and analysis on three new experiments, one at MIT, one at Brandeis, and one at Mt. Sinai. Two other experiments are very close to finishing the data collection stage (both at MIT). Finally, one experiment at JSC is set up and close to starting data acquisition. The preliminary results are summarized in the next paragraphs. Detailed reports on each specific Aim, as well as a list of papers, manuscripts and presentations are appended.

Work at MIT has shown that incremental adaptation is a promising venue that needs to be pursued further. Depending on the complexity and frequency of head movements, a substantial proportion of our subjects (approximately 75 %) experience severe motion sickness. We have demonstrated that adaptation to a 23 rpm stimulus occurs even if it is never experienced. During the training phase rotation rates were slowly incremented such that the symptoms remained around or below perceptual threshold. This is an encouraging case of generalization that has an impact on designing the eventual adaptation schedules when implementing AG (relevant for Aims 4 and 6). One experiment testing the role of vision in the adaptive process (Aim 3) and one investigating the effect of graviceptive information on Coriolis effects (Aim 5) are nearing completion. It would be too early to draw any conclusions yet.

Work at Brandeis (Aim 2) has produced the encouraging result that arm movements recalibrate quickly regardless of the rotation rate of the centrifuge (range 5 - 25 rpm). This suggests that the motor system may be more easily adaptable than the vestibular system. However, this conclusion may not generalize to more complex movements than the stereotyped reaches studied thus far. Such complex movements will be studied in year 2 and 3.

A joint pilot experiment (MIT and Brandeis, Aim 1) has shown that it is practically feasible and theoretically interesting to adapt subjects in one environment and then test them on a different centrifuge. The full study will give important insights in the usefulness of ground-based pre-training.

A full experiment to test the potential interference with the potent anti-motion-sickness drug promethazine has been completed and partially analyzed at Mt. Sinai (Aim 8). A double-blind crossover study of adaptation to roll head movements showed that subjects who used promethazine were able to adapt as quickly and as thoroughly (over the course of 4 daily sessions) as did the placebo control group. Further data analyses are required to ascertain that the dosage of promethazine that was administered has been potent enough to reduce motion sickness significantly.

In summary, we have obtained some promising results about the adaptability of human motor response, neurovestibular signals, illusory percepts, and motion sickness. We also have shown that incremental adaptation might be a valid alternative to sudden stimulus exposure. The work during year 1 has shown that AG is a promising candidate for a universal countermeasure. During the next two years our investigations have to be extended to the adaptability to more complex head and limb movements in the rotating environment.

NSBRI RESEARCH PROGRAM
NUTRITION, PHYSICAL FITNESS AND REHABILITATION

Team Leader: **Lupton, J. R.** **Texas A&M**

Cabrera, M. E.	**PI**	**Case Western**	**Metabolic Adaptations of Skeletal Muscle to Training/Detraining: A Systems Model**	**125**
Saidel, G. M.	CO-I	Case Western		
Stanley, W. C.	CO-I	Case Western		
Radhakrishnan, K.	CO-I	Ohio Aerospace/NASA		
Lupton, J. R.	**PI**	**Texas A&M**	**Nutritional Countermeasures to Radiation Exposure**	**126**
Turner, N. D.	CO-I	Texas A&M		
Chapkin, R. S.	CO-I	Texas A&M		
Mallick, B. K.	CO-I	Texas A&M		
Braby, L. A.	CO-I	Texas A&M		
Ford, J. R.	CO-I	Texas A&M		
Schneider, S. M.	**PI**	**Univ. of New Mexico**	**Treadmill Exercise as a Countermeasure for Microgravity Deconditioning (Flight Study)**	**127**
Cavanagh, P.	CO-I	Penn State		
Smith, S.	CO-I	NASA JSC		
Greenisen, M.	CO-I	NASA JSC		
Tobin, B. W.	**PI**	**Mercer**	**Nutritional Modulation of Pancreatic Endocrine Function in Microgravity**	**128**
Leeper-Woodford, S.	CO-I	Mercer		
Uchakin, P. N.	CO-I	Mercer		
Rothenberg, M. R.	CO-I	Mercer Southern		
Smith, S. M.	CO-I	NASA JSC		
Lakey, J. R. T.	Co-I	U of Alberta		
Wolfe, R. R.	**PI**	**UTMB**	**Skeletal Muscle Response to Bed Rest and Cortisol-Induced Stress**	**131**
Ferrando, A. A.	CO-I	UTMB		
Urban, R. J.	CO-I	UTMB		
Fitts, R. H.	CO-I	Marquette		

RESEARCH AREA:	**Nutrition, Physical Fitness & Rehabilitation**
PRINCIPAL INVESTIGATOR:	**Marco E. Cabrera, Ph.D.**
ORGANIZATION:	**Case Western Reserve University**
PROJECT TITLE:	**Metabolic Adaptations of Skeletal Muscle to Training/Detraining: A Systems Model**

Project Executive Summary

Space travel (*detraining*) has detrimental effects on skeletal muscle structure, metabolism, and function, including reductions in muscle size, strength, and endurance. Exercise (*training*) in space can counteract some of these deleterious effects. Experimental studies are still being conducted to determine both the cause of muscle deterioration and the exercise training programs needed to counteract the detrimental effects of long-duration space travel on muscle function. In addition to obtaining relevant metabolic data from space and ground-based studies, physiologically-based computational models of human function are needed to integrate cellular to whole-body data and to provide a framework for quantitative understanding of the skeletal muscle metabolic adaptations to periods of *training and detraining*.

The specific aims of this project are:

1. To identify the metabolic adaptations to training and detraining in order to develop databases containing (a) information on the structural, metabolic, and functional adaptations of skeletal muscle to microgravity and exercise training and (b) the underlying biochemical mechanisms mediating these adaptations.
2. To develop mathematical models of intermediary metabolism in skeletal muscle that account for the effects of training and detraining.
3. To investigate the relative significance of model parameters affected by training or detraining on work capacity and efficiency.
4. To simulate the effects on skeletal muscle intermediary metabolism and energetics of space flight and exercise in space, to quantitatively test the hypotheses that after a period of space travel or exercise training, the observed changes in the rates of carbohydrate and fatty acid oxidation in skeletal muscle are a result of (a) a partial conversion of slow-twitch to fast-twitch fibers and (b) alterations in glycolytic and oxidative enzymes.

During the first year of the project we have identified specific structural, metabolic, and functional muscle adaptations to training and detraining from previously published studies in humans. We developed a mathematical model of skeletal muscle metabolism that integrates cellular, tissue, and whole body data, as well as incorporates specific parameters that have been identified as playing a major role in the responses to training and detraining such as muscle mass, enzyme activities, mitochondrial content, and fiber type distribution. We are currently collaborating with other Integrated Human Function projects and projects in the Nutrition, Physical Fitness and Rehabilitation team to link our model with other models that are being developed (muscle energetics, cardiovascular function, and ionic changes in heart) or with experimental projects which can provide data for validation of our model but that require a theoretical framework for interpretation of their results. We are also collaborating with the Smart Medical Systems team to evaluate the effectiveness of exercise training programs in space. In the upcoming year we will continue to validate our model and plan to further integrate our project with other NSBRI projects.

RESEARCH AREA:	**Nutrition, Physical Fitness & Rehabilitation**
PRINCIPAL INVESTIGATOR:	**Joanne Lupton, Ph.D.**
ORGANIZATION:	**Texas A&M University**
PROJECT TITLE:	**Nutritional Countermeasures to Radiation Exposure**

Project Executive Summary

Original Aims. The overall goal of this research program is to develop nutrition countermeasures to radiation-induced colon tumorigenesis, using male Sprague Dawley rats as a model system. Superimposed on the background of irradiation with Fe-ions or no irradiation is the injection of a known colon specific carcinogen, azoxymethane (AOM) in order to simulate the potential exposure to environmental contaminants. The diet interventions to be tested are combinations of a lipid component (fish oil vs corn oil) and a fiber component (pectin vs cellulose). At the end of the three year period we will know: (1) if radiation exposure synergistically enhances colon tumor induction by AOM; (2) which diet combination(s) are protective against colon cancer and if this effect is due to less DNA damage, greater removal of DNA-adducted cells by apoptosis or greater repair of DNA-adducted cells; (3) if short term studies (e.g. initiation or aberrant crypt formation) are predictive of later tumor development; and (4) if noninvasive technology can be used to detect specific mRNAs that are predictive for radiation exposure and/or response to that exposure, which would have later application to humans.

Key Findings. The preliminary project results demonstrated that our selected radiation dose and sampling times were appropriate for the proposed experimental design. We discovered that prior exposure to radiation before exposure to a chemical carcinogen increased the severity of the preneoplastic lesions formed during colon tumorigenesis. Therefore, it will be critical to minimize the effect galactic cosmic radiation has on increasing the risk of colon cancer in astronauts.

Impact of Findings on Project Goals. Because the preliminary results supported our proposed experimental design, there will be no need to modify the proposed research.

Proposed Research Plan for the Coming Year. Samples from the tumor stage will be collected in June of 2002 from the first half of the rats treated only with the carcinogen. Work with the first half of the rats to be exposed to radiation prior to carcinogen treatment will begin and samples from these rats will be collected for the initiation stage (April), and aberrant crypt stage (June 2002), and the tumor stage (January 2003). If the next run at Brookhaven National Laboratory occurs as planned (November 2002), we will be conducting the work with the remaining half of the rats to receive treatment with both radiation and the carcinogen. Samples from the initiation and ACF stages will be collected from those rats prior to the completion of the second year of the project.

RESEARCH AREA:	**Nutrition, Physical Fitness & Rehabilitation**
PRINCIPAL INVESTIGATOR:	**Suzanne Schneider, Ph.D.**
ORGANIZATION:	**University of New Mexico**
PROJECT TITLE:	**Treadmill Exercise as a Countermeasure for Microgravity Deconditioning**

Project Executive Summary

Treadmill exercise is the primary countermeasure during space flight to maintain aerobic, cardiovascular fitness. It also may provide some protection against the atrophy in bone and muscle. Yet little is known about the effect of microgravity and the bungee-harness system that must be used to provide footward loading on the physiological responses to treadmill exercise. The purpose of this proposal is two-fold: 1) to obtain cardiovascular (heart rate), metabolic (oxygen consumption), and biomechanical data (peak forces, foot pressure, gait analyses) during treadmill exercise at several treadmill speeds in microgravity, and 2) to evaluate the effectiveness of two treadmill countermeasures to maintain aerobic capacity, leg muscle strength, and to prevent increases in bone resorption and muscle atrophy markers. We hypothesize that daily, moderate treadmill exercise for 30 minutes each day will maintain aerobic capacity, leg strength, and reduce the increase in bone and muscle markers. Ten Shuttle crewmembers will exercise either daily (n=5) as a simulation of the level of aerobic exercise currently planned for ISS or every third day (n=5) as a simulation of the minimum level of aerobic exercise currently required for crewmembers during Shuttle missions > 10 days. The effectiveness of these countermeasures to maintain post-flight aerobic fitness will be assessed using a graded treadmill test; to maintain leg strength and muscle performance will be assessed using isotonic and isokinetic tests, respectively; and, to prevent degradation of muscle and bone will be assessed by measuring changes in catabolic markers for muscle (3-methyl-histidine) and bone (collagen cross-links) from 24 hr urine pools. Simultaneous video analysis with heart rate and metabolic responses in 1-G and 0-G environments will allow us to understand the effect of the bungee-harness system and microgravity to alter the cardiovascular and metabolic responses to the treadmill. The information from these tests are required to determine the most appropriate treadmill prescriptions during long duration stays on ISS and during exploratory missions.

RESEARCH AREA:	**Nutrition, Physical Fitness & Rehabilitation**
PRINCIPAL INVESTIGATOR:	**Brian Tobin, Ph.D.**
ORGANIZATION:	**Mercer University School of Medicine**
PROJECT TITLE:	**Nutritional Modulation of Pancreatic Endocrine Function in Microgravity**

Project Executive Summary

Our specific aims in this study are to: 1) assess the effect of a microgravity model cell culture on basal amino acid requirements and endocrine secretory function in human islets of Langerhans, and 2) determine human islet endocrine function while testing amino acid countermeasures in the microgravity model.

Ground based and in-flight investigations illustrate changes in insulin, glucose, and amino acid metabolism in spaceflight. These observations may relate to altered pancreatic endocrine function which is insufficient to meet the needs of microgravity induced insulin resistance, and altered amino acid metabolism. The changes observed include decreased glucose tolerance, increased circulating insulin, and increased reliance upon glucose in muscles. The metabolic meliu resembles an insulin resistant syndrome, accompanied by a compensatory increase in pancreatic insulin secretion. However, the increase in insulin secretion is insufficient to ameliorate muscle atrophy. The increased insulin secretion is well correlated to muscle atrophy in spaceflight. The influence of these changes upon the loss of muscle mass and general endocrine metabolic state are not well established, however. Countermeasures which could modulate insulin and glucagon secretion in a compensatory manner to overcome insulin resistance and promote amino acid uptake by peripheral musculature might decrease muscle atrophy and reduce injury following re-adaptation to unit gravity.

We hypothesize that human pancreatic islets of Langerhans have an increased requirement for amino acids in microgravity. We further hypothesize, that supplementation with specific additional amino acids will augment, enhance and normalize insulin secretion, when spaceflight paradigm stressors known to decrease insulin secretion, are applied.

It is anticipated that these studies will further refine our understanding of human pancreatic amino acid requirements and endocrine regulation: phenomenon which may be limiting to extended-duration spaceflight missions. These studies will test countermeasures to augment pancreatic endocrine function, while considering both insulin and glucagon production in a way that will involve supplementation of diet with additional amino acids. These measures are ultimately aimed at improving spaceflight induced muscle atrophy, and ameliorating current re-adaptation constraints.

Key Findings

We have accomplished a part of Specific Aim 1: "To assess the effect of a microgravity model cell culture on basal amino acid requirements and endocrine secretory function in human islets of Langerhans."

Our results of experiments conducted this year in which human pancreatic islets of Langerhans were cultured in the HARV bioreactor and contrasted to controls show reveals the following key findings:

1. There is a tendency towards less glucose utilization in HARV-cultured islets of Langerhans
2. There is a tendency towards enhanced insulin secretion in islets maintained in the HARV,
3. We observed differential alterations in the pattern of amino acid utilization in the HARV,
4. Islet TNF production favors greater activity in the HARV cultures.

Impact of these findings on the hypotheses or requirements (technology), objectives and specific aims of the original proposal:

Observation A: The tendency towards decreased glucose utilization in HARV-cultured human islets of Langerhans, supports the hypothesis that microgravity is associated with a sub-clinical diabetogenic state. The observation of lesser glucose utilization in human islets is consistent with observations of rat islets cultured in the HARV system when contrasted to controls.

Observation B: The increased insulin secretion in the pancreatic islets cultured in the HARV suggests that islets are responding to some stimuli similar to that observed in insulin resistant states. It is well established that even in the face of severe insulin resistance, and decreased uptake of amino acids by muscle in diabetic individuals, the output of insulin by the pancreas is dramatically increased. This scenario is consistent with the observations in human pancreatic islets of Langerhans in the HARV microgravity model system.

Observation C. The differential pattern of amino acid utilization is consistent with thew hypothesis that microgravity causes alterations in the pattern of metabolic substrate utilization. This is consistent with published data, and supports the hypothesis that the peripheral tissues are not the only sites of altered amino acid metabolism. The pancreatic islets of Langerhans also appear to be altered in their patterns of metabolite use when cultured in a microgravity model system.

Observation D: The greater TNF production in pancreatic islets of Langerhans supports the hypotheses that insulin secretion is suppressed from reaching an adequate level sufficient to over come peripheral insulin resistance in muscle tissue. That TNF can suppress insulin action is well established. That TNF is secreted by pancreatic islets of Langerhans was previously reported by our laboratory. Given that TNF in HARV cultures is increased, this scenario suggests that even in the face of a need for increased insulin section to overcome insulin resistance in muscle, that TNF may be suppressing a maximal beneficial response in the islets of Langerhans

Proposed research plan for the coming year

In the coming year we plan to accomplish a comprehensive analysis of the effects of: 1) microgravity simulation, 2) LPS, 3) epinephrine, 4) cortisol, and 5) amino acid administration, upon endocrine and cytokine function as well as the nutritional utilization of glucose, amino acids, and fatty acids.

We will accomplish this by carrying out studies according to the following description.

1) Approximately 24,000 human cadaveric pancreatic islets of Langerhans are isolated and purified by collaborator JRT Lakey, PhD, at the University of Alberta and shipped in Medium-199 to Mercer University School of Medicine (MUSM).

2) At MUSM, human islets of Langerhans are prepared for bioreactor culturing by collaborator SK Leeper-Woodford, BW Tobin, PhD, and PN Uchakin, with the technical expertise of Cynthia Bruin, and are allocated into 10 ml disposable High Aspect Ratio Vessels (HARV) or standard 10 ml cell culture plates.

3) The 24,000 human islets of Langerhans are divided into independent variable group.

EFFECTS OF STRESSORS

HARV w/ LPS	HARV w/ Cortisol	HARV w/ Epinephrine	HARV w/ no treatment
Plate w/ LPS	Plate w/ Cortisol	Plate w/ Epinephrine	Plate w/ no treatment

EFFECTS OF AMINO ACIDS

HARV with Arginine	Plate with Arginine
HARV with WOLFE Amino Acids	Plate with WOLF Amino Acids

4) The islets are cultured for 48 hours and samples are taken at 0, 3, 6, 12, 24 and 48 hours for analysis of metabolites by our collaborative group. e) Aliquots of islet medium are frozen at -70^0 C and are subsequently shipped to the following collaborators for dependent variable analysis.

Dr Uchakin (MUSM): glucose, lactate, insulin, glucagons
Dr Leeper-Woodford (MUSM): TNF-alpha, Il-1, Il-6, NF kappa beta
Dr. Walzem (TAMU): fatty acids, lipids,
Dr. Smith (NASA-JSC): amino acids, nitrogenous compounds

5) Data are returned from the collaborators to MUSM and are analyzed by Drs. Uchakin, Tobin and Leeper-Woodford. All members of the PI and Co-I and add-on project team confer on data analysis and interpretation. All project team members are eligible for inclusion as authors on any or all abstracts, presentations, or manuscripts resulting from these studies. NSBRI is properly acknowledged in all presentations and publications.

RESEARCH AREA:	**Nutrition, Physical Fitness & Rehabilitation**
PRINCIPAL INVESTIGATOR:	**Robert Wolfe, Ph.D.**
ORGANIZATION:	**The University of Texas Medical Branch - Galveston**
PROJECT TITLE:	**Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress**

Project Executive Summary

SPECIFIC AIMS

Prolonged space flight causes a loss of skeletal muscle mass that is detrimental to physical function, and amelioration of this response is essential for successful prolonged missions. There are two components of the loss of muscle mass in space flight. Prolonged muscular inactivity causes a reduction in protein synthesis, while at the same time stress (mediated by moderate hypercortisolemia) accelerates the rate of muscle protein breakdown, at least insofar as it relates to the rate of synthesis. Our previous work in normal volunteers has shown that a supplement containing a mixture of essential amino acids and carbohydrate stimulates muscle protein synthesis. Further, whereas ingested amino acids normally do not affect the rate of muscle protein breakdown, they limit the accelerated rate of breakdown that occurs in stress states, such as in severely burned patients. Consequently, we anticipate a mixture of essential amino acids (15g) and carbohydrate (30g) given as a supplement three times per day will limit the loss of muscle, and in turn muscle function, during our model of space flight, which is prolonged bed rest + hypercortisolemia. We are testing the hypothesis that essential amino acid/carbohydrate supplementation will ameliorate the loss of lean body mass and muscle function that occur after 28d of bed rest, while improving nitrogen balance over the duration of the experiment. Further, we have quantified muscle amino acid and protein kinetics at the beginning and the end of bed rest in order to gain insight into the mechanisms responsible for the loss of muscle mass in untreated subjects, as well as into the mechanisms by which supplementation serves to decrease muscle catabolism. Specifically, we have determined muscle amino acid and protein kinetics over 24 hour periods before and at the end of bed rest in order to address the following hypotheses:

1. The normal anabolic response of muscle to a meal diminishes with prolonged inactivity and stress.
2. An amino acid/carbohydrate supplement will stimulate net muscle protein synthesis over the one-hour immediately following ingestion.
3. The normal anabolic effect of meals will not be affected by prior ingestion of a supplement.
4. The post-absorptive nadir in net muscle protein synthesis will be no greater in subjects receiving supplementation than in control subjects.

KEY FINDINGS

To date, we have studied 7 subjects on the essential amino acid/carbohydrate supplement (EAA group) and 6 subjects receiving placebo (Placebo group). The completed data is forthcoming. Based on findings thus far, results indicate supplementation with EAA enables maintenance of lean body mass (LBM) throughout 28 days of bed rest, while the placebo group experiences a loss of LBM. The EAA supplement maintains LBM by stimulating net muscle protein synthesis to a much greater extent than meal ingestion alone. Although this stimulation is diminished with increased inactivity, the net gain in muscle protein is still significantly greater than that produced by meals alone. In other words, even though the anabolic response to the EAA supplement decreases after 28d of bed rest, it is still capable of producing a significant increase in net muscle protein synthesis.

Though EAA supplementation is capable of maintaining LBM, it does not maintain muscle strength. Measures of leg muscle strength decline after 28d of bed rest despite the preservation of leg lean mass. These findings demonstrate that the maintenance of LBM alone is insufficient in terms of muscle function. Apparently, some neuromuscular component is also required to preserve muscle strength and function.

Our findings also demonstrate that the EAA supplement is capable of stimulating net protein synthesis when given in a stressed state, as simulated by cortisol infusion. The presence of elevated blood cortisol induces a loss of muscle protein even when a meal is given. Though the EAA supplement can slow this loss, it only does so temporarily, such that within 1-2 hours after the supplement, the muscle protein balance is again catabolic. After 28d of inactivity, the response to a meal during elevated cortisol is further diminished, such that the muscle is dramatically catabolic. The EAA supplement is not capable of eliciting an anabolic response in the muscle after 28 of bed rest. On the contrary, when the supplement is given without the presence of cortisol, the net effect is muscle anabolism over the study time period.

IMPACT OF FINDINGS

Thus far, our findings demonstrate that the anabolic response to a meal diminishes with prolonged inactivity and a stress challenge. The stimulation of net muscle protein synthesis immediately following each EAA supplement translates to a maintenance of muscle protein over a 24 hr period, and in turn, over the 28d of bed rest. However, the maintenance of LBM does not translate to a maintenance of muscle strength. The interaction of inactivity and stress exacerbates the ineffectiveness of ordinary meals. Though the EAA supplement can offset muscle catabolism during the stress state, the response is transient and incapable of ameliorating the overall loss of muscle protein. Taken together, these findings indicate that a nutritional supplement alone can reduce the muscle atrophy associated with space flight. However, whereas muscle mass can be maintained with a specified nutritional intervention, other modalities are required to preserve muscle function.

PROPOSED RESEARCH PLAN

Our plans for the coming year include the completion of analysis and interpretation of data for the 13 subjects studied. Further, we plan to include an examination of intermittent exercise throughout 28d of bed rest to determine if we can maintain both LBM and muscle function with minimal exercise. Taken together, these investigations will determine an optimal operational countermeasure that can be economically (in terms of crew time and payload) utilized to ameliorate muscle loss during prolonged space flight.

NSBRI RESEARCH PROGRAM
RADIATION EFFECTS

Team Leader: **Dicello, J. F.** **Hopkins/SOM**

Associate Team Leaders:
Kennedy, A. R. **Penn**
Vazquez, M. E. **Brookhaven**

RESEARCH AREA:	**Radiation Effects**
PRINCIPAL INVESTIGATOR:	**Polly Chang, Ph.D.**
ORGANIZATION:	**SRI International**
PROJECT TITLE:	**Charged Particle Radiation-Induced Genetic Damage in Transgenic Mice**

Project Executive Summary

Evaluations of risks involving alterations in the genome using whole animal systems are essential to missions in space. The *lacZ* transgenic mouse model is the only system available, to date, for the assessment of alterations in the genome in every tissue of the animal. In this model system, every cell of the animal contains multiple copies of an integrated but inert target transgene. Radiation-induced mutations can be measured and specific genetic alterations characterized using established protocols. Genetic alterations in tissues that are of high priority in NASA's Strategic Program Plans but are not accessible using conventional techniques, e.g., the central nervous system, can be evaluated using this model system. In addition to measuring short (1 week) and long term (up to 16 weeks after treatment) mutagenicity in the reporter transgene, concomitant evaluation of the clastogenic potential of particle radiation can also be done using the same experimental animals. Some of these include examining radiation responses in the hematopoietic system by enumerating micronuclei (MN) in peripheral blood, evaluating chromosomal damage in either circulating or bone marrow lymphocytes by using fluorescence *in situ* hybridization (FISH) techniques, and induced gene expressions in tissues by using RT-PCR. Specifically, our research aims for this project include the use of *lacZ* transgenic mice to characterize the dose- and time-dependent radiation-induced responses in *lacZ* transgenic mice after high LET iron particle beams generated at Brookhaven National Laboratory and low LET proton irradiation at the Loma Linda University Medical Accelerator. We will measure the initial effects and long-term residual consequences of radiation exposure in tissues that are of high priority to NSBRI and NASA, namely the brain (CNS) and compare these responses to the spleen (highly proliferative tissue with stem cell populations). We hypothesize that the *lacZ* mutation frequency (MF) in individual tissues will increase as a function of dose for each tissue, that this response is LET dependent, but the level of induction of MF is dependent on the specific tissues analyzed. Micronuclei (MN) in peripheral blood have been used extensively as a biomarker to evaluate radiation toxicity in the human population. We aim to examine radiation responses in the hematopoietic system [immature polychromatic reticulocytes (RETs) and mature normochromatic erythrocytes (NCEs)] and lymphatic system in the same experimental animals. We expect that the level of genetic damage as well as the kinetics of removal of aberrant cells and the spectrum of chromosome aberrations is dose dependent.

Variations in genetic background have been shown to impact an individual's sensitivity to radiation exposure. The tumor suppressor *p53* gene function has been shown to be radiation responsive and very important in the regulation of cell growth, proliferation, differentiation, and apoptotic signaling pathways in many tissues. We cross-bred the C57 *lacZ* transgenic mice that are wild type for *p53*(*p53*+/+) with *p53* nullizygous (*p53* -/-) mice to establish breeding colonies of transgenic mice, possessing the *lacZ* transgene and are either hemizygous or nullizygous for *p53*. These animals will be used to assess tissue-specific *p53*-dependent (or -independent) molecular and genetic mechanisms in radiation-induced damage resulting from exposure to particle beams in the energy range corresponding to space radiation. Specifically, animals with different *p53* genetic backgrounds will be exposed to a range of doses of either iron particles or proton radiation and tissue-specific radiation responses using the same endpoints as mentioned in the previous section will be evaluated. Results from these studies will reveal the impact of variation of genetic background to an individual's sensitivity to radiation exposure of different LETs.

The cytokine interleukin-1 (IL-1) is known to be a biomolecule that is radiation responsive and has been shown to be an effective countermeasure that protects animals from low LET radiation toxicity. We will test the hypothesis that IL-1 protects against radiation lethality by enhancing repair and reducing adverse long-term consequences such as mutagenesis *in vivo* and therefore, can be considered as a biological countermeasure for particle radiation. We aim to determine the ability of the pro-inflamatory cytokine IL-1 to alter the level of radiation-induced genetic damage after proton radiation. Based on current knowledge that IL-1 reduces DNA damage in the hematopoietic system, our hypothesis is that the yield of *lacZ* mutations in the spleen, MN-RET, and chromosome aberrations will decrease in *p53+/+* animals with administration of IL-1.

The focus of our research during the first ten months of funding was to examine proton radiation-induced genetic damage in the transgenic mouse mutation model system. C57/*lacZ* transgenic animals were exposed to doses ranging from 0.1 Gy to 4 Gy of 250 MeV/amu proton particles at the Loma Linda University Medical Accelerator. Peripheral blood samples were collected at various times (from 24 hrs to 7 days) after radiation treatment and chromosome damage in circulating reticulocytes was measured by enumerating the frequency of micronucleated reticulocytes (MN-RET) using flow cytometry. Tissues from treated and sham irradiated animals were harvested at 1 day, 8 weeks and 16 weeks after irradiation, snap frozen and stored at –70°C until processing.

We have preliminary evidence showing that low doses of protons are effective in inducing elevated levels of MN-PCEs in peripheral blood of mice, in an early time course after radiation. The frequency of MN-RET in peripheral blood varied as a function of time post irradiation, with a linear dose-dependent increase of up to 6-fold above control levels after low doses of 0.1 Gy – 1 Gy proton exposure at 48 hrs after radiation treatment. This effect appeared to saturate at higher doses. Transient systemic toxicity in the hematopoietic system was noted in animals exposed to 4 Gy of proton as evidenced by the dramatic decreases in the percent of reticulocytes in the total circulating erythrocytes. The % of MN-RET in most animals returned to control levels at 1 week after exposure. These results points to the feasibility of using MN-RET in peripheral blood as a biomarker for measuring radiation damage at early time points after radiation exposure. However, chromosomal aberrations in these transient populations of erythrocytes are eliminated from the peripheral circulating erythrocyte populations within 1-week post-proton exposure, and questions regarding the long-term persistent consequences of radiation exposure in tissues remain unanswered in these studies.

We examined radiation-induced alterations in the genome in tissues by measuring the MF in the surrogate *lacZ* transgene. *LacZ* mutation frequencies (MF) were evaluated in spleen tissues harvested from animals at 1-week and 8-weeks after proton exposure. We noted that there was a modest dose-dependent increase in MF at 1 week after proton exposure - from 1.2 fold above control spontaneous levels after 0.5 Gy of protons, up to 1.8-fold increase above spontaneous level after 4 Gy of protons. The levels of induced MF were significantly higher at 8-weeks post irradiation, with greater than 2-fold above spontaneous levels after 0.5 Gy and 1 Gy of protons. Preliminary evidence also shows that doses higher than 2 Gy did not result in higher MFs. We hypothesize that, at high doses, damaged cells may be eliminated from the cell population and do not contribute to increased mutation incidences in late responses in the spleen. Mutants obtained from these samples were cored and work is now in progress to examine the spectrum of damage in the transgene using restriction digestion.

Our findings thus far are consistent with our proposed aims and hypothesis. For the coming year, we have applied for and been awarded 17 hrs of beam time in the upcoming Heavy-ion accelerator run (BNL-8, 2002), scheduled for early spring, 2002. We are planning to characterize the dose and time-dependent radiation induced responses in *lacZ* transgenics after 1 GeV/amu iron particle radiation. Animals with different *p53* genetic backgrounds will also be used in this study.

RESEARCH AREA:	**Radiation Effects**
PRINCIPAL INVESTIGATOR:	**John Dicello, Ph.D.**
ORGANIZATION:	**Johns Hopkins University School of Medicine**
PROJECT TITLE:	**Radiation Effects Core Project: In Vivo and In Vitro Studies**

Project Executive Summary

This is a continuation of the "Core Project" of the NSBRI Radiation Effects Team begun two and a half years ago. Our main objective has been to determine the risks of human diseases arising from exposures to galactic and solar radiations during interplanetary missions and to test the hypothesis that pharmaceuticals could be used to reduce the risk of relevant diseases, particularly carcinogenesis. There has been a close relation between this project and notably the Chemoprevention and Cytogenetic, but also the Technology and Immunology Teams, the Johnson Space Center, and several other universities. We have designed and constructed experimental systems and developed procedures and methods for transporting large numbers of animals and related cells safely to and from the heavy-ion accelerator at the Brookhaven National Laboratory, the proton facility of the Loma Linda University Medical Center (LLUMC), and Johns Hopkins University (JHU). We are accumulating medical and biological data for a group of more than 3000 rats and innumerable cells exposed to 1-GeV iron ions, 250-MeV protons, or cobalt-60 or cesium-137 gamma rays. At the recommendation of the External Review Council of the National Space Biomedical Research Institute, the research will examine a mouse model for a tumor site having minimal hormone stimulation, and will use that same model to evaluate the possibility of damage to the central nervous system. We have chosen the Min (multiple intestinal neoplasia) mouse and intestinal tumors as this major endpoint. Colon cancer was chosen because it is one of the major tissues contributing to the effective doses to be received by astronauts in space. Moreover, recent advances with this model at the University of Pennsylvania have resulted in relatively non-specific, non-toxic pharmaceuticals, such as Bowman-Birk Inhibitor, that reduce the risk of multiple types of late cancers. Further, these drugs work primarily by reducing oxidative stresses, suppressing the initiation stage of carcinogenesis while retaining the desirable characteristic of working as well in the promotion and progression stages. Such drugs have the potential for reducing the risks for cancer in astronauts because they appear to be relatively nontoxic, broadly effective in a variety of tumors and tumor types, and can be used effectively as diet supplements after the exposures. The hypothesis to be examined to this end is that there exist non-specific, non-toxic drugs that would effectively reduce the risks of multiple types of cancers or CNS damage.

RESEARCH AREA:	**Radiation Effects**
PRINCIPAL INVESTIGATOR:	**David Huso, Ph.D.**
ORGANIZATION:	**Johns Hopkins University School of Medicine**
PROJECT TITLE:	**Chemoprevention and Radiation-Induced Neoplasms**

Project Executive Summary

Chemoprevention is a pharmaceutical approach to arresting or reversing the process of carcinogenesis during cancer's typically prolonged latent period (often 20 years or more) before invasion or metastasis occurs. Surging scientific and public interest in applying chemoprevention strategies to people in the general population that have been identified to carry even slight increases in the risk of developing cancer (e.g. genetic risk) is fueling the identification of exciting new chemopreventive agents. Some now argue that future development of chemopreventive agents offers greater potential for the long-term control of cancer than the much more widely studied and aggressively pursued chemotherapy agents.

The major long-term risk associated with radiation exposure received during space travel is predicted to be radiation-induced cancer. The cancer-causing effects of low-LET radiations such as x-rays, g-rays, or electrons, typical of environmental earth exposures, have been relatively well-established. However, radiation likely to be encountered in space includes mainly heavy ions and protons along with their secondaries. Much less is known about the biology and risks associated with these types of radiation. The doses of radiation likely to be received even for long missions are probably low, but cover a broad range and are very unpredictable due to solar events. Like other types of radiation, the increased cancer risk associated with proton and heavy ion exposure is troubling because many radiation-induced cancers do not appear until later in life. Therefore, a large amount of uncertainty exists in how best to assess and manage the radiation risks associated with space travel.

Two high priorities in preparation for long term missions are 1) providing a better understanding of both the short-term and long-term carcinogenic risks of heavy ion or proton radiation and 2) developing pharmaceutical countermeasures to mitigate the carcinogenic risk associated with low-dose and mid-dose exposures to these types of radiation. Currently there are 3 cancer chemopreventive strategies that have clearly proven efficacy in preventing human familial and sporadic cancers 1) tamoxifen for prevention of breast cancer, 2) NSAID's (nonsteroidal antiinflamatory drugs) for prevention of colorectal cancer, and 3) retinoids for certain epithelial cancers. As countermeasures to the cancer risk associated with space travel, these chemopreventive approaches offer a particularly promising approach for countermeasure investigation because of: 1) these compounds are currently being used as preventives for human cancers although they are untested against proton or heavy ion-induced cancer, 2) there are difficulties associated with absolutely blocking radiation-induced mutagenic damage to DNA during prolonged space travel, either with shielding or pharmaceuticals, and 3) the prolonged latency period of most radiation-induced cancers (especially at low doses) offers a prolonged time period to administer chemopreventives and the latency period is time when the most successful chemopreventives exert their effects. For most cancers, compounds that modulate the regulation of cell growth and apoptosis (rather than blocking mutagenic damage to DNA) have to date shown particular promise in preventing overt cancer from developing in susceptible organs.

Organs are not equally sensitive to the carcinogenic effects of radiation. Tissues that appear to be at higher risk for developing radiation-induced neoplasms include the female breast, the gastrointestinal tract (colorectal cancer), the thyroid, the bone marrow/lymphoid system (leukemia), and the lung. Women have an increasing role in the space program. The female breast is particularly sensitive to the carcinogenic effects of radiation and therefore a relevant tissue in which to study chemoprevention of radiation-induced cancer. Chemoprevention of radiation-induced cancer in this sensitive target organ provides an excellent system in which to initially gain insights into the chemoprevention of radiation-induced cancer in general.

Over the past few years, tamoxifen has not only emerged as an effective chemopreventive against breast cancer, but it has also become the most widely prescribed anticancer drug in the world. It had been used for over 25 years for breast cancer treatment prior to its application as a chemopreventive. This level of acceptance for use in humans along with its proven chemopreventive efficacy against sporadic breast cancer provides a strong rationale for investigating its safety and efficacy against breast tumors induced by heavy ions and protons. As a potential countermeasure to the risks associated with prolonged space missions, the tamoxifen family of compounds have outstanding potential with a high level of readiness.

The class of compounds that includes tamoxifen, the selective estrogen receptor modulators (SERM's), are thought to have outstanding potential both in estrogen replacement therapy and as chemopreventive agents. Burgeoning research and development of new SERM compounds has led to many new and improved SERM's undergoing trials. Tamoxifen, however, remains the prototype SERM for breast cancer chemoprevention. Newer SERM's will hopefully further improve on tamoxifen's effects while reducing its side effects. SERM's are ligands for the estrogen receptor (ER) and modify carcinogenesis in breast epithelial cells by antagonizing ER signaling. However, in other tissues SERM's can act as partial ER agonists and promote the beneficial effects of estrogens in, for example, the skeletal and cardiovascular systems. Interestingly, tamoxifen may also affect carcinogenesis in a number of organ systems by disrupting apoptosis regulation in proliferating cells. In spite of the widespread use of tamoxifen, very little is known about its lifetime effectiveness against radiation-induced neoplasms-particularly those induced by radiation likely to be encountered in space such as protons and heavy ions.

In vivo studies provide a powerful means for directly evaluating the effectiveness of particularly promising chemopreventives against cancers that may occur following radiation exposure. The rat mammary tumor model has been used extensively to analyze the carcinogenic effects of both chemical xenobiotics and physical agents. The Sprague Dawley rat mammary tumor model is particularly well-suited for studies in the low dose range because it is prone to develop induced mammary neoplasms early in life. Previous studies using the Sprague Dawley model have shown that sublethal doses of radiation (xrays, gamma rays, neutrons-not particularly relevant to space travel) induce mammary tumors, often within one year, and with a linear dose-effect relationship. Thus the Sprague Dawley rat mammary carcinogensis model not only closely resembles human breast cancer biologically, but it also is a highly sensitive model in which to examine the effects of radiation exposure and for testing pharmaceutical countermeasures against radiation effects. Our initial studies have focused on the effects of whole body, low level heavy ion and proton radiation along with chemoprevention of similarly induced mammary tumors using the female Sprague-Dawley rat mammary tumor model. The well-studied, widely prescribed, protoypte SERM, tamoxifen has been effectively and safely used in humans for chemotherapy for almost two decades. These advantages, along with an understanding of its molecular mechanism of action suggests it would be an excellent candidate for successful long-term chemoprevention of specific proton and heavy ion-induced cancers. The prospect for successful long-term chemoprevention of this potentially important, late-appearing cancer relevant to space radiation exposure is indeed an exciting prospect.

Hypothesis and Aims:
There is an uncertain, but serious risk of cancer potentially associated with prolonged space travel. These risks cannot be addressed with shielding alone. Our first hypothesis is that modeling these risks can remove much of the uncertainty and would allow better management of some of the radiation-risks associated with prolonged space missions. Our second hypothesis is that the increased cancer risk that may be associated with radiation in the space environnment can be mitigated by chemopreventive countermeasures implemented during the long cancer latency period that follows radiation exposure. The cancer causing effects of radiation as well as the safety and efficacy of chemopreventives have not been determined under conditions relevant to space. Animal models provide the best tools to test these hypotheses in relevant settings.

Specific Aims:
1) To determine the relative risks associated with exposure to the types of radiation encountered in space using a sensitive *in vivo* model of radiation-induced cancer.
2) To determine if pharmaceutical cancer chemopreventives could provide a safe and effective countermeasure approach to mitigate the cancer risk that may be associated with exposure to the types of radiation likely to be encountered in space.

Key findings:
Although our studies are not complete, preliminary trends in our tamoxifen studies have pointed to a proof of principle for a strategy in which chemopreventive agents could play an important role in preventing breast cancer following exposure to radiation during space travel. Confirmation of these trends is still pending the completion of these studies. Since Dr. Huso took over as PI of the chemoprevention studies, considerable progress has been made in this area. These results have important implications in the use of chemopreventives to prevent cancer in the general population as well as for astronauts. Since cancer chemoprevention in general is still in its infancy as an emerging field, chemoprevention based on new targets and emerging compounds, hold considerable promise for continued improvement of strategies to effectively mitigate risks associated with radiation and other predisposing factors for cancers. Further studies are required to confirm the long-term safety and effectiveness of chemoprevention strategies, to identify additional agents that are effective against specific neoplasms, and to continue to improve chemoprevention effectiveness and implementation.

The following are the implications of our findings for: 1) Future Research, and 2) Risk reduction for both space exploration as well as for the general population:

The implications are clear. Our results, though preliminary, provide a glimpse of the enormous potential payoff that chemoprevention research could provide in the battle against cancer. Regardless of the reason for an individual to be at increased risk for developing particular cancers, be it radiation exposure as in our studies (relevant to space travel) or genetic and environmental factors (relevant to the general population), specific chemopreventive compounds and strategies can be identified and implemented to mitigate risks that predispose individuals to cancer. Much work remains to be done to fully realize the benefits of chemoprevention strategies in the battle against cancer. Support for research into chemoprevention of radiation-induced neoplasms such as that provided by NSBRI therefore benefits not only space exploration efforts, but what is learned in this important area also could provide unique insight into cancer chemoprevention for the general population.

RESEARCH AREA:	**Radiation Effects**
PRINCIPAL INVESTIGATOR:	**Ann Kennedy, Ph.D.**
ORGANIZATION:	**University of Pennsylvania School of Medicine**
PROJECT TITLE:	**Countermeasures for Space Radiation Biological Effects**

Project Executive Summary

The hypothesis to be tested in this research program is that control of radiation induced oxidative stress will reduce the risk of cancer development. The overall objective of the proposed investigations for the initial 1.5-year grant period is to determine the types of dietary supplement agents or agent combinations that are the most effective at reducing the level of oxidative stress associated with exposure to ionizing radiation in space. The efficacy of the dietary supplement agents will first be evaluated in cultured human cells, in which the effects of the dietary supplement agents on the baseline levels of oxidative stress and radiation induced oxidative stress will be determined. The agents or agent combinations that are effective in reducing oxidative stress in the *in vitro* assay will then be evaluated alone or together in irradiated Sprague-Dawley rats to assess the efficacy of these agents in reducing radiation induced oxidative stress *in vivo*. The levels of oxidative stress will also be measured in Sprague-Dawley rats that are irradiated with 1-GeV iron ions or protons. For all studies to be performed as part of this program, surrogate endpoint biomarkers (SEBs) of carcinogenesis will be monitored, including bio-reduction capacity and oxidative stress in cells and animals. Oxidative stress will be determined by the dichlorofluorescein fluorescence assay, the protein carbonyl measurement and the isoprostane levels in urine (in animals). The breast cancer incidence rates in Sprague-Dawley rats are already known for various doses of photons, protons and 1-GeV iron ions from previous work performed by Dr. John Dicello and colleagues as part of the NSBRI Radiation Effects Team. Thus, the results from studies on SEBs can be directly compared with results obtained from the cancer induction studies performed previously. It is expected that there will be a dose-response relationship observed between doses of radiation and the levels of oxidative stress, and that the levels of oxidative stress will be directly related to breast cancer induction. It is hypothesized that a reduction in levels of radiation induced oxidative stress will be correlated with a parallel decrease in breast cancer rates. In the first 1.5 year part of the program, the best possible dietary supplement for reduction of radiation induced oxidative stress *in vivo* will be developed. SEBs will be studied in several tissues, including breast, colon and blood, as well as in urine samples. In future years of the program, the effect of the dietary supplement agents on the levels of oxidative stress will be compared to the effect of these agents on cancer development to determine whether the two effects are correlated. Assuming that there is a reduced cancer rate in the animals receiving the dietary supplement, the dietary supplement studies will also be extended to human trials in the future.

The original aims of the project

The experiments proposed in this application are designed to select a formula of dietary supplements that will protect against space radiation-induced biological effects, with particular emphasis on radiation-induced oxidative stress and cancer. In the initial phase of the study, which is expected to take 18 months, we will select dietary supplement agents that are most effective in suppressing radiation-induced oxidative stress *in vitro* and in animals. The levels of oxidative stress in cultured cells will be determined by the dichlorofluorescein (DCF) fluorescence assay and the protein carbonyl measurement. In animals, the protein carbonyl content in breast tissue, colon epithelial cells and blood (white cells and plasma) and the isoprostane concentration in urine will be measured as the indicators of oxidative stress. It is expected that a radiation carcinogenesis study will take place after the initial phase of the study to determine the effects of the selected dietary supplement agents in preventing radiation-induced cancer development. The effects of the selected dietary supplement agents on radiation-induced oxidative stress and radiation induced carcinogenesis will then be compared to determine whether the two effects are related.

a. Selection of dietary supplement agents and agent combinations that reduce radiation induced oxidative stress in cultured cells. Human breast epithelial cells (MCF10) will be irradiated with γ-rays, with and without supplementation of the media with agents known to reduce oxidative stress. The supplements to be added to the cultures will include the following as single agents or as combinations: vitamins C, E, folic acid, glutathione, N-acetyl cysteine, selenium, lipoic acid, niacin, thiamin, Co-enzyme Q10 and the soybean-derived Bowman-Birk inhibitor. The dietary supplement agents or agent combinations that are effective in reducing γ-ray-induced oxidative stress will be tested in the cells irradiated with protons and 1-GeV iron ions to determine their efficacy in reducing oxidative stress induced by these types of radiation. It is expected that studies on oxidative stress *in vitro* will go on throughout the grant period.

b. Determination of the effect of selected dietary supplement agents on radiation induced oxidative stress in Sprague-Dawley rats. Sprague-Dawley rats will be irradiated with γ-radiation to determine the optimal dose of radiation and time for the measurement of oxidative stress in the irradiated animals. The levels of oxidative stress will be determined by measuring the protein carbonyl content in breast tissue, colon epithelial cells and blood (white cells and plasma) and the isoprostane concentration in urine. After the optimal dose and time are established in the system, Sprague-Dawley rats will be irradiated with and without dietary supplements to determine the ability of these agents to reduce radiation induced oxidative stress *in vivo*. The dietary supplements to be evaluated will include the agents shown to be effective at reducing the levels of radiation induced oxidative stress in the *in vitro* studies described above. It is also planned that Sprague-Dawley rats will be exposed to a single dose of radiation from 1-GeV iron ions, protons or photons with and without a single dietary supplement. The plasma carbonyl content and urine isoprostane concentration will be measured in the samples collected from irradiated and control animals to assess the efficacy of the dietary supplement agents in inhibiting radiation-induced oxidative stress in the animals.

The key findings of the project

This grant was funded as of 10/01/01; thus, the experiments described for this project have only recently begun (this report is being written on November 16, 2001). A discussion of research findings is not reasonable at this time.

The impact of these findings on the hypotheses or requirements (technology), objectives and specific aims of the original proposal.

As the project has only recently been funded, the impact of the findings is unknown.

The proposed research plan for the coming year.

The research plans for the coming year are as described in the original project.

RESEARCH AREA:	**Radiation Effects**
PRINCIPAL INVESTIGATOR:	**Marcelo E. Vazquez, M. D., Ph.D.**
ORGANIZATION:	**Brookhaven National Laboratory**
PROJECT TITLE:	**CNS Damage and Countermeasures**

Project Executive Summary

Space travel beyond the Earth's protective magnetic field (for example, to Mars) will involve exposure of astronauts to irradiation by high-energy nuclei such as ^{56}Fe (HZE radiation), which are a component of galactic cosmic rays. These particles have high linear energy transfer (LET) and are expected to irreversibly damage cells they traverse. Exposure to HZE radiation may therefore cause progressive deterioration of brain function, adding to other inescapable damage involved in normal aging. We propose a study of the hypothesis that long-term behavioral alterations are induced after exposure of the brain to 1 GeV/n iron particles with fluences of one to eight particles/cell targets. Previous studies support this notion but are not definitive, especially with regard to long-term effects. Our principal goal is to examine the neurological effects of high-LET radiation on C57BL/6 mice using a series of behavioral tests to unveil the temporal expression of altered behaviors in the radiation response, as well as the means, which can modulate these responses. The studies proposed in this application are designed to: 1) Characterize the behavioral consequences after exposure to low-fluences of heavy ions and protons on C57BL/6 mice. The main behavioral endpoints to be used in these studies are locomotor activity to evaluate the integrity of striatal dopaminergic pathways, and spatial reference memory to probe hippocampal cholinergic pathways. 2) Characterize the neurochemical and structural changes induced by heavy ions and protons. 3) To develop countermeasures to protect neural cell populations exposed to low fluences of heavy ions and protons. The project will test methods to protect injured neural cells based on their molecular and cellular mechanisms that may regulate neural cell survival in the central nervous system. Among the methods that will be studied is the direct administration of neuroprotective molecules as well as the modulation of apoptotic pathways by pharmacological manipulation. The effects of three different neuro/radioprotectors (GM1, melatonin and PTF-α) on the levels of radiation induced neurochemical and structural damage will be compared with the level of behavioral alterations to determine a cause/effect relationship.

RESEARCH AREA:	**Radiation Effects**
PRINCIPAL INVESTIGATOR:	**Marcelo Vazquez, M. D., Ph.D.**
ORGANIZATION:	**Brookhaven National Laboratory**
PROJECT TITLE:	**Risk Assessment and Chemoprevention of HZE Induced CNS Damage**

Project Executive Summary

Because successful operations in space depend on the performance capabilities of astronauts, radiation-induced neurological damage, could jeopardize the successful completion of mission requirements, as well as have long-term consequences on the health of astronauts. It is therefore necessary to understand the nature of this risk in order to assess its seriousness and to develop countermeasures. Compared to the large literature associated with radiation therapy, knowledge is limited about the cellular and molecular responses of cells to high-LET HZE radiation in general, and very limited about the central nervous system (CNS) specifically. Therefore, we propose to compare the effects of charged particle (Fe, Si), protons, gamma and x-ray radiation on the cells of the CNS, namely neurons and glial (astrocytes and oligodendrocytes). Cell cultures of CNS cells, both cycling and post-mitotic differentiated cells, will be utilized as model systems. We will test the hypothesis that exposure to low fluences/doses of heavy ions and protons can induce cell death in neural CNS neural cells and that increasingly dense ionizing radiation will be increasingly toxic. The activation of two separate stress signal transduction pathways will be examined (p53 and ceramide) for their role in causing cell death or other deleterious changes caused by irradiation. And with respect to p53, we will determine which of the post-translational modifications in regulating p53 function are relevant for charged particle induced cell death. Finally, we will test the hypothesis that modulating the stress signal transduction pathways will modify the radiation response of brain cells exposed to heavy ions and protons, and test the efficacy several compounds as potential countermeasures for HZE radiation toxicity.

NSBRI RESEARCH PROGRAM
SMART MEDICAL SYSTEMS

Team Leader: **Sutton, J. P.** **Harvard**

Associate Team Leader: **Crum, L. A.** **Washington**

Crum, L. A.	**PI**	**Washington**	**Guided High Intensity Focused Ultrasound (HIFU) for Mission-Critical Care**	**147**
Carter, S. J.	CO-I	Washington		
Bailey, M. R.	CO-I	Washington		
Kaczkowski, P. J.	CO-I	Washington		
Vaezy, S.	CO-I	Washington		
Davies, P. F.	**PI**	**Penn**	**Vascular Genomics in Gravitational Transitions**	**148**
Stoeckert, C.	CO-I	Penn		
Klempner, M. S.	**PI**	**Boston Univ.**	**Smart Medical System for Detection of Microorganisms**	**150**
Putcha, L.	**PI**	**NASA JSC**	**Microcapsule Gel Formulation of Promethazine Hydrochloride for Intranasal Administration**	**151**
Soller, B. R.	**PI**	**UMass**	**Noninvasive Measurement of Blood and Tissue Chemistry**	**152**
Heard, S. O.	CO-I	UMass		
Puyana, J. C.	CO-I	UPittsburgh Medical Center		
Sutton, J. P.	**PI**	**Harvard/MIT**	**Near Infrared Brain Imaging for Space Medicine**	**153**
Boas, D. A.	CO-I	Harvard		
Koroshetz, W. A.	CO-I	Harvard		
Rosen, B. R.	CO-I	Harvard/MIT		
Strangman, G. E.	CO-I	Harvard		

Thomas, J. D.	**PI**	**Cleveland Clinic**	**Diagnostic Three Dimensional Ultrasonography: Development of Novel Compression, Segmentation and Registration Techniques for Manned Space Flight Applications**	**155**
Greenberg, N. L.	CO-I	Cleveland Clinic		
Shakar, R.	CO-I	Cleveland Clinic		
Hale, J. C.	CO-I	Cleveland Clinic		
Shiota, T.	CO-I	Cleveland Clinic		
Thomas, J. D.	**PI**	**Cleveland Clinic**	**Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity**	**157**
Garcia, M. J.	CO-I	Cleveland Clinic		
Greenberg, N. L.	CO-I	Cleveland Clinic		
Morehead, A. J.	CO-I	Cleveland Clinic		

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**Lawrence Crum, Ph.D.**
ORGANIZATION:	**University of Washington**
PROJECT TITLE:	**Guided High Intensity Focused Ultrasound (HIFU) for Mission-Critical Care**

Project Executive Summary

Objective:
The principal objective of this NSBRI Smart Medical Systems Team project is to develop an image-guided ultrasound therapy system for mission critical care. In long-term space flight missions, a number of medical situations could develop that if not adequately addressed would result in mission failure. For example, although gravity is significantly reduced in space, inertia is not, and the collision of an astronaut with a heavy object could result in blunt internal trauma and its often associated internal bleeding. In addition, as recent experiences in Antarctica demonstrate, medical conditions that require some form of surgery may well appear without warning, even when extensive pre-screening is undertaken. We are developing a smart medical device that will provide a versatile capability to treat a variety of these mission-critical medical conditions. We have demonstrated that a device that produces High Intensity Focused Ultrasound (HIFU) can be combined with a device that provides ultrasound imaging to produce a duplex system that can both image a particular condition of interest and provide therapy to relieve the condition. "Image-Guided Therapy" provides enormous potential for the treatment of a variety of medical conditions. In addition, we have demonstrated that the components of such a smart medical system can reasonably be expected to be lightweight and portable.

Summary of Year 1 Results:
Smart Medical System. A small portable image-guided HIFU system has been built for mission critical care. Year 1 objectives were met. The engineering objectives included adding computer control of the system, a dynamically focusing transducer, focus tracking, a point and shoot trigger for ease of use, and flexibility to synchronize with any ultrasound imaging system. These advances have reduced the size of the system and the complexity of use. EAC members tested the system on a tissue phantom in an October demonstration. The R&D objectives were to test the ergonomics of the new transducer, to calibrate the system, to improve testing systems, to develop a means to collect RF data from an ultrasound imager, and to work with RF data to develop new imaging techniques. These objectives were also met and will be implemented in year 2 and 3 prototypes.
Beyond NSBRI. We are leveraging our other HIFU work to assess the best treatment protocols for a variety of injuries, diseases, and procedures. That work has been on animals but our devices are entering clinical trials for some applications. In addition we have teamed with a US company Engineering Acoustics, Inc. and applied for SBIR grants from NIH and DARPA to produce and to commercialize a portable amplifier for HIFU. Collaboration with the company will accelerate advances in amplifier design that we have initiated with NSBRI funding and will dramatically reduce our system size.
NSBRI Collaboration. With success on our own project in Year 1, we have also identified new close collaborations with other NSBRI teams. There is synergy with other teams in ultrasound imaging, bubble detection for decompression sickness, kidney stone diagnosis and treatment, and stimulation of bone growth by vibration.

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**Peter Davies, Ph.D.**
ORGANIZATION:	**University of Pennsylvania**
PROJECT TITLE:	**Vascular Genomics in Gravitational Transitions**

Project Executive Summary

Aims When changes in the biomechanical environment of the circulation occur, blood vessels undergo well-orchestrated structural and metabolic remodeling to restore optimal function. We propose that this remarkable adaptive ability lies at the center of orthostatic intolerance exhibited by most astronauts on return to earth's gravitational field after modest-to-long periods in microgravity. We are therefore mapping gene expression (transcription profiling) of the different vascular steady states exhibited *in vivo (mouse)* in simulated hypergravity and microgravity, and the transitions between them, in order to design better countermeasures for undesired vascular consequences in long-term space flight.

Key findings

During the first 9 months we have refined the antisense RNA techniques necessary to amplify RNA from small numbers of cells with high fidelity. This became necessary when it was apparent that no literature exists for a rigorous test of the new RNA amplification protocols required in the mouse experiments. In a model experiment, vascular cells were stimulated with the cytokine TNF for which a small number of genes are known (through conventional Northern analyses) to change. RNA from the same pool was analyzed by microarray with and without amplification. Sophisticated bioinformatics analysis of 13,800 genes was performed. The data from unamplified and amplified RNA were analyzed for fidelity, sensitivity and utility. The expected prominent changes in known genes were detected in both groups with high retention of accuracy, an essential requirement for the proposed *in vivo* gravity experiments. An interesting additional and unexpected finding is that RNA amplification increased the detection rate of genes whose differential expression was just below a significance threshold in the unamplified assay i.e. greater sensitivity of detection of differential gene expression conferred by the linear amplification techniques employed. Most important, these differences were confirmed by real-time quantitative PCR of unamplified RNA. A manuscript is near completion (ref 2 below). This work was necessary for the gravitational studies because no such analysis existed that rigorously evaluates the accuracy of the transcription profiles arising from amplification of small amounts of blood vessel.

Techniques for the dissection of mouse blood vessels, RNA isolation and amplification has been verified under normal gravitational conditions. The microarray experiments are pending. These are evaluative experiments to ensure that we can successfully perform the entire sets of protocols from animal to bioinformatics and annotation prior to imposing simulated gravitational shifts.

Impact

The improved sensitivity of the amplification technique enhances the database of changes in gene expression expected by simulated gravitational shift. Validation of this by real-time PCR (the 'gold-standard' in the field) strengthens the data that will be generated using our approach.

Coming Year Plans

The murine suspension model of simulated *micro*gravity is a well-characterized approach suitable for inducing orthostatic changes that mimic microgravity. For studies of *hyper*gravitational changes, the facilities of the Chronic Hypergravity Exposure Centrifuge at NASA/Ames are suitable for long-term exposure of mice at 3G to simulate return to earth (or landing on Mars surface) after long term space travel.

Mice will be exposed to micro or hyper gravity for upto 28 days and the effects upon gene expression in the major arterial system will be measured by the techniques outlined above. Reversal of the conditions in both sets of experiments will also be evaluated on a temporal basis.

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**Mark S. Klempner, M.D.**
ORGANIZATION:	**Boston University**
PROJECT TITLE:	**Smart Medical System for Detection of Microorganisms**

Project Executive Summary

The goal of this program is to develop a revolutionary, non-culture based microbial detection, identification and quantification system that can be used as part of a Smart Medical System for exploratory space travel. Rapid detection and identification of microorganisms are critical to many military and civilian applications ranging from food and water safety monitoring, biological warfare agent detection and to diagnostic microbiology of human and other biological specimens. For long-term exploratory space travel there will be a critical need for a smart medical system to monitor the air and water supply for microbial contaminants, as well as an intermittent need for assessment of biological specimens from symptomatic astronauts.

Current microbial identification systems are based on the gold standard of *in vitro* culture or DNA/RNA fingerprinting. Both require considerable sample manipulation, delay in readout, are semiquantitative and subject to interfering substances and contamination, and require additional processing to resolve complex mixtures of microorganisms. This proposal involves the development of a novel smart medical system to detect and identify bacteria through the use of microsensors and includes three steps: 1) Development of "fingerprinting" phage display libraries which can detect, identify, quantify and discriminate bacterial species in environmental and biological specimens; 2) Application of phage displayed peptides and antibody fragments in a microarray to the surface of a microsensor to demonstrate the microarray microbial fingerprint response to selected bacterial species using optical readout and electronic MEMS resonator arrays and to characterize the sensitivity and specificity for detecting and discriminating between bacterial species using surface "fingerprints;" and 3) Development of algorithms from the microarray response for the real time identification and discrimination of bacterial species.

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**Lakshmi Putcha, Ph.D.**
ORGANIZATION:	**NASA Johnson Space Center**
PROJECT TITLE:	**Microcapsule Gel Formulation of Promethazine Hydrochloride for Intranasal Administration**

Project Executive Summary

A continuing challenge for space medical operations at NASA is the management of pathology associated with neurovestibular adaptation during space flight. A primary manifestation of this problem, particularly in the first few flight days of shuttle missions, is space motion sickness (SMS). The current treatment of choice for symptoms associated with SMS is promethazine (PMZ). Although oral tablets and rectal suppositories have been used during space flights, the intramuscular route appears to be most effective. On the other hand, intramuscular administration of drugs is an invasive procedure and PMZ causes irritation at the site of injection. A key research topic in the Smart Medical Systems area of the NSBRI 99-02 research announcement is development of novel therapeutic modalities for remote site medical operations such as space missions. In response to this initiative, the goal of the proposed research is to develop an intranasal dosage formulation of PMZ that will provide crewmembers with a non-invasive means of self-administering SMS medications. Accordingly, the following three aims will be addressed: 1) Develop a microencapsulated, pH-balanced gel dosage formulation and a combination form with a corticosteroid for intranasal administration of PMZ; 2) Establish the release kinetics and shelf life of the optimized dosage forms; and 3) Assess bioavailability, nasal mucosal irritability and toxicity of the selected dosage forms in rats.

The proposed formulation development will focus on tailoring the release characteristics of the dosage form to optimize therapeutic index and minimize irritability at the site of administration. Once the optimal dosage form has been identified based on release kinetics and stability characteristics, bioavailability, nasal irritability and toxicity after single and multiple dose administration will be assessed in an animal model. Development of an intranasal drug delivery system for motion sickness treatment will benefit pharmacotherapeutics in space as well as on Earth.

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**Babs R. Soller, Ph.D.**
ORGANIZATION:	**University of Massachusetts Medical School**
PROJECT TITLE:	**Noninvasive Measurement of Blood and Tissue Chemistry**

Project Executive Summary

Medical monitoring and diagnosis of acute and chronic conditions during long-duration space flight is critical to the success of these missions and must be able to be carried out by personnel with limited medical training and equipment. The most successful technologies will be those that allow noninvasive measurement of multiple parameters that can be combined for algorithm-driven decision making. Near infrared spectroscopy (NIR) has been successfully used to noninvasively assess blood and tissue for the measurement of oxygenation, pH, glucose and hematocrit and the diagnosis of cancer because NIR light can penetrate through skin and bones. Currently, this technology is limited in its ability to accurately measure these parameters for people with dark skin color and significant fat content. The hypothesis of this proposal is that NIR, in combination with unique statistical methods, can be used to noninvasively measure blood and tissue chemistry for any human subject. This project will develop new statistical methods which will enhance the processing of NIR spectral data so that medical parameters can be accurately measured on all humans, irrespective of skin color and gender. This new approach will be demonstrated by developing techniques to noninvasively measure blood hematocrit and muscle pH and oxygenation on human surgical and ICU patients. These parameters are important in diagnosing and treating hypoxia and trauma that may arise from exposure to radiation, toxic chemicals and blunt or sharp injury. They may also be useful in evaluating exercise as a countermeasure for extended weightlessness. The measured patient data will then be used to develop algorithms to diagnose shock and hypovolemia and guide resuscitative therapies. Finally, optical specifications will be developed to build a miniaturized system to collect NIR data. This system will serve as a platform for NIR measurement of multiple parameters and the development of computerized algorithms to assist in the diagnosis and treatment of several medical conditions. The specific system demonstrated in this proposal is intended to evolve into a medical monitoring system for use during extended space flight, but will also find immediate application in terrestrial hospitals, emergency vehicles and emergency rooms.

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**Jeffrey Sutton, M.D. Ph.D.**
ORGANIZATION:	**Harvard – Massachusetts General Hospital**
PROJECT TITLE:	**Near Infrared Brain Imaging for Space Medicine**

Project Executive Summary

This project is part of the NSBRI Smart Medical Systems Team. It develops and applies a new technology, diffuse optical tomography (DOT), for portable non-invasive functional monitoring suitable for neuroimaging in space. The technology has potential capabilities to:

- Quantitatively assess physiological adaptation (e.g., changes in intracranial pressure and blood flow) associated with microgravity;
- Detect regional brain activity correlated with performance under altered circadian and mental loads;
- Provide remote clinical assessment; and
- Guide treatment.

As assessed by NASA, the project addresses two of the four highest priority risk areas on the Critical Path Roadmap (CPR). These are (1) trauma and acute medical problems, and (2) human performance failure because of poor psychosocial adaptation. In addition to applications for space, the developments of this project have relevance to Earth medical research and care. For example, DOT is now being tested for monitoring stroke progression in patients with acute cerebrovascular accidents.

The project brings together scientists, engineers and physicians at the Massachusetts General Hospital/Harvard-MIT Division Health Sciences and Technology, and medical operations personnel at NASA Johnson Space Center (JSC), to work collaboratively on the development and testing of DOT as a space relevant technology. The **original aims** are to:

1. Refine current DOT technology to build an instrument with improved spatial and temporal resolution to detect brain activity non-invasively, and in real time, through the intact skull;

2. Validate the improved instrument using functional magnetic resonance imaging (fMRI), which is a standard technology, and test DOT as a portable brain imaging device for assessing motor and cognitive activity under normal and sleep deprived conditions in normal human subjects;

3. Assess DOT, along with optical coherence tomography (OCT), to non-invasively measure altered intracranial pressure (ICP) in neurological patients, given that altered ICP may occur in the space environment; and

4. Refine a system for automated image interpretation using individualized brain models and computational techniques.

During the first year, **key findings** and accomplishments include:

- The refinement of DOT instrumentation to validate the technology using fMRI;
- Observations of an excellent correlation between DOT and fMRI brain activity across time during simple motor tasks;
- The successful application of anatomical and functional MRI data, as constraints on the calculation of DOT detected oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) changes, for brain mapping; and
- The development and off-line testing of a visuomotor task, termed SpaceDOCK, which simulates a space relevant performance task and can be used in the optical/MRI environment.

The **impact of these findings** are that they address the technology requirements set forth in Aim 1, and begin the validation process for DOT as laid out in the objectives and hypotheses of Aims 2 and 4. The preliminary motor data using simultaneous DOT and fMRI confirm one of the hypotheses contained in Aim 2, namely that DOT and fMRI will be able to detect changes in regional brain activity contralateral to motor movement. The development of SpaceDOCK allows for testing a second hypothesis contained in Aim 2 concerning DOT and fMRI, and the ability to detect frontal cortex changes as a function of mental load in normal and sleep deprived subjects. The overlay of MRI and DOT data speaks to the issue of individualized, digitized human, anatomical brain models upon which time-derivative functional data are used for interpretation and display in real time (Aim 4).

In the coming year, the **proposed research plan** follows the timeline described in the initial proposal. The project is on schedule and meeting all milestones. In year two, further DOT instrument design and development will be achieved, with continued validation of DOT using fMRI. Preliminary data on motor-sensory cortex activation will be confirmed and the results are being prepared for publication. DOT testing using SpaceDOCK will commence in year 2, as will studies on sleep deprived subjects. Patient populations with elevated ICP will begin to be investigated, and continued development will take place on the informatics system towards more automated machine/human interface for DOT imaging in analog settings.

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**James Thomas, M.D.**
ORGANIZATION:	**The Cleveland Clinic Foundation**
PROJECT TITLE:	**Diagnostic Three Dimensional Ultrasonography: Development of Novel Compression, Segmentation and Registration Techniques for Manned Space Flight Applications**

Project Executive Summary

The NSBRI has identified that the efficient and automated delivery of health care in space is a key research arena for the future. Specifically, they propose to develop a "Smart Medical System" that will be able to monitor crew health, identify deviations from ground-based norms, and allow timely intervention by crew members who may have only a moderate amount of training in medicine. For the last three years, the principal investigator and colleagues have worked closely with NASA scientists, flight surgeons, and engineers to optimize research and diagnostic ultrasound aboard the International Space Station (ISS) and thus are well positioned to develop the necessary tools and techniques to integrate ultrasound into the Smart Medical System. A principal limitation of ultrasound technology is its extreme dependence on the expertise of both the acquiring examiner and the interpreting physician. This is particularly true of two-dimension ultrasound, where the examiner is required to obtain precisely oriented anatomical sections of the organ of interest.

Three-dimensional ultrasound has the advantage of acquiring a large anatomic volume from a single ultrasonic window, and thus may be less dependent upon the expertise of the examiner. Furthermore, this large volume may contain sufficient anatomic landmarks to allow unambiguous registration with previously obtained three-dimension data from either ultrasound or other modalities such as magnetic resonance imaging (MRI) or computed tomography (CT). One could thus envision a system by which whole organs or even the entire body would be imaged in three-dimensions prior to launch; data which could be used to compare with subsequently obtained three-dimensional data sets using in-flight ultrasonography. The overall purpose of this grant is therefore to perform ground-based research, development, and validation aimed at optimizing diagnostic ultrasound in manned space flight, with the following general hypothesis:

Unifying hypothesis: Serial three-dimensional ultrasound examinations will enhance diagnostic capabilities in manned space flight.
The technical aspects of this program will be pursued with the following specific aims:

1. Optimize the acquisition methods for three-dimensional sonography, utilizing reconstruction and real-time techniques.
2. Develop techniques for registering anatomical images from two- and three-dimensional ultrasound with those obtained from prior ultrasound examination and from magnetic resonance and computed tomographic imaging, considered "gold standards" for non-invasive anatomical imaging.
3. Develop tools for abstracting, in an automated fashion, anatomical changes from serial three-dimension and two-dimension ultrasound studies.

4. Develop algorithms for the optimal compression of three-dimensional ultrasound images and refine current two-dimensional compression algorithms.
5. Assess the ability of novice examiners to obtain three-dimensional sonographic data sets following minimal training.

These objectives will be pursued using data from a variety of *in vitro*, animal and clinical models. In particular, we will take advantage of a well-established collaboration with the National Institutes of Health, which permits highly sophisticated chronic animal models to be examined with a minimum of additional resources. Although the tools developed here should be applicable to any organ of the body, we will focus our efforts on the kidneys and the heart.

At the conclusion of this project, we anticipate delivering to the NSBRI and its Smart Medical System a set of algorithms and software for the non-rigid morphological registration and comparison of serial two- and three-dimensional ultrasound data sets and validated algorithms for optimal compression of four-dimensional ultrasound data. In addition to these technical deliverables, our validation work on nephrolithiasis will provide important diagnostic clues for assessing this condition in manned space flight. Similarly, the work on cardiac mass regression following unloading will be invaluable to the NASA research and medical operations community in assessing the impact of long-term space flight on cardiac atrophy and utility of prophylactic countermeasures.

RESEARCH AREA:	**Smart Medical Systems**
PRINCIPAL INVESTIGATOR:	**James Thomas, M.D.**
ORGANIZATION:	**The Cleveland Clinic Foundation**
PROJECT TITLE:	**Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity**

Project Executive Summary

The cardiovascular system undergoes significant changes in microgravity, including an early cephalad shift of lower extremity blood volume, loss of plasma volume over 24 to 48 hours, and long-term reduction in ventricular chamber volume and mass. In the weightless environment, these alterations generally are well tolerated, but upon return to Earth, astronauts often suffer from serious orthostatic intolerance and reduced exercise capacity, changes that may limit the long-term presence of man in space. It is essential that the mechanisms for these alterations be understood so that reliable countermeasures can be tested and implemented. Hypovolemia, cardiac atrophy, and autonomic dysfunction have each been hypothesized to contribute to this post-flight debility, but their relative importance is unclear. Furthermore, it is unknown whether actual abnormalities in the myocardium itself develop with long-term space flight. Therefore, reliable portable noninvasive methods will be needed in order to detect and quantify these changes.

Alone among such imaging modalities of radiography, magnetic resonance imaging and computerized tomography, echocardiography has the unique ability to characterize cardiovascular anatomy and physiology in ground-based models, pre- and post-flight, and most importantly during flight. Indeed, the Science Working Group (SWG) for the International Space Station (ISS) Human Research Facility (HRF) has recognized the primacy of ultrasound for medical diagnosis and physiology research, with plans to launch a specially modified commercial ultrasound instrument to the ISS in 2001. Echocardiography is similarly being used before and after shuttle flights and in a variety of bed-rest studies sponsored by NSBRI and NASA. Unfortunately, while ultrasound has the potential for high spatial and temporal resolution imaging of the heart, in the past it has been severely limited by operator inexperience and inconsistency in its subjective interpretation. Needed are new methodologies for assessing the load-independent function of the heart and consistent, objective quantification of a wide range of NASA echo studies, whether obtained on the ground, in flight or in experimental models. We propose to provide such a facility while validating novel methods for the load independent assessment of myocardial function. Our central hypothesis is that:

Microgravity affects cardiovascular function not only through changes in chamber volume and mass but also through changes in myocardial properties.

A definitive test of this hypothesis is at least several years away when dedicated life science missions are possible aboard the ISS. However, within the scope of this grant, we propose several specific aims that will be critical to the ultimate comprehensive study of the cardiovascular system in space. Key issues: 1) Validation of non-invasive Doppler echocardiographic indices for the assessment of left ventricular contractility and relaxation including color M-mode Doppler derived diastolic intraventricular pressure gradients (IVPG) and tissue Doppler derived myocardial systolic and diastolic strain rates (e's, e'd); 2) Validation of Doppler derived exercise cardiac output and contractile reserve and their potential utility for the

early detection of myocardial dysfunction during prolonged space flight. Additional deliverables to NSBRI: 3) Development and distribution of stand-alone software and algorithms for implementing the quantitative analysis of Doppler echocardiographic data, as described above, so they may be applied to ultrasound data obtained from remote sources; 4) Establishment of an Echocardiographic Core Facility to the NASA research and clinical community, capable of applying standard and novel analysis techniques in a rigorous fashion to echocardiographic data obtained from selected ground-based experimental models, pre- and post-flight examinations, and eventually from in-flight acquisitions.

If successfully implemented, these aims will allow the cardiovascular sequellae of space flight to be studied much more rigorously, while providing consistent, objective echocardiographic interpretation to the entire NASA community.

NSBRI RESEARCH PROGRAM
TECHNOLOGY DEVELOPMENT

Team Leader: **Charles, H. K. Jr.** **Hopkins/APL**

Associate Team Leader: **Buckey, J. C.** **Dartmouth**

Bankman, I. N.	**PI**	**Hopkins/APL**	**Development of a Space Qualifiable MRI System**	**161**
Chacko, V. P.	CO-I	Hopkins/SOM		
Feldmesser, H. S.	CO-I	Hopkins/APL		
Wetsel, G. C.	CO-I	Hopkins/APL		
Buckey, J. C.	**PI**	**Dartmouth**	**Improved Bubble Detection for EVA**	**162**
Magari, P. J.	CO-I	Creare Inc.		
Leiter, J. C.	CO-I	Dartmouth		
Charles, H. K. Jr.	**PI**	**Hopkins/APL**	**AMPDXA Scanner for Precision Bone and Muscle Loss Measurements During Long-Term Space Flight**	**163**
Beck, T. J.	CO-I	Hopkins/SOM		
Feldmesser, H. S.	CO-I	Hopkins/APL		
Magee, T. C.	CO-I	Hopkins/APL		
Davis, B. L.	**PI**	**Cleveland Clinic**	**Design and Validation of a Dynamic Exercise Countermeasure Device**	**166**
Yue, G. H.	CO-I	Cleveland Clinic		
Hoadley, D. J.	CO-I	Foster-Miller Inc.		
Maurer, R. H.	**PI**	**Hopkins/APL**	**Neutron Energy Spectrometer Flight Experiments**	**167**
Dicello, J. F.	CO-I	Hopkins/SOM		
Fainchtein, R.	CO-I	Hopkins/APL		
Gold, R. E.	CO-I	Hopkins/APL		
Goldsten, J. O.	CO-I	Hopkins/APL		
Kinnison, J. D.	CO-I	Hopkins/APL		
Roth, D. R.	CO-I	Hopkins/APL		
Potember, R. S.	**PI**	**Hopkins/APL**	**Real-Time Analysis of Biomarkers and Countermeasures Using a Miniature Time-of-Flight Mass Spectrometer**	**170**
Bryden, W. A.	CO-I	Hopkins/APL		

Qin, Y.	**PI**	**SUNY**	**A Non-Invasive Scanning Confocal Ultrasonic Diagnostic System for Bone Quality**	**172**
Rubin, C. T.	CO-I	SUNY		
Gruber, B.	CO-I	SUNY		
Radeka, V.	**PI**	**Brookhaven**	**Heavy Ion Microbeam and Micron Resolution Detector**	**174**
Brown, K. A.	CO-I	Brookhaven		
Li, Z.	CO-I	Brookhaven		
Vazquez, M. E.	CO-I	Brookhaven		
DeGeronimo, G.	CO-I	Brookhaven		

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Isaac N. Bankman, Ph.D.**
ORGANIZATION:	**Johns Hopkins University Applied Physics Laboratory**
PROJECT TITLE:	**Development of a Space Qualifiable MRI System**

Project Executive Summary

This proposal is to develop a proof-of-concept engineering model of a space qualified Magnetic Resonance Imaging (MRI) system for small animals and astronaut limbs with mass of < 130 kg and average power when on but not scanning < 1 kW and when scanning < 1.2 kW, not including the processor. An onboard processor or a high-performance PC can be adapted. MRI provides high-resolution, high-quality anatomical information without ionizing radiation so it can be safely used repeatedly to track changes without deleterious effects. As a result, the study of physiological alterations in space and the development, verification, and maintenance of countermeasures will be significantly enhanced. Mice and small rat models are useful surrogates to carry out in-orbit physiological studies. Measuring alterations in the limbs of astronauts, especially the lower limbs, will provide partial confirmation of the effectiveness of proposed countermeasures and the utility of Earth-based animal models. In-flight MR imaging of mice and rats will especially benefit the countermeasure developments of several of the NSBRI research teams. The proposed concept is based on traditional MRI principles and uses advanced technology and advanced engineering techniques to reduce mass and power to acceptable levels. The system consists of a 1 to 1.5 Tesla cryogen-free high temperature superconducting magnet subsystem and advanced electronics that will have magnetic field inhomogeneities ≤ 8 ppm over a spherical imaging volume of 10 cm diameter and ≤ 10 ppm out to 15 cm diameter. The magnet cryocooler subsystem will be designed using high temperature superconducting materials to significantly reduce the mass and power of the cryocooler. The highest resolution mode gives a resolution of 117 microns for small animals over a spherical imaging volume of 6 cm diameter and a resolution of 352 microns for human limbs over a spherical imaging volume of 18 cm diameter. The standard resolution mode will provide a resolution of 234 microns and 703 microns, respectively. The pulse sequence scenarios used will be those traditionally used in MR imaging to achieve images that are proton-density, T1 or T2 weighted so that a significant amount of structural information will be available. Because of budget limitations, only selected electronics will be reengineered to demonstrate the minimum mass and power that can be achieved. We ask that the panel consider a supplemental budget request that allows redesign and fabrication of all of the electronics to minimize mass and power. The team is composed of individuals and organizations with a unique combination of expertise including: MRI systems development at the General Electric Research and Development Center, advanced MRI development and small animal experimentation at the Johns Hopkins School of Medicine, and the development of reliable medical and low-mass, low-power systems for space applications at the Johns Hopkins University Applied Physics Laboratory.

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Jay C. Buckey, M.D.**
ORGANIZATION:	**Dartmouth Hitchcock Medical Center**
PROJECT TITLE:	**Improved Bubble Detection for EVA**

Project Executive Summary

Assembly of the International Space Station (ISS) requires extensive and unprecedented extra-vehicular activity. Because spacesuits operate at low internal pressure, astronauts are highly susceptible to decompression sickness (DCS), and a range of pre-breathe strategies are employed to mitigate this risk. During ISS construction, in-suit Doppler bubble monitoring will be provided to monitor for DCS risk. Doppler bubble detection is effective, but (1) it is motion sensitive, (2) detects only moving bubbles, and (3) only detects bubbles that are approximately 80 μm greater in size. Our goal is to build on the successful development of two novel transcutaneous ultrasonic bubble detection and sizing instruments developed under NASA funding that exploit bubble resonance (not Doppler), making the instruments capable of sizing bubbles as well as detecting stationary bubbles. One instrument is optimized for intravascular bubbles in the 30 to 200 μm size range, and the other is optimized for extravascular bubbles in the 1 to 10 μm size range. The intravascular bubble instrument has been demonstrated in extensive *in-vitro* trials and preliminary *in-vivo* trials to detect and size intravascular bubbles down to 30 μm in size. The extravascular bubble instrument is currently under development and is intended to detect stationary bubbles in tissue. The ability to detect these small tissue bubbles may be highly advantageous in terms of assessing DCS risk and developing efficient pre-breathe strategies. The extravascular bubble-sizing instrument has been demonstrated *in vitro* down to bubble sizes of approximately 1 μm, and it is presently being tested with tissue phantoms to demonstrate *in-vitro* transcutaneous operation. This project will combine the Creare development team with the hypo- and hyperbaric facilities at Dartmouth-Hitchcock to validate the application of these instruments for *in-vivo*, transcutaneous bubble detection. Testing and application of these instruments in research and practical field applications may lead to (1) better understanding of DCS and (2) improved monitoring and prevention techniques for DCS.

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Harry K. Charles, Jr., Ph.D.**
ORGANIZATION:	**Johns Hopkins University Applied Physics Laboratory**
PROJECT TITLE:	**AMPDXA Scanner for Precision Bone and Muscle Loss Measurements During Long-Term Space Flight**

Project Executive Summary

The purpose of the Advanced Multiple Projection Dual Energy X-ray Absorptiometry (AMPDXA) Scanning System project is to design, build, and test a precision scanner system for monitoring the deleterious effects of weightlessness on the human musculoskeletal system during prolonged spaceflight. The instrument uses dual energy X-ray absorptiometry (DXA) principles and is designed to measure bone mineral density (BMD), decompose soft tissue into fat and muscle, and derive structural properties (cross-sections, moments of inertia). Such data permits assessment of microgravity effects on bone and muscle and the associated fracture risk upon returning to planetary gravity levels. Multiple projections, coupled with axial translation, provide three-dimensional geometric properties suitable for accurate structural analysis. This structural analysis coupled with bone models and estimated loads defines the fracture risk. The scanner will be designed to minimize volume and mass (46 kg goal), while maintaining the required mechanical stability for high-precision measurement. The AMPDXA will be able to detect 1% changes in bone mass and geometry and 5% changes in muscle mass.

The AMPDXA project is a joint effort between the NSBRI's Technology Development Team, the Bone Demineralization/Calcium Metabolism Team, and the Muscle Alterations and Atrophy Team. Its goal is to provide the high precision monitoring system necessary to fully assess both the deleterious effects of weightlessness on the bones and muscles and the effectiveness of any countermeasures. We believe that any pharmacological or exercise-related countermeasures used by astronauts to mitigate microgravity effects will require efficient and timely monitoring. Moreover, the monitoring device must be capable of being used by astronauts during spaceflight so that feedback can be dynamically employed to regulate countermeasure doses. The system design will be such that intelligent, but not necessarily medically trained, personnel will be able to create scans that will provide all of the accuracy and precision necessary. Readouts and displays for the AMPDXA instrumentation will be specifically designed to provide useful (real-time) feedback information to both the astronauts and the ground-based physician monitoring team (as permitted by the mission dynamics).

We believe the key to understanding the mechanism of bone (and muscle) loss in space (microgravity) lies in the bone's structural details and the changes in the structure due to prolonged weightlessness. Our hypothesis is that throughout most of adult life, aging bones become more structurally efficient and retain their strength even though BMD declines. The homeostatic mechanism for strength maintenance depends on skeletal loading. Thus, to maintain bone strength, normal loading on the skeletal system must be maintained. Absence of loading during prolonged spaceflight (or disuse) can cause uncompensated loss of bone strength. Even reduced loading (caused by muscle wasting and inactivity in the elderly) can cause a disruption in the bone strength maintenance mechanism.

Current bone and muscle mass measurements (via conventional DXA or ultrasound) are regional averages that obscure structural details. Since the mechanical consequences of lost bone and muscle are reflected in the structure, an absolute determination of skeletal mechanical competence is needed to supplement the loss measurements. Engineering properties of the bones can be derived from DXA-generated BMD data. Our method derives geometrical measurements from the BMD images. From such images, we extract BMD profiles at important skeletal locations (e.g., proximal shaft and femoral neck). Key properties measured and derived from these profiles include the BMD, the subperiosteal width, the section modulus (related to strength), and the cortical dimensions.

Under the original proposal effort, FY 1998-2000, the AMPDXA project made significant progress in several key areas: (1) instrument development, (2) algorithm development for BMD image extraction and structural analysis, and (3) bone reconstruction and modeling techniques. During the FY 1998-2000 period, both a full-sized (1-meter source-to-detector distance) Laboratory Test Bed and a Clinical Test System were constructed. The Laboratory Test Bed was utilized to verify principles and theoretical predictions and demonstrate that the AMPDXA techniques worked and produced results with the expected precision. Results demonstrated improvement in spatial and contrast resolution.

The Clinical Test System incorporates high-precision, rotational and translational stages to provide the scanning capability to carry out qualification tests on human subjects. Since the Clinical Test System is designed to operate only on Earth, the table, gantry, and associated equipment were not built to the size and mass requirements of an AMPDXA unit for spaceflight. In fact, the unit was built on a used CT scanner. Employing used equipment for some of the structural elements and rotating parts and machinery allowed critical resources to be focused on the information extraction and analysis issues leading to human testing.

The image extraction capability of the AMPDXA, where not only is the BMD image higher resolution, but also the mass distribution in a projected thickness of a femur slice contains much more structural detail than conventional DXA's. The high frequency content of the BMD spatial projections are reproducible and provide information on the bone's microstructure. Using multiple projections about the bone axis allows structural properties (e.g., bending strength) to be obtained independent of patient position. To do this, at least three arbitrary projections over 90 degrees (two of which are orthogonal) must be obtained. Such analysis can provide maximum and minimum moments of inertia for bending or torsion in any plane. Initial experimental measurements with different sets of three projections showed that the principal moments of inertia could be determined within 3 to 4%. Additional projections (above 3) reduce this number further. Our original experimental system also had some known non-linearities, which have since been removed, and our error in the three-projection estimation of moments to less than 1%.

With the above baselines established under the original NSBRI funding, the specifications of the FY 2001 (to FY 2003) follow-on proposal were:

1. Clinical Test System Calibration, Validation, and Optimization – Items to be considered are the improvement of bone and soft tissue discrimination and the reduction of scatter in the image data.
2. Algorithm/Software Development – Development of advanced algorithms for the AMPDXA, including those for BMD, bone structure, soft tissue decomposition, bone model reconstruction, and the risk of fracture simulation.
3. Pre-Clinical Testing – Ensure the reliability and safety of the AMPDXA system prior to use on humans.
4. Human Testing – Study human subjects to demonstrate the accuracy and utility of the AMPDXA.

5. Test Process Automation – Automate the control and image data gathering process for the AMPDXA.
6. Protoflight Technology Development/Demonstration Unit – Address technological needs necessary to produce a space qualifiable AMPDXA weighing approximately 46 kg.

Based upon review comments and funding limitations, most activities associated with the development of the protoflight AMPDXA have been postponed or eliminated. Instead, we are focusing on resolving certain key issues about the AMPDXA and then successfully using the AMPDXA for human testing. These key issues include: (1) unequivocal demonstration that multiple projection technology improves BMD accuracy and collects structural details, (2) the structural details can be converted into bone reconstruction models that preserve mechanical behavior, (3) the reconstruction models can be utilized to predict risk of fracture, (4) soft tissue can effectively be distinguished from bone and decomposed into fat and muscle, (5) data can be collected reliably and repeatedly on human subjects using the Clinical Test Unit, and (6) the Clinical Test Unit can be utilized in research studies on bone and muscle loss.

In pursuit of these aims, the Clinical Test System has been moved to a dedicated facility and is in the process of being tested and calibrated. The system was moved specifically so that human testing could begin. Approval for our human testing protocol has been granted by the Institutional Review Board at the Johns Hopkins Medical Institutions.

The scattering problem has been solved by the introduction of a new high aspect ratio (15:1) grid. The grid, while performing in a superior manner, causes some image and machine control complications that are being corrected. This image has higher resolution than the images from our test bed and offers great promise for the system's ultimate performance.

Instrument control software with computerized graphical user interfaces has reduced the requirement from two system operators to one. The features of the individual system building blocks have been retained while creating automated image collection sequences and safety interlocks.

A fully tapered calibration phantom has been introduced to provide the most accurate conversion of the x-ray attenuation into bone and muscle equivalents and, hence, a high resolution BMD image. Such inputs allow the creation of advanced analysis software, which ultimately will lead to a direct prediction of fracture risk..

The AMPDXA project has many implications for future research and development. The AMPDXA, as described above, has direct application to risk reduction in NASA's Critical Research Path. The AMPDXA is capable of real-time monitoring of bone and muscle loss at extremely high precision. Since the results are patient-specific and not tied to volumetric averages and statistical norms, the AMPDXA is a very useful tool for monitoring the effectiveness of countermeasures as well as determining risk of fracture under various loading conditions and activity scenarios. The AMPDXA also appears to be a natural adjunct to Earth-bound research on the effect of aging and disuse on bone integrity. It could also be used as a routine screening tool for osteoporosis and as a monitoring instrument for osteoporosis drug therapy.

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Brian L. Davis, Ph.D.**
ORGANIZATION:	**The Cleveland Clinic Foundation**
PROJECT TITLE:	**Design and Validation of a Dynamic Exercise Countermeasure Device**

Project Executive Summary

Bone demineralization is a well-documented physiologic effect of space flight. In 1-G, animal experiments have clearly indicated that (i) certain bone strains and strain rates do stimulate bone deposition, and (ii) repetitive loading of the lower extremity can increase osteonal bone formation even as proximally as the vertebral column. Such studies have also indicated that a relatively small number of appropriate loading cycles may lead to bone deposition. Based on prior research that we have performed with foot loading experiments, we propose the development of a dynamic exercise countermeasure device (DECD) that utilizes jumping as the mode of exercise for astronauts. This project falls under the technology development designation of the NSBRI program.

Our project will be divided into three phases. In year one we will collaborate with Foster Miller Inc., a company that has expertise in the design of both lightweight structures and vibration isolation methodology. The goal of this phase is to construct a device that permits dynamic jumping exercise in microgravity and that is suitable for the International Space Station. A key design component of this apparatus will be its ability to prevent vibrations and/or unbalanced forces from being transmitted to the surrounding environment. In year two we will test the system using our zero-gravity simulator that has been developed under NASA NAGW-5006. Specifically, we will verify that muscle activation patterns and limb loading data are similar to the results we have obtained thus far for tethered jumping in microgravity. In year three we will confirm the efficacy of the DECD in true microgravity through KC-135 experiments.

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Richard H. Maurer, Ph.D.**
ORGANIZATION:	**Johns Hopkins University Applied Physics Laboratory**
PROJECT TITLE:	**Neutron Energy Spectrometer Flight Experiments**

Project Executive Summary

High-energy charged particles of extra-galactic, galactic and solar origin collide with spacecraft structures in Earth orbit outside the atmosphere and in interplanetary travel beyond the Earth's magnetosphere. These primaries create a number of secondary particles inside the structures that can produce a significant ionizing radiation environment. This radiation is a threat to long term inhabitants or travelers for space missions and produces an increased risk of cancer and DNA damage. The primary high energy cosmic rays and trapped protons collide with common spacecraft materials such as aluminum and silicon and create secondary particles inside structures that are mostly protons and neutrons. Indeed, the effect of tens of grams per square centimeter of structure or atmosphere is to convert and multiply the primary proton "beam" into a secondary environment dominated by neutrons between several MeV and several tens of MeV. Charged protons are readily detected and instruments are already in existence for this task. Neutrons are electrically neutral and therefore much more difficult to measure and detect. These neutrons are reported to contribute 30-60% of the dose inside space structures and cannot be ignored. Currently there is no compact, portable and real time neutron detector instrumentation available for use inside spacecraft or on planetary surfaces where astronauts will live and work.

As a product of our previous NSBRI funding during FY 1998-2000 we had designed and fabricated an engineering prototype neutron spectrometer that was being prepared for F-15 and F-18 aircraft flights from NASA Dryden Flight Center. The spectrometer consists of both low and high energy subsystems. The detection of low energy neutrons (0.025 eV-1 MeV) is accomplished using a conventional helium 3 gas tube and includes thermal and epithermal neutrons. The detection of high energy neutrons (5-800 MeV) is achieved using a 5 mm thick lithium drifted silicon solid state device. Both low and high energy spectrometers have undergone ground based evaluation and calibration using radioactive sources and accelerator facilities.

We took data up to 39,000 feet in April 2000 on ascent (the plane was to fly at a planned 40,000 feet cruise level) when we experienced a corona breakdown in the high voltage supply systems for both detectors. The instrument was returned to APL so that significant re-design of the detector high voltage power supply systems could occur. The high voltage electronics of the low energy detector were all co-located in the same compact volume so that it could all be adequately potted for protection against breakdown at high altitude in the corona region. In contrast, a hermetic enclosure was designed and fabricated from just two pieces of aluminum, a three dimensional box and its top, for the high energy silicon detector and its associated high voltage electronics. The aluminum top was grooved to accommodate a vacuum seal O-ring. The design and fabrication of these improvements to the spectrometer took place between February and May 2001. The complete instrument was re-qualified in a medium sized vacuum chamber at APL during late May and early June 2001 to a maximum altitude of 61,000 feet with a substantial dwell time of two hours at 56,000 feet to provide almost 50% margin on the aircraft flight altitude of 40,000 feet. The instrument was shipped to NASA Dryden on June 15, 2001.

The neutron spectrometer was flown 13-14 August in a pod under the wing of an F-18. Both flights were successful and the data is being analyzed. A third successful flight in the same pod under the fuselage of an F-15 was executed in October 2001. The main positive result from the three flights is the verification of our engineering design and qualification and not the limited data obtained. The value for our hardware is the proven approach to handle the high voltage at high altitude in the corona region that will be employed for a future balloon flight during which scientifically interesting data will be acquired.

A proposal for MANES (MArtian Neutron Energy Spectrometer) was submitted in August 1999. It was selected for a stage of further definition in November 1999 as a potential instrument for the then-scheduled Mars 2003 Lander. The status of this instrument and its funding evolved from potential individual Mars 2003 Lander instrument (December 1999-February 2000), to possible combination with the JSC MARIE instrument after cancellation of the 2001 Lander in April (March-May 2000), to proposal for an extended definition phase for a 2005 Lander instrument after cancellation of the large 2003 Lander and selection of the two Athena-Rovers-in-a-bag for 2003 in July 2000 (May-August 2000), to cancellation after NASA's restructuring of the Mars exploration program in November 2000. A grant of $123,000 was received from Johnson Space Center for accommodation and definition phase work on MANES from February to August of 2000.

In January 2000 we were notified that our proposal titled "Development of a Neutron Spectrometer to Assess Biological Radiation Damage Behind Spacecraft Materials" submitted in March 1999 in response to NASA NRA 98-Heds-05 would be funded for a period of 3.5 years from May 2000 to November 2003 at a level of $90,000 per year for a total of $315,000. Originally, our primary responsibility under this grant was to support Lawrence Berkeley Laboratory (LBL) personnel in the evaluation of spacecraft structural and shielding materials by supplying a version of the neutron spectrometer compatible with ground-based accelerator research. The first and only collaborative experiment was carried out in January 2001. Lack of NASA funds for beam time have cancelled heavy ion experiments at the Brookhaven Alternating Gradient Synchrotron (AGS) originally scheduled for September 2001 and March 2002. We fabricated a detector stack system specifically for these accelerator experiments during the summer of 2001. We have verified its successful operation at Columbia University's RARAF in November 2001 and will now proceed with our own spacecraft shielding experiments using proton and heavy ion beams during FY 2002. We have submitted a second Materials Science proposal titled "Determination of Optimal Spacecraft Neutron Shielding Material Configurations" in November 2001 in response to NASA NRA 01-OBPR-05. Funding, if available from NASA, would begin about August 2002 and extend for four years at approximately $130,000 per year (requested).

The major effort in detector evaluation in FY 2000 was a series of experiments at the Los Alamos Neutron Science Center (LANSCE) to measure energy deposition in the 5mm thick lithium drifted silicon detector by neutrons with an energy range from 20-800 MeV. The experiments were performed by integrating our 5mm silicon detector with the LANSCE time-of-flight neutron spectrometer on the 90 meter beam line to give simultaneous measurements of the incident neutron energy (LANSCE fission chamber) and energy deposited in our detector. Energy depositions of up to 150 MeV were seen from the up to 800 MeV incident neutrons in our 5mm detector. A major effort during FY 2001 was the extensive analysis of the LANSCE data and the successful development of a response function for the detector between 20 and 600 MeV. We verified our procedure for deducing the response function by successfully comparing its outcomes with the LANSCE beam monitor data in a blind experiment. By using several thicknesses of polyethylene shields in these experiments we began gathering experimental data on the effectiveness of this material as a high energy neutron moderator. The report of these shielding experiments will be published in the December 2001 volume of the IEEE Transactions on Nuclear Science. The development of the silicon detector response function is now in manuscript form and will be submitted to the journal Radiation Research before the end of 2001. We have recently completed a set of experiments at Columbia University RARAF using mono-energetic neutron beams between 10-20 MeV to extend the silicon detector response function down to those energies. These experiments included a Cesium Iodide scintillation crystal enclosing the thick silicon detector to discriminate against background gamma rays prevalent in the target room.

The modeling component of this research program occurred on a continuous basis in FY 2000 and FY 2001. We concentrated on modeling the high-energy channel from detailed cross sections of the basic neutron-silicon interactions using state-of-the-art computer codes. There are four reasons to develop this advanced modeling capability: 1) to assess the accuracy of the codes themselves to predict energy deposition in a silicon detector (by comparison with experimental data); 2) to use the codes in understanding the experimental results; 3) to determine whether the codes can be used to calculate the shielding and scattering effects of the instrument packaging and surrounding environment (structure or atmosphere); 4) to assess the ability of the codes to supplement the determination of the instrument response function at interpolated and extrapolated energies (since it is impractical to test at intervals of 10 MeV for the whole energy range). We have found that the GEANT4 code originally developed at CERN is the easiest to use, is maintained in a timely fashion by its developers and reproduces our RARAF (2-20 MeV) energy deposition data reasonably well. We have also contracted for the services of an experienced modeler, Thomas Jordan, for use of the DOE-developed MCNPX code in simulation and experimental planning and comparison with GEANT4 predictions.

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Richard S. Potember, Ph.D.**
ORGANIZATION:	**Johns Hopkins University Applied Physics Laboratory**
PROJECT TITLE:	**Real-Time Analysis of Biomarkers and Countermeasures Using a Miniature Time-of-Flight Mass Spectrometer**

Project Executive Summary

Original Aims of the Project:

- To design, develop and test a fast, portable gas chromatograph – time-of-flight mass spectrometry (GC-MS) system for future human spaceflight applications. It will provide complementary information to the MALDI method.

- To demonstrate that the miniature TOF system is capable of detecting and quantifying different biomarkers that appear in serum or urine during space flight. Detection and quantification of critical biomarkers using the miniature TOF technology will allow real-time monitoring of damage on-orbit, and the mass spectrometer can also be used to study the effectiveness of countermeasures in spaceflight. The results of this effort should be comparable to measurements made in a clinical laboratory facility using established assays.

- To validate that the miniature time-of-flight mass spectrometer is an important diagnostic tool that can be applied to measure important bone biomarkers and the effectiveness of applied countermeasures in human urine and serum samples.

- To compare standard methods of hormone analyses for melatonin and cortisol to that of the Miniature Mass Spectrometer. The development of online methods for monitoring and assessing the status of circadian organization is listed as one of the five primary themes for the Human Performance, Sleep and Chronobiology Team.

- To develop sampling and sample preparation techniques that enable the MALDI TOF mass spectrometer system to reliably detect, identify and quantify extremely low levels of chemical and biological substances in complex body fluids with very low error rates.

Key Findings:

We have designed and built a portable gas chromatograph - mass spectrometry (GC-MS) system for human spaceflight applications. This combination of miniature instruments will provide new capabilities in the area of sampling, sample preparation, rapid quantitation of biomarkers and it will allow us to apply our technology to other space based problems such as monitoring the spacecraft environment for chemical and biological contaminants.

We have also completed our initial studies on oxidative stress biomarkers for the early detection of oxidative damage to DNA caused by oxygen-derived free radicals. Potential sources of oxidative stress of interest to NSBRI and NASA include ionizing radiation, chemical oxidants and physiological and psychological stress. Accurate measurement of oxidative damage to DNA and its repair is essential for understanding the mechanisms of disease for developing effective countermeasures for the astronauts. Specifically, we have shown that oxidative stress biomarkers can be measured using MALDI Time-of-Flight Mass Spectrometry at physiological concentrations. We studied two compounds, 8-OH-Adenine and 8-OH Adenine(L) to evaluate the degree of detectability of each compound. Our results show that detectability is consistent and independent of the type of nucleoside used. We are currently testing these biomarkers in urine samples at this concentration level and comparing the results from the MALDI instrument to a measurement made on a GC-MS.

We have also begun an investigation to detect Zoledronate by MALDI-TOF. Zoledronate (Novartis) is being proposed as a countermeasure bone loss in space. Based on preclinical pharmacological studies reported by Novartis, the drug is reputedly 100-850 times more active than pamidronate that is in wide clinical use. Further studies with matrix selection and analysis of patent samples will be conducted in year 2 to determine if this is a viable method to track the excretion of Zoledronate and it's byproducts.

Impact of These Fnding on Technology Objectives:

We are developing and testing a small, efficient time-of-flight mass spectrometer coupled to a miniature gas chromatograph to rapidly identify important biomarkers and countermeasures for human space exploration. We are using the time-of-flight mass spectrometer to evaluate critical biomarkers and countermeasures that are indicators of bone loss, oxidative stress and the human sleep cycle associated for extended space travel.

Mass spectrometry is a technique for determining the masses of molecules and specific fragmentation products formed during vaporization and ionization. From detailed analysis of the mass distribution of the molecule and its fragments, molecular identification is accomplished. These molecular measurements can be carried out at the attomole (10^{-18} mole) level of material using specialized laboratory-based instruments. The combination of specific molecular identification and extreme sensitivity makes mass spectrometry one of the most powerful analytical laboratory tools yet developed for detection and identification of chemical and biological substances.

Proposed Research for Year II:

(1) Portable Gas Chromatograph - Mass Spectrometry (GC-MS) System for Human Spaceflight Applications
In year 2, we will complete the Year 2 milstones begun in year 1: test and evaluate new instrument system with spiked samples. We also expect to begin to work on the year 3 milestone to test and evaluate system with complex urine samples.

(2) Measurement of Oxidative Stress using TOF Mass Spectrometry
In year 2, we will complete the milstones: Validate mass spectral analysis using GC, HPLC or RIA and down select biomarkers for study with urine samples.

(3) Zolendronate: a Countermeasure to Bone Loss in SCI Patients
In year 2, we will Analyze serum andurine samples for Zolendronate and related biproducts.

(4) Assessment of Circadian Status Using the Miniature Mass Spectrometer
In year 2 we will analyze the urine samples from Harvard for the excretion of the melatonin metabolite, 6-sulphatoxymelatonin.

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Yi-Xian Qin, Ph.D.**
ORGANIZATION:	**State University of New York – Stony Brook**
PROJECT TITLE:	**A Non-Invasive Scanning Confocol Ultrasonic Diagnostic System for Bone Quality**

Project Executive Summary

The goal of this project is to develop a new technology for monitoring bone quality of humans during long-term space missions and on Earth. This will lead to a better understand of the progressive adaptation of bone loss in astronauts subject to microgravity and aging populations, and the ensuing musculoskeletal complications such as osteoporosis. Results of the joint Russian/US studies of the effect of microgravity on bone tissue demonstrated that bone loss proceeds at an average rate of 2% per month, ranging from no loss in the area of upper skeleton to as much as 14-20% loss in the skeleton of the lower body following a 14.5-month long mission. While these results are detected only when astronauts returned to Earth, the rate of bone loss *during* space mission is still unclear.

This research is to develop a portable scanning confocal acoustic diagnostic (SCAD) system capable of generating non-invasive, high-resolution ultrasound (US) attenuation and velocity maps of bone, and thus determining the relationship between ultrasonic specific parameters and bone mineral density (BMD), bone quality, as well as bone's physical properties (i.e., stiffness and modulus). This system is relevant not only for ground-based determination of bone's physical properties, but can effectively be used in the space environment for determining even subtle changes in density and strength during extended flights. In this study, we plan to develop a 2-D ultrasound scanning system, and validate the structure and density information, detected by SCAD, using μCT and mechanical testing methods in *ex vivo* animal models, as well as correlating to *in vivo* DEXA data derived from humans. The system will thus contribute to monitor degree and risk of bone loss in space and Earth, as well serve as a major step towards clinic usage as an early diagnostic of osteoporosis. There are proposed a series of four original specific aims (S.A.): (1) *Develop a scanning confocal acoustic diagnostic system for non-invasively mapping wave velocity and attenuation in bone; (2) Determine an interrelationship between ultrasound determined parameters, i.e., velocity and attenuation, and micro architectural parameters in a quantitative manner; (3) Develop a practical SCAD system for determining bone quality properties with quantified bone mass reduction; and (4) Map and monitor special directional and orthotropic strength of bone to predict BMD and structural modulus in vivo using the SCAD, and correlate these measurements to DEXA results.*

During the award year (2001-2002), the research team focused on technology development of SCAD system (S.A.1) and validation between SCAD determined acoustic parameters and bone quality data (S.A.2). In a step further, human cadaver and in vivo subject testing were also initiated. The SCAD system for non-invasively mapping of wave velocity and attenuation in bone has been developed for measuring ex vivo trabecular samples. A system design of an experimental prototype was completed which includes acoustic, electrical, control and mechanical components. As an important step towards a prototype for human testing, a 2-D ultrasound scanning system has been built including converging ultrasonic transducers, micro-controller controlled 2-D scanning stages, ultrasonic wave generator, low noise amplifier, and real-time analog/digital (A/D) transformer. A special designed controller is developed and synchronizes digital signals in acoustic wave, scan automation, and A/D transform. This development greatly reduces the scan time, e.g., it requires less than 2 minutes for a 30x30 pixel region acoustic image with 1 mm resolution. Ultrasonic attenuation and velocity are measured and calculated, and can be converted to image, e.g., gray scale or virtual color mapping. A serial of testing for acoustic wave propagation in the bone tissue were performed using ultrasonic characteristic frequencies of 500 kHz, 1.0 1.25, 1.5, 5.0, 7.5, 10.0 and 15.0 MHz. The optimal frequency was determined depending on the sites of testing. A group of ex vivo bone samples was tested to evaluate bone quality and quantity. Trabecular samples were prepared as 1x1x1 cm cubes, which were harvested from sheep femoral distal condyle. These sheep were previously under a mechanical stimuli protocol for 1~2 years and identified distinct bone mineral density using dual-energy X-ray absorptionmetry (DEXA). All bone samples were mechanically tested by direct force-deformation in orthogonal directions, i.e., longitudinal, medial-lateral, and anterial-posterial, using a MTS universal test machine. The central plane of the samples was scanned with ultrasonic attenuation and velocity using SCAD system. The results of ultrasonic attenuation and velocity were correlated with mechanical moduli of the sample. While using a single transmitted ultrasound signal, there were weak correlations between measured BUA and micro-CT determined osteo-parameters, e.g., BMD (R=0.53), porosity (R=0.53), trabecular thickness (R=0.20) and trabecular space (R=0.75), as well as average modulus (R=0.63). These correlations were significantly improved using the scanning confocal ultrasound method. Strong correlations are observed between SCAD determined BUA and micro-CT determined parameters, i.e., BMD (R=0.78), porosity (R=0.78), trabecular thickness (R=0.5) and trabecular space (R=0.88), as well as average modulus (R=0.81).

These results suggest that SCAD can provide much detailed information than the single ultrasonic measurement in determining osteoporotic related parameters. Thus, a well-established SCAD system may provide a significant impact in diagnostic of osteoporosis and bone quality. Preliminary results may provide insight for addressing the risks of bone loss during prolonged space mission, age-related acceleration of osteoporosis, and monitoring healing of fracture.

RESEARCH AREA:	**Technology Development**
PRINCIPAL INVESTIGATOR:	**Veljko Radeka, Ph.D.**
ORGANIZATION:	**Brookhaven National Laboratory**
PROJECT TITLE:	**Heavy Ion Microbeam and Micron Resolution Detector**

Project Executive Summary

The ability to place discrete numbers of particles in defined cellular and extracellular locations is now possible by using microbeam irradiation facilities. Such a facility permits heavy-ion radiobiology to address specifically the impact of signal transduction between cellular compartments as well as issues related to intercellular communication at limiting low fluences where not all the cells in a population have been traversed by even a single particle. Moreover, a high-energy, heavy-ion microbeam will permit to address an important unanswered question: whether neurons that survive traversal by HZE particles develop changes as a late consequence of the damage they incurred. Therefore, these low-fluence studies promise to aid in our understanding of the consequences of exposure to high-LET radiation such as encountered in the space radiation environment.

The purpose of the proposed project is to make possible such studies by developing the following tools:

1. A microbeam of heavy ions (e.g., iron) at energies higher than at existing microbe am facilities (3GeV/nucleon). The microbe am would have a sufficiently small diameter (about 10 micrometers) to localize the ions to a single cell.
2. An electronic position-sensitive detector for heavy ions with a position resolution better than 1 micrometer, to localize the position of ion impact within a particular region of the cell. These developments will advance significantly the state-of-the art of high-energy, heavy ion microbeams and of high-resolution heavy-ion detectors. For the cell studies employing these tools, the necessary infrastructure will include a micropositioning stage with a microscope and auxilliary detectors.

Appendix F

NATIONAL
SPACE BIOMEDICAL
RESEARCH INSTITUTE

RESEARCH TEAM PROGRAM REPORTS
FY 2002

National Space Biomedical Research Institute
Research Team Program Reports
FY 2002

CONTENTS

CARDIOVASCULAR ALTERATIONS TEAM

National Space Biomedical Research Institute

Annual Program Report

October 1, 2001 – September 30, 2002

Team Leader
Richard J. Cohen, M.D., Ph.D.
Whitaker Professor of Biomedical Engineering
Harvard - MIT Division of Health Sciences and Technology
Room E25-335a
Massachusetts Institute of Technology
45 Carleton Street
Cambridge, Massachusetts 02142
Telephone: 617-253-7430
Fax: 617-253-3019
Email: rjcohen@mit.edu

Associate Team Leader
Artin A. Shoukas, Ph.D.
Professor of Biomedical Engineering
Professor of Physiology
The Johns Hopkins University
School of Medicine
Traylor 623
720 Rutland Avenue
Baltimore, Maryland 21205
Telephone: (410) 955-2871
Fax: (410) 614-0019
Email: ashoukas@bme.jhu.edu

Richard J. Cohen

Richard J. Cohen, M.D., Ph.D.

November 8, 2002

Date

Listing of Team Projects

Possible Countermeasures to Post-Suspension Hypotension in the Head-Down Tilt Rat Model.

Principal Investigator:
Mohamed Bayorh
Associate Professor
Morehouse School of Medicine
Department of Pharmacology
720 Westview Drive, S.W.
Atlanta, GA 30310-1495
Tel: (404) 752-1714
Fax: (404) 752-1164
Email: bayorh@msm.edu

Integrative Cardiac Myocyte Model: Ion Channels, Ca and Contraction

Prinicipal Investigator:
Donald M. Bers
Dept. of Physiology
Loyola University Chicago
Stritch School of Medicine
2160 South First Ave.
Maywood, IL 60153
Tel: 708-216-1018
Fax: 708-216-6308
Email: dbers@lumc.edu

Microgravity and Circadian Cardiovascular Function

Principal Investigator:
Vincent Cassone
Department of Biology
Texas A & M University
College Station, TX 77843
Tel: (979) 845-2301
Fax: (979) 845-2891
Email: vmc@bio.tamu.edu

Cardiovascular Effects of Simulated Microgravity in Man (1)
Effects of Space Flight on on Cardiovascular Stability (2)

Principal Investigator:
Richard J. Cohen, M.D., Ph.D.
Whitaker Professor of Biomedical Engineering
Harvard - MIT Division of Health Sciences and Technology
Room E25-335a
Massachusetts Institute of Technology
45 Carleton Street
Cambridge, Massachusetts 02142
Tel: 617-253-7430
Fax: 617-253-3019
Email: rjcohen@mit.edu

Distributed Simulation of Integrated Human Function

Principal Investigator:
James E. Coolahan
Johns Hopkins University
Applied Physics Laboratory
11100 Johns Hopkins Road
Laurel, MD 20723-6099
Tel: 240-228-5155
Fax: 240-228-5881
Email: James.coolahan@jhuapl.edu

Circulatory Remodeling with Simulated Microgravity

Principal Investigator:
Michael D. Delp (Mike)
Dept. of Health & Kinesiology
Texas A&M University
4243 TAMU
College Station, TX 77843
Tel: (979) 845-0515
Fax: (979)847-8987
Email: mdd@hlkn.tamu.edu

Cardiac Unloading: Biologic Mechanisms and Countermeasures for Cardiac Atrophy

Principal Investigator:
Beverly H. Lorell
Beth Israel Deaconess Medical Ctr.
Cardiovascular Div., East Campus
330 Brookline Ave.
Boston, MA 02215
Tel: (617) 667-8727, (617) 668-8727
Fax: (617) 667-4124
Email: blorell@caregroup.harvard.edu

Computational Models of the Cardiovascular System and its Response to Microgravity and Disease

Principal Investigator:
Roger Mark
MIT; E25-505
Harvard-MIT Div. Of Health
Sciences and Technology
Massachusetts Institute of Technology
45 Carleton St.
Cambridge, MA 02142
Tel: (617) 253-7818
Fax: (617) 258-7859
Email: rgmark@mit.edu

Integrated Modeling of Cardiac Mechanical and Electrical Function

Principal Investigator:
Andrew D. McCulloch
Univ. of California, San Diego
Dept. of Bioengineering
EBU 1, Room 4109
9500 Gilman Dr., Dept. 0412
La Jolla, CA 92093-0412
Tel: 858-534-2547
Fax: 858-534-5722
Email: amcculloch@ucsd.edu

Mechanisms of Post-Spaceflight Orthostatic Intolerance

Principal Investigator:
Janice Meck
Johnson Space Center
SD-3
Houston, TX 77058
Tel: (281) 244-5405, (281) 483-7103
Fax: (281) 483-4181
Email: jmeck@ems.jsc.nasa.gov

Development of a Soluble Guanylyl Cyclase Knockout Mouse Model

Principal Investigator:
Ferid Murad
Dept. Integrative Biol & Pharma
Room MSB 4.098
University of Texas-Houston
PO Box 20708
Houston, TX 77225
Tel: 713-500-7509
Fax: 713-500-0790
Email: Ferid.Murad@uth.tmc.edu

Effect of Simulated Microgravity on the Vestibulosympathetic Reflex in Humans

Principal Investigator:
Chester A. Ray (Chet)
Pennsylvania State University
College of Medicine
Division of Cardiology, H047
500 University Drive
Hershey, PA 17033-2390
Tel: (717) 531-5110
Fax: (717) 531-1792
Email: caray@psu.edu

Mechanics of Cardiovascular Deconditioning

Principal Investigator:
Artin Shoukas (Art)
Johns Hopkins School of Medicine
Traylor Res. Bldg. Rm. 623
720 Rutland Ave.
Baltimore, MD 21205
Tel: (410) 955-2871
Fax: (410) 614-0019
Email: ashoukas@bme.jhu.edu

Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity

Principal Investigator:
James D. Thomas
The Ohio State University
Department of Cardiology, F-15
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195
Tel: (216) 445-6312/3
Fax: (216) 445-7306
Email: thomasj@ccf.org

Influence of Gender and Age on Renal and Cardio-Endocrine Responses to Simulated Microgravity

Principal Investigator:
Gordon H. Williams
Program Director, GCRC
Brigham and Women's Hospital
221 Longwood Ave. 2nd Flr., RFB2
Boston, MA 02115-5817
Tel: (617) 732-5661
Fax: (617) 732-5764
Email: gwilliams@partners.org

I. ABSTRACT

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to microgravity and other factors. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. The extent of cardiovascular adaptation appears to increase with duration of space flight. The extent and implications of these adaptations for long-duration (months to years) space flight remain largely unknown. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume, and a modest decrease in arterial pressure. During space flight the cardiovascular system is not subjected to the stresses associated with changes in posture in a gravitational field. Space flight is associated with, in addition to microgravity, other physiologic stressors such as sleep disruption, confinement and other environmental alterations which may also adversely affect cardiovascular structure and function. As a result of the foregoing factors, space flight results in remodeling of the heart, arterial and venous blood vessels, and the lymphatics. In addition there are alterations in the neural and hormonal control systems.

Adverse effects of space flight on the cardiovascular system: 1) Upon reentry into the Earth's gravitational field, astronauts experience orthostatic intolerance, which limits their ability to function during reentry and after landing and possibly could interfere with the ability of astronauts to egress from the spacecraft under emergency conditions. Currently-used countermeasures, such as oral administration of salt and water prior to reentry and application of anti-gravity suits, do not adequately prevent orthostatic intolerance, especially following long-duration space flight. 2) A number of anecdotal reports suggest that long-duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. If space flight does in fact significantly decrease cardiac electrical stability, the effects could be catastrophic, potentially leading to sudden cardiac death. 3) Long-term space flight may lead to a measurable reduction in cardiac mass. It is not known whether these cardiac alterations are reversible and whether they pose a long-term health risk to astronauts. 4) Long-duration space flight may exacerbate previously undetected cardiovascular disease, such as coronary artery disease. 5) Long-term space flight may impair cardiovascular response to exercise.

The objective of the Cardiovascular Alterations Team is minimize these risks using the following approach:

- Characterize and quantify the adverse effects of space flight on cardiovascular structure and function
- Determine the mechanisms of these adverse effects
- Develop effective countermeasures to these adverse effects
- Develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on earth

This approach involves an integrated team effort involving projects ranging from the molecular, cellular, organ system, and whole animal investigations as well as computer simulations.

The team has already achieved advanced development of one countermeasure for orthostatic hypotension, the alpha agonist midodrine. The team has progressed from ground based studies to having two flight studies approved, one of which will be testing the midodrine countermeasure, the other of which will focus on alterations in vascular control mechanisms.

The team has successfully developed two new technologies. One of these technologies, measurement of microvolt T-wave alternans is a non-invasive means of assessing risk of ventricular arrhythmias and sudden cardiac death. This technology is being used to determine whether microgravity predisposes astronauts to ventricular dysrhythmias. This technology has been successfully commercialized, cleared by the FDA, reimbursed by Medicare, and is in widespread clinical use to reduce sudden cardiac here on earth. Sudden cardiac death claims 350,000 lives in the United States each year. The other technology is Cardiovascular System Identification which non-invasively quantifies closed-loop cardiovascular regulation. This technology is being used to assess mechanisms of post flight orthostatic hypotension, and also has applications for diagnosis and management of heart failure, diabetes and hypertension.

The team has developed effective cardiovascular computer models which have been used to analyze and integrate data from multiple studies and evaluate potential countermeasures.

The cardiovascular alterations team looks forward to a continuation of the integrated team effort to diminishing the risks associated with the adverse effects of space flight on the cardiovascular system.

II. INTRODUCTION

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to weightlessness and other factors, such as sleep disruption, confinement and additional environmental alterations. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume, and a modest decrease in arterial pressure. In addition, there are alterations in the lymphatic, neural and hormonal control systems. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. Furthermore, the extent of cardiovascular adaptation appears to increase with duration of space flight, and the magnitude and implications of these adaptations for long-duration space flight (that is, months to years) remain largely unknown.

Specific adverse effects of space flight on the cardiovascular system include:

1) **Impaired Cardiovascular Response to Orthostatic Stress** Upon reentry into the Earth's gravitational field, astronauts experience orthostatic intolerance, which limits their ability to function during reentry. In many cases, the orthostatic intolerance is sufficiently severe that astronauts cannot stand erect for some time after landing and thus may interfere with the ability of astronauts to egress from the spacecraft under emergency conditions. Upon reentry into a gravitational field blood pools in the dependent veins and arteries which leads to reduction in preload to the heart resulting in a decrease in stroke volume, cardiac output and arterial blood pressure. Factors involved in the development of orthostatic intolerance may include structural and functional adaptations of the heart and arterial and venous blood vessels and lymphatics, alterations in volume control mechanisms, alterations leading to an inadequate or defective neural and hormonal regulatory response, alterations in local vascular reactivity, and mechanisms controlling regional distribution of blood volumes and flows. Factors such as age, gender, genotype, as well as occupational, physical training and dietary history may affect individual susceptiblity to the development of post-flight orthostatic intolerance. Currently-used countermeasures, such as oral administration of salt and water prior to reentry and application of anti-gravity suits, do not adequately prevent orthostatic intolerance, especially following long-duration space flight.

2) **Occurrence of Serious Cardiac Dysrhythmias** A number of anecdotal reports suggest that long-duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. If space flight does in fact significantly decrease cardiac electrical stability, the effects could be catastrophic, potentially leading to sudden cardiac death. It will be important to determine the mechanisms underlying this phenomenon in order to develop appropriate countermeasures. Potential mechanisms that might lead to reduction in the stability of the electrical substrate include electrolyte changes, changes in the neural and hormonal milieu, and alterations of cardiac myocytes, myocyte connectivity and extracellular matrix resulting from space flight. These alterations may in turn lead to changes in cardiac conduction and repolarization processes which predispose to sustained rhythm disturbances.

3) **Diminished Cardiac Function** Long-term space flight may lead to a measurable reduction in cardiac mass, probably associated with cardiac remodeling. It is not known whether these cardiac alterations are reversible and whether they pose a long-term health risk to astronauts. Factors that may be involved in alterations in cardiac function include changes in myocyte number, size, and geometry; changes in myocardial matrix and microvasculature; alterations in myocyte and organ-level mechanical performance; changes in cardiac gene programming; stimuli and signals that lead to loss of cardiac mass and remodeling; factors affecting reversibility and recovery from these alterations.

4) **Manifestation of Previously Asymptomatic Cardiovascular Disease** Long-duration space flight may exacerbate previously undetected cardiovascular disease, such as coronary artery disease. Little is known about what conditions of space flight may tend to make pre-existing disease symptomatic or accelerate the progression of the underlying disease. Also, we do not know what procedures should be applied to screen astronauts for the presence of asymptomatic cardiovascular disease prior to long term missions

5) **Impaired Cardiovascular Response to Exercise Stress** Long-term space flight may impair cardiovascular response to exercise. Current inflight exercise programs appear adequate to maintain aerobic exercise capacity.

The Objectives of the NSBRI Cardiovascular Alterations Team are to:

- Characterize and quantify the adverse effects of space flight on cardiovascular structure and function
- Determine the mechanisms of these adverse effects
- Develop effective countermeasures to these adverse effects
- Develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on earth

The Critical Issues faced by the Cardiovascular Team in addressing the Critical Risks include:

- Development of Suitable Experimental Models
- Development of Suitable Experimental Approaches
- Development of Mathematical and Computer Models
- Development of New Cardiovascular Technologies
- Addressing the Multiple Conditions Imposed by Space Flight
- Countermeasure Development Issues
- Determinants of Individual Susceptibility to the Adverse Cadiovascular Effects of Space Flight
- Development of Spin-off Technologies to Benefit Clinical Medicine on Earth
- Development of a Space Flight Database

III. Research Program Structure and Design

The overarching intentions of the Cardiovascular Alterations Team are to:

- Characterize and quantify the adverse effects of space flight on cardiovascular structure and function
- Determine the mechanisms of these adverse effects
- Develop effective countermeasures to these adverse effects
- Develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on earth

The program's overall strategy is dictated by the relevant risks: The following risks are deemed to be high priority and are the focus of the team's efforts:

- Impaired Cardiovascular Response to Orthostatic Stress (14)
- Occurrence of Serious Cardiac Dysrhythmias (13)
- Diminished Cardiac Function (15)

The remaining two risks are deemed to be of lower priority:

- Manifestation of Previously Asymptomatic Cardiovascular Disease (16)
- Impaired Cardiovascular Response to Exercise Stress (17)

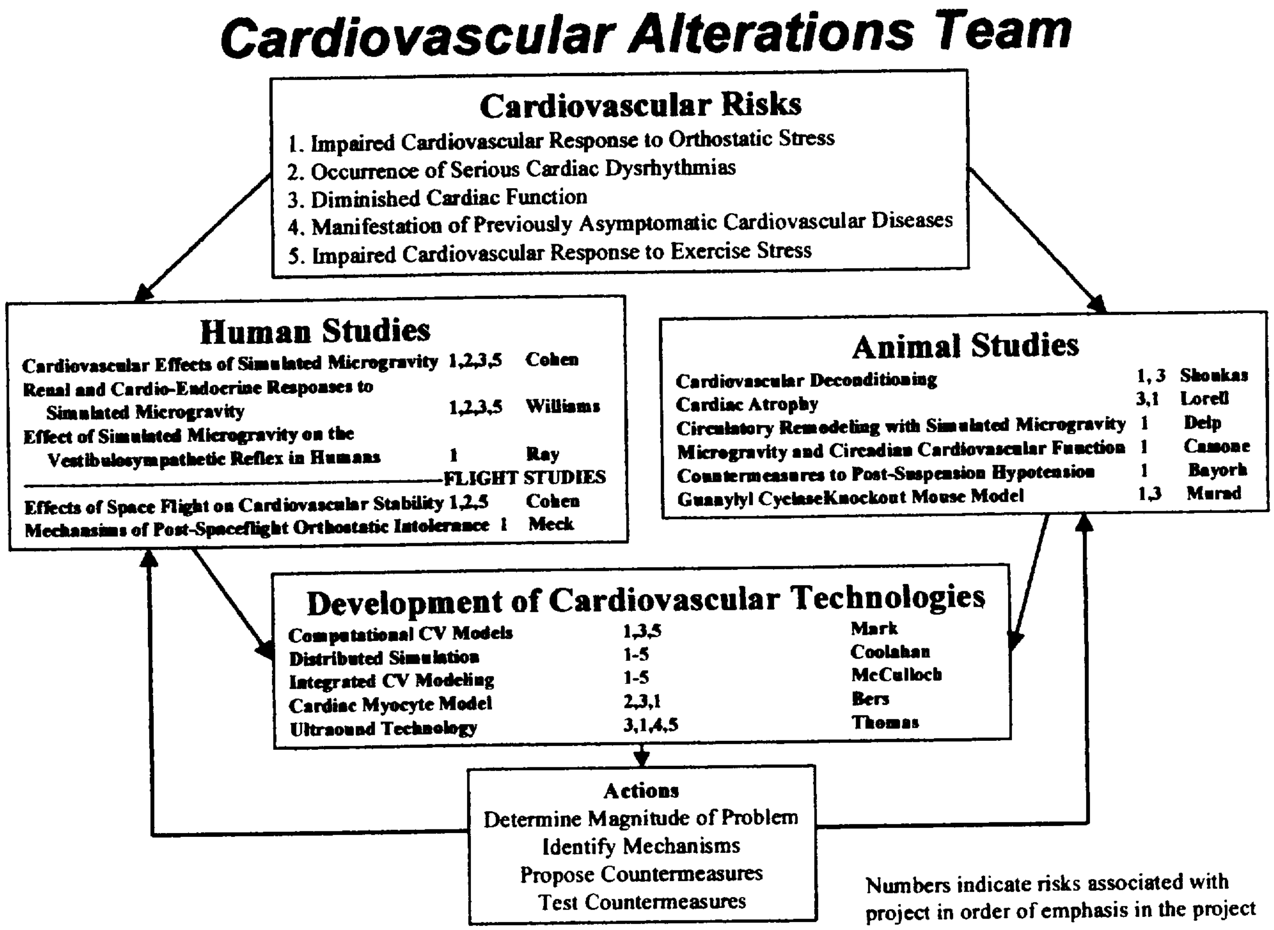
While some of the projects do address some aspects of these two risks, no one project principally addresses these risks.

Additional non risk-based goals include those associated with the development of new cardiovascular technologies for use in space and for earth based applications.

The current program is summarized in the Figure.

The Cardiovascular Alternations Team has recently been enlarged by having had three projects (Bers, Coolahan, McCulloch) transferred from the former Integrated Physiology Team. This transfer was the result of an NSBRI management decision that it was better for the computer modeling and simulation projects to reside in specific teams rather than to be grouped in a separate Integrated Physiology team. Mark's cardiovascular modeling project has been part of the Cardiovascular Alterations Team since its inception and very well integrated into the team's activities. Also, Dr. Murad's project was also just recently incorporated into the team. The Cardiovascular Alterations Team now involves 16 projects (see Figure). While we have always attempted to have horizontal communication across all team projects, with the growth of the team to 16 projects we have decided to organize the projects into groups of Human Studies, Rodent Studies, and Cardiovascular Technologies.

FIGURE


Cardiovascular Alterations Team
Cardiovascular Risks
1. Impaired Cardiovascular Response to Orthostatic Stress
2. Occurrence of Serious Cardiac Dysrhythmias
3. Diminished Cardiac Function
4. Manifestation of Previously Asymptomatic Cardiovascular Diseases
5. Impaired Cardiovascular Response to Exercise Stress
Human Studies
Cardiovascular Effects of Simulated Microgravity 1,2,3,5 Cohen
Renal and Cardio-Endocrine Responses to Simulated Microgravity 1,2,3,5 Williams
Effect of Simulated Microgravity on the Vestibulosympathetic Reflex in Humans 1 Ray
FLIGHT STUDIES
Effects of Space Flight on Cardiovascular Stability 1,2,5 Cohen
Mechanisms of Post-Spaceflight Orthostatic Intolerance 1 Meck
Animal Studies
Cardiovascular Deconditioning 1,3 Shoukas
Cardiac Atrophy 3,1 Lorell
Circulatory Remodeling with Simulated Microgravity 1 Delp
Microgravity and Circadian Cardiovascular Function 1 Cassone
Countermeasures to Post-Suspension Hypotension 1 Bayorh
Guanylyl CyclaseKnockout Mouse Model 1,3 Murad
Development of Cardiovascular Technologies
Computational CV Models 1,3,5 Mark
Distributed Simulation 1-5 Coolahan
Integrated CV Modeling 1-5 McCulloch
Cardiac Myocyte Model 2,3,1 Bers
Ultrasound Technology 3,1,4,5 Thomas
Actions
Determine Magnitude of Problem
Identify Mechanisms
Propose Countermeasures
Test Countermeasures
Numbers indicate risks associated with project in order of emphasis in the project

IV. RESEARCH PROGRAM ACCOMPLISHMENTS

Below we provide a summary of the accomplishments of the Cardiovascular Alterations Team.

Perhaps the principal overall achievement of the Cardiovascular Alterations Team in 2002 was the advancement to flight testing of the midodrine countermeasure to the development of post flight orthostatic hypotension.

This was a team effort that included animal studies that demonstrated that hind limb suspension leads to venous and arteriolar hyporesponsiveness in particular to alpha-sympathetic stimulation, computer simulations that demonstrated that increasing venous and arterial tone would be an effective countermeasure, and human studies that demonstrated that a single small dose of midodrine was highly effective in increasing tolerance to tilt after 16 days of bed rest. The human studies also demonstrated that cardiovascular system identification measures obtained pre bed rest can identify those individuals at greatest risk for post bed rest orthostatic hypotension.

This year a flight study has been approved in which the midodrine countermeasue will be tested as a countermeasure to the development of postflight orthostatic hypotension as well as testing the ability of CSI measures to identify preflight those most likely to suffer post flight orthostatic hypotension.

Midodrine has been used under a Supplemental Medical Objective to date on one astronaut with a history of severe post flight orthostatic hypotension. This individual took a single dose of midodrine post flight and did not have any symptoms of orthostatic hypotension post flight.

Discussion of Progress towards meeting Goals

Projects addressing risk of Impaired Cardiovascular Response to Orthostatic Stress Most of the effort of the Cardiovascular Alterations Team has been focused on the problem of post-flight orthostatic hypotension, for this is a known current operational problem. In animal and human studies we have studied mechanisms, proposed and tested countermeasures. We are examining a wide range of factors including neural, vestibular, hormonal, vascular, cardiac, lymphatic, and genetic factors that may contribute to the development of orthostatic hypotension. We have also developed new non-invasive techniques to study alterations in cardiovascular regulation resulting from space flight. One such technique is Cardiovascular System Identification which involves mathematical analysis of spontaneous second-to-second fluctuations in physiologic signals such as heart rate, arterial blood pressure, cardiac output, and respiration to create an individualized closed loop model of cardiovascular regulation. Finally, we have developed and utilized computer simulations of the cardiovascular system to analyze data, investigate mechanisms, evaluate proposed countermeasures, and refine hypotheses to be tested experimentally. The dynamic interplay between animal, human and computer simulations has already led to the proposing of the alpha-symphathetic agonist, midodrine, as a pharmacologic countermeasure to the development of orthostatic hypotension, and the successful testing of this countermeasure in animal and ground based human studies. Flight studies of this countermeasure have been approved and will begin soon. We are also developing an innovative pulsatile G-suit as a new countermeasure.

Projects addressing risk of Occurrence of Serious Cardiac Dysrhythmias Several of the projects relate to the development of life threatening dyshythmias in space. The focus here has been to establish specifically whether simulated microgravity increases the risk of these ventricular tachyarrhythmias. To test this hypothesis a new non-invasive technique has been developed for the identification of subjects at risk of developing ventricular tachyarrhythmias - measurement of microvolt T-wave alternans. This technique was has developed under NASA and NSBRI support. This technique has been validated in multiple studies of patients with increased sudden cardiac death. The technique has proven to be the best non-invasive predictor of susceptibility to ventricular tachyarrhythmias and sudden cardiac death. It has been successfully commercialized, cleared by the FDA, and approved by Medicare for reimbursement, and is in widespread clinical use. Initial bed rest data using microvolt T-wave alternans suggests that simulated microgravity increases the risk of ventricular tachyarrhythmias and and flight studies will shortly be initiated to test this in astronauts pre and post flight. Mechanistic ground based studies will examine the effects of age and gender on susceptibility to ventricular tachyarrhythmias. Also, current studies plan to evaluate aldosterone antagonists (spironolactone) and alterations in dietary intake of electrolytes as potential countermeasures.

Projects addressing risk of Diminished Cardiac Function One project (Lorell) deals primarily with the risk of diminished cardiac function and several other projects relate to this problem as well. The focus here is to establish the development of atrophy and remodeling in ground based models and to study molecular and genetic mechanisms and functional sequelae. We require more flight data documenting the extent of space induced cardiac atrophy and remodeling that occurs during flight.

Projects addressing risk of Manifestation of Previously Asymptomatic Cardiovascular Disease There are no current projects in this area. Although this is a lower priority risk than the first three, we are interested in the question of determining what is the optimum set of screening tests for astronauts to detect asymptomatic cardiovascular disease that may cause problems during long duration space flight. We plan to solicit proposals in this area in the future.

Projects addressing risk of Impaired Cardiovascular Response to Exercise Stress Although several of the projects address exercise this is not a primary focus of any of the current projects. The reason for this is that the current in-flight exercise regimen appears to be adequate to maintain aerobic exercise capacity.

Progress towards Development of New Cardiovascular Technologies for Space flight and Earth-based Applications The progress of the Cardiovascular Alterations Team has been heavily dependent on the development of new technologies which allow us to better understand, measure and alter physiological processes. Technologies which we have developed and applied include computer simulation technologies, Cardiovascular System Identification technology for the non-invasive quantification of closed cardiovascular regulation, measurement of Microvolt T-Wave Alternans to assess cardiac electrical stability, and ultrasound technologies for the non-invasive assessment of cardiovascular function. One of these technologies (Microvolt T-Wave Alternans) has already been successfully commercialized for clinical use here on Earth. We are just beginning to develop a novel pulsatile G-suit as a countermeasure to the development of orthostatic hypotension. Future progress of the Cardiovascular Alterations Team will continue to be dependent, in part, on the development of new diagnostic and therapeutic technologies. In the future we plan to solicit proposals which specifically focus on the development of novel cardiovascular technologies with applications to both space and earth medicine.

Progress towards Integration The cardiovascular team strives to have a dynamic interplay/integration between projects focused on animal studies, human studies, and cardiovascular simulations. This intra-team interaction has been facilitated by team retreats and telecons. With the recent enlargement of our team from 12 to 16 projects discussed above, going forward we will have projects within each of the three areas (animal studies, human studies, and cardiovascular simulations) also meet separately in addition to the team wide meetings.

In addition to our intra-team integration we interact with a number of other teams including Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems. Two of our project leaders (Cassone, Thomas) are integrated into the functioning of other teams (Human Performance, Smart Medical Systems). We plan to further promote this inter-team interaction.

In addition we have undertaken a critical review of past cardiovascular countermeasures that have been proposed and/or tested so that we may incorporate evaluation of suitable countermeasures into our program.

HIGHLIGHTS

- The team's activities have been reported by the National Geographic, the NASA Headlines website, and the NASA Spinoff Magazine
- Dr. Shirakawa of NASDA (Japan) spending one year at MIT in joint research effort.
- Low sympathetic and high parasympathetic responsiveness as measured by CSI pre bed-rest identifies subjects who will develop orthostatic intolerance post bed-rest.
- Nearly all females are tilt intolerant following simulated microgravity while only 50 % of males are - mechanisms being investigated.
- One day bed rest does not alter MSNA to otolith organ stimulation.
- Under Supplemental Medical Objective process one astronaut with a history of post flight orthostatic hypotension treated with midodrine with good results.
- Impaired HR, blood pressure, and myocardial contractility responses to transient. hypotensive stimulus in mouse model (HLU) using conductance/micromanometric catheter.
- Cardiac unloading directly modifies contractile reserve at level of myocyte, with distinct molecular signature of reprogrammed Ca^{2+} regulatory genes.
- Hindlimb unloading model of microgravity in rats produced an intense reduction of contractile function in isolated thoracic duct lymphatics.
- Hindlimb suspension abolishes the daily rhythm in heartrate, but body temperature rhythms not affected.
- Post-suspension hypotension is associated with increased levels of nitric oxide and prostacyclin.
- The genomic structure of the alpha and beta subunits of soluble guanylyl cyclase and the intron-exon boundaries have been completed.
- Computer simulations indicate that post-flight orthostatic intolerance cannot be explained by a change in any single cardiovascular parameter.
- Built High Level Architecture (HLA) based federation of APL medium-fidelity cardiac simulation with MIT (Mark Group) RCVSIM cardiovascular simulation.
- Develped a working three-dimensional model of cardiac electromechanics and mechanoelectric feedback.
- Developed computer model of cardiac myocyte.
- 3D finite element simulation demonstrates impact of pericardium in microgravity

Summary of Accomplishments of Individual Projects

Human Studies Ground Based

Cardiovascular Effects of Simulated Microgravity in Man

Richard J. Cohen, M.D

Specific Aims

- Apply Cardiovascular System Identification (CSI) to study alterations in CV regulation during head-down tilt bedrest
- Use Microvolt T Wave Alternans (MTWA) to assess alterations in cardiac electrical stability
- Evaluate alpha agonist midodrine as a countermeasure to the development of orthostatic hypotension
- Evaluate the aldosterone antagonist spironolactone as a countermeasure to the development of alterations in cardiac electrical stability
- Evaluate the effects of age, gender and sleep deprivation

Accomplishments/Findings

- CSI analysis completed on 29 subjects
- Low sympathetic and high parasympathetic responsiveness as measured by CSI pre bed-rest identifies subjects who will develop orthostatic intolerance post bed-rest
- Bed-rest reduces autonomic reflexes as measured by CSI
- Midodrine effective countermeasure to the development of orthostatic intolerance in bed-rest studies, flight study approved.
- Bed rest appears to induce MTWA, MTWA in widespread clinical use
- Dr. Shirakawa of NASDA (Japan) spending one year at MIT in joint research effort

Renal and Cardio-Endocrine Responses in Humans to Simulated Microgravity

Gordon H.Williams

Specific Aims:

- Influence of gender and age on RAAS following Simulated Microgravity(SM)
- Effects of midodrine on orthostatic intolerance in women following SM
- Effects of spironolactone in older men on RAAS and on changes in myocardial electrical stability resulting from Microgravity exposure

Accomplishments:

- SM and Sleep deprivation produced greater K^+ loss through the bed rest period than SM alone as well as a substantial decrease in serum K^+ levels
- Tilt intolerant males post SM have significantly more Na+ retention and K+ loss than males who remain tilt tolerant
- Nearly all females are tilt intolerant following SM while only 50 % of males are. Potential differences in Na+ and K+ balance are being assessed.
- 3 days after returning to normal posture activities, nearly all tilt intolerant males become tilt tolerant even those who were tilt intolerant pre-SM.

Effect of Simulated Microgravity on the Vestibulosympathetic Reflex in Humans

Chester A. Ray, Ph.D.

- There is not differential control of MSNA in the arm and leg during altered feedback from otolith organs in humans, but that greater vasoconstriction occurs in the calf than the forearm. (Monahan and Ray. *J Physiol Lond* 538:303-308, 2002)
- Semicircular canals but not otolith organs mediate changes in ventilation. (Monahan et al. *Am J Physiol* 282:R689-R694, 2002)
- Mental stress and hypoxia does not affect the vestibulosympathetic reflex. (Carter et al., *J Appl Physiol* and Monahan and Ray. *Am J Physiol*, in press)
- One day bed rest does not alter MSNA to otolith organ stimulation

HUMAN STUDIES FLIGHT

Mechanisms of Post Flight Orthostatic Intolerance

Janice Meck

Specific Aims

- Determine whether diminished post flight dorsal hand vein responsiveness distinguishes between non-presyncopal and pre-syncopal astronauts
- Characterize changes in nitric oxide physiology pre and post flight

Accomplishments

- Completed definition phase review and final flight approval received

Effects of Space Flight on Cardiovascular Stability

Richard J. Cohen

Specific Aims

- Apply Cardiovascular System Identification to study flight induced alterations in cardiovascular regulation
- Apply Microvolt T Wave Alternans testing to investigate the effects of space flight on cardiac electrical stability
- Test the effects of midodrine in preventing post flight orthostatic hypotension

Accomplishments

- Completed definition phase review and final flight approval received
- Under Supplemental Medical Objective process one astronaut with a history of post flight orthostatic hypotension treated with midodrine with good results

Animal Studies

Mechanisms of Cardiovascular Deconditioning

Artin Shoukas

Specific Aims

- To determine mechanisms of impaired stroke volume response (SV) in a rat model of microgravity.
    - To determine the role of myocardial contractility and loading conditions in the impaired SV response
    - To determine the role of cardiac atrophy in cardiovascular deconditioning.
- To determine molecular mechanisms of vascular (systemic and pulmonary arterial, and venous) hypo responsiveness in a rat model of micro-gravity.
    - To determine the role of abnormalities in vascular smooth muscle Ca^{2+} influx/release and myofilament Ca^{2+} sensitivity in vascular hyporesponsivenss
    - To determine the role of the endothelium in vascular contractile hypo-responsiveness
- To test pharmacologic countermeasures based on mechanisms that impair both SV responses, and vascular hypo-responsiveness in a rat model of micro-gravity

Accomplishments

•Impaired HR, blood pressure, and myocardial contractility responses to transient hypotensive stimulus in mouse model (HLU) using conductance/micromanometric catheter

•Impaired contractile response to beta -agonist stimulation (as measured by sarcomere shortening) in isolated cardiac myocytes from HLU mice

•Endothelial dependent (NO dependent) and independent mechanisms contributing to vascular hyporesponsiveness in multiple vascular beds

•Attenuated venular responses to exogenous NE in HLU rat model

•Established assay for periarterial nerve stimulation (endogenous NE release) in mesenteric vascular preparations and characterized alpha-1 adrenergic receptor responsible for signaling at neuroeffector junction (alpha-1 A and B).

•Inhibition of intracellular pathway involved in modulating Ca2+ sensitivity (Myosin Light Chain Phosphatase) by antisense oligonucleotides can enhance vascular contractility in ring bioassay: potential therapeutic approach to OI and hypotension

Cardiac Unloading: Biologic Mechanisms & Countermeasures

Beverly H. Lorell

Specific Aims

•To determine functional consequences of cardiac remodeling due to microgravity unloading using surrogate model of heterotopic transplantation:

- •Effects on adult myocyte contractile function and Ca^{2+} regulation.
- •Regulation of adult myocyte growth and programmed cell death (apoptosis).
- •Identification of countermeasures which blunt cardiac atrophy and/or enhance functional cardiac reserve.

Accomplishments/Findings

•*Cardiac unloading directly modifies contractile reserve at level of myocyte*, with distinct "molecular signature" of reprogrammed Ca^{2+} regulatory genes.

•Changes in contractile reserve relate to duration of unloading: implications for short vs long-term human spaceflight on cardiac work capacity.

•Identification of 2 novel pathways for preservation of cardiac mass: cyclin-dependent kinase-9 and anti-aging gene, telomerase reverse transcriptase.

•*Alpha-adrenergic stimulation selectively enhances myocyte contractility* following long-term cardiac unloading: major implications as human countermeasure to *rescue* cardiac work capacity after long-term spaceflight.

Circulatory Remodeling With Simulated Microgravity: Effects of Simulated Microgravity on Lymphatic Function:

Michael Delp

Specific Aims

•Study the effects of simulated microgravity (hindlimb unloading in rats) on the contractile function of isolated lymphatics.

•Evaluate the effects of hindlimb unloading on the sensitivity of the lymphatic pump and vessel tone to changes in transmural pressure in rat lymphatics.

•Study the influence of hindlimb unloading on the sensitivity of the lymphatic pump and vessel tone to changes in lymph flow in rat lymphatics.

•Accomplishments/Findings

•Hindlimb unloading model of microgravity in rats produced an intense reduction of contractile function in isolated thoracic duct lymphatics:

•Reduction (50-75%) in the resting tone of thoracic duct.

•Reduction (30-60%) in the phasic contraction frequency of the lymph pump.

•Reduction (60-80%) in the strength of phasic contractions of the lymph pump.

•Reduction of pressure-sensitive stimulation of the lymph pump.

•Increased flow-sensitive inhibition of the lymph pump.

•Overall intense reduction in thoracic duct fractional lymph pump flow (40-90%).

Microgravity and Circadian Cardiovascular Rhythms

Vincent M. Cassone

Specific Aims

- In a rat model:Determine the central pathways(s) by which the hypothalamic suprachiasmatic nucleus (SCN) influences circadian changes in heart, blood pressure and regional blood flow.
- Determine the effects of microgravity, employing an accepted method for simulation of microgravity in rodents, on circadian changes in these cardiovascular parameters.
- Determine the pathways by which these changes are mediated, so as to better design countermeasures for future human uses.

Findings

- Hindlimb suspension abolishes the daily rhythm in heartrate
- But, body temperature rhythms are unaffected.
- This is similar to the situation observed in weightless conditions in which daily heartrate patterns are decreased in amplitude, while body temperature rhythms persist.

Possible Countermeasures to Post-Suspension Hypotension in the Head-Down Tilt Rat Model

Mohamed A. Bayorh

Specific Aims:

- Define the roles of nitric oxide and prostacyclin in post-suspension hypotension in the Sprague-Dawley rat.
- Evaluate gender differences in post-suspension hypotension.

Accomplishments:

- Post-suspension hypotension is associated with increased levels of nitric oxide and prostacyclin.
- U-51605 reverses the post-suspension reduction in blood pressure.
- There appears to be a gender difference in the vasodilatory mediators involved in post-suspension hypotension. The prostanoids seem to be more affected in males; whereas, nitric oxide is more involved in females.

Development of a Soluble Guanylyl Cyclase Knockout Mouse Model

Ferid Murad

Specific Aims

- Develop a soluble guanylyl cyclase conditional and tissue specific knock- out mouse model. Targeted tissues will be heart, vascular smooth muscle and brain.
- Using a tail suspension mouse model to simulate microgravity, examine the cardiovascular functions of the animals.

Accomplishments/Findings/Progress

- The genomic structure of the alpha and beta subunits of soluble guanylyl cyclase and the intron-exon boundaries have been completed.
- The promoters of alpha and beta soluble guanylyl cyclase have been identified.
- The construct for the plasmid for microinjection of blastocyst stem cells is almost complete.

Modeling and Technology Development

Computational Models of the Cardiovascular System and Its Response to Microgravity and Disease

Roger G. Mark

Specific Aims

- Develop computational models of cardiovascular system capable of simulating short-term gravitational stress
- Interface with human studies (at NSBRI and NASA) to optimize model design
- Test hypotheses regarding physiologic basis of orthostatic intolerance (OI) by matching model to pre- and post-spaceflight astronaut data
- Aid countermeasure research by simulating interventions designed to prevent OI
- Apply cardiovascular model to clinical problem of intelligent patient monitoring in intensive care units (ICUs)

Accomplishments/Findings

- Validated model against population average and individual subject data
- Established many collaborations to obtain and archive data for model comparison
- Simulations indicate that post-flight OI cannot be explained by a change in one single cardiovascular parameter
- Created an extensive, searchable database of physiologic waveforms, parameters, and clinical information from nearly 800 ICU patients (10^5 patient-hours)
- Interfaced with Integrated Human Function Core by simulating exercise

Distributed Simulation of Integrated Human Function

James E. Coolahan

Specific Aims

•Develop a computational model of the human ventricular myocyte, and a finite element model of the geometry and fiber structure of the human heart

•Develop a distributed simulation integrating cardiac electrical activity at JHU with cardiac mechanical activity at UCSD, with simulation control at JHU/APL

•Working with the NSBRI Team, select other cardiovascular simulations and develop a distributed simulation of cardiovascular function linking several centers

•Working with the NSBRI team, select muscle and bone models, and develop a multi-center distributed simulation of multiple functions

Accomplishments/Findings

•Built High Level Architecture (HLA) based federation of APL medium-fidelity cardiac simulation with MIT (Mark Group) RCVSIM cardiovascular simulation

- Integrated and running in multi-computer configuration at JHU/APL
- Used to analyze arterial/ventricular pressures tracings and baroreflex responses during a run of ventricular tachycardia (not yet validated with clinical data)
- Presented at March 2002 Simulation Interoperability Workshop (selected as best paper)

•Working to expand cardiac-cardiovascular federation to include skeletal muscle and whole-body metabolism simulations for human exercise simulation federation

Integrated Modeling of Cardiac Mechanical and Electrical Function

Andrew D. McCulloch, Ph.D.

Specific Aims

- to develop anatomically detailed dynamic finite element models of three-dimensional cardiac electromechanics
- To use these models to bridge systems models cellular dynamics and signaling with systems models of hemodynamics and cardiovascular regulation
- To apply these models to investigate cardiac responses to chronically altered external loading conditions and develop simulations of cardiac adaptation to microgravity
- To implement the models using modular object-oriented software engineering techniques that allow them to be readily integrated and used interactively

Accomplishments/Findings

- A working three-dimensional model of cardiac electromechanics and mechanoelectric feedback
- New cellular systems models of cardiac excitation-contraction coupling, energy metabolism, myofilament activation and adrenergic signaling
- A new release of our integrated object-oriented modeling software Continuity 6.0 that includes a new graphical user interface, scripting language support and visualization engine (http://cmrg.ucsd.edu)

Integrative Cardiac Myocyte Model: Ion Channels, Ca and Contraction

Donald M. Bers

Specific Aims

- Develop more up-to-date electrophysiological myocyte model.
- Incorporate new Ca transport data on NaCaX, SR Ca uptake and release.
- Extend the model to include cooperative Ca-dependent contraction & relaxation.
- Implement model in highly accessible computer formats.

Progress

- Finish, Publish & Distribute LabHEART 4.7
- Finalize new compartment model I_{NCX}, SR, I… ?
- Develop user-modifiable equation version LabHeart 5.
- Add exercise (adrenergic) to models.
- Transport new model to LabHEART format.
- Develop Parameter sets: human, rat, dog, G-P (atria?)
- Tune currents (add I_{KACh}, I_{KATP}, $I_{Cl(CFTR)}$ & $I_{Cl(Ca)}$, other?)
- Develop local control Model variant (discrete junctions)
- Add ATP counter (SR-Ca-, Na/K- & SL Ca-ATPase)
- Add Mitochondrial Ca transport (to match our data)
- Connect TnC Ca-Binding to MF Mechanics model
- Connect AP-Ca-transient + Mito Ca & MF to energetics

Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity

James D. Thomas

Specific Aims

- Assess LV mass regression during chronic volume and pressure unloading
- Validate new echo modalities to assess myocardial function in microgravity
- Validate exercise contractile reserve for detection of early LV dysfunction
- Perform core echo measurements for other NASA and NSBRI researchers
- Extend quantitative tools to 3D echo

Accomplishments/Findings

- Recruitment of 20 AR and AS patients undergoing AVR
- 10 publications in Circ, JACC, AJP demonstrating basic validation and clinical application of Doppler tissue imaging, strain rate imaging and transmitral color M-mode quantification of ventricular diastolic suction
- Extension of strain rate imaging to bicycle exercise, applicable in space
- Core measurements performed for Boston bedrest studies (Cohen) and Dallas bedrest studies (Levine)
- Software developed for compression, segmentation, and quantification of 3D echos, several publications in JACC, JASE, AJP
- 3D finite element simulation demonstrates impact of pericardium in microgravity

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

ANNUAL PROGRAM REPORT November 12, 2002

Team Name: **Human Performance Factors, Sleep and Chronobiology Team**

Team Leader: **Charles A. Czeisler, Ph.D., M.D.**
Professor of Medicine, Harvard Medical School
Director, Division of Sleep Medicine
Brigham and Women's Hospital; 221 Longwood Avenue;
Boston, MA 02115 USA
Telephone: (617) 732-4013; Fax: (617) 732-4015
E-mail:caczeisler@hms.harvard.edu

Associate Team Leader: **Megan E. Jewett, Ph.D.**
Instructor in Medicine, Harvard Medical School
Director, Biomathematical Modeling Unit
Brigham and Women's Hospital; 221 Longwood Avenue;
Boston, MA 02115 USA
Telephone: (617) 732-6445; Fax: (617) 264-6785
E-mail: megan_jewett@hms.harvard.edu

Team Principal Investigators:

Project 1: Optimizing Light Spectrum for Long Duration Space Flight
PI: George.C. Brainard, Ph.D. Jefferson Medical College of Thomas Jefferson University, Department of Neurology, 1025 Walnut Street, Room 310, Philadelphia, PA 19107 USA
Telephone: (215) 955-7644; Fax: (215) 923-7588;
e-mail: George.Brainard@mail.tju.edu

Project 2: Circadian Entrainment, Sleep-Wake Regulation and Performance during Space Flight
PI: Charles A. Czeisler, Ph.D., M.D. (See address above under Team Lead)

Project 3: Countermeasures to Neurobehavioral Deficits from Partial Sleep Loss
PI: David F. Dinges, Ph.D.; Professor of Psychology in Psychiatry; Chief, Division of Sleep and Chronobiology; Director, Unit for Experimental Psychiatry, Department of Psychiatry, University of Pennsylvania School of Medicine; 1013 Blockley Hall, 423 Guardian Drive; Philadelphia, PA 19104-6021 USA
Telephone: (215) 898-9949; Fax: (215) 573-6410;
e-mail: dinges@mail.med.upenn.edu

Project 4: Primate Circadian Rhythms in the Martian Environment
PI: Charles Fuller, Ph.D.; Section of NPB, University of California, One Shields Avenue, Davis, CA 95616-8519 USA
Telephone: (530) 752-2979; Fax: (530) 752-5851;
e-mail: cafuller@ucdavis.edu

Project 5: Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure
PI: Megan Jewett, Ph.D. (See address above under Associate Lead)

Project 6: A Model of Circadian Disruption in the Space Environment
PI: Michael Menaker, Ph.D.; University of Virginia, Department of Biology, Gilmer Hall, POB 400328, Charlottesville, VA 22904-4328
Telephone: (804) 982-5767; Fax: (804) 982-5626;
e-mail: mm7e@virginia.edu

Project 7: Circadian and Vestibular System Relationships
PI: Lawrence P. Morin, Ph.D. Department of Psychiatry, Health Science Center, SUNY, Stony Brook, NY 11794
Telephone: (631) 444-1613; Fax: (631) 444-7534;
e-mail:lmorin@epo.som.sunysb.edu

Project 8: Long-term Exposure to Dim Light Desynchronizes the Circadian System of Rat
PI: Gianluca Tosini, Ph.D.; Assistant Professor, Anatomy/Neuroscience, Morehouse School of Medicine, 720 Westview Dr., S.W., Atlanta, GA 30310-1495
Telephone: (404) 756-5214; Fax: (404) 752-1041; e-mail: tosinig@msm.edu

Project 9: Animal Model for Sleep Loss and Circadian Disruption
PI: Fred W. Turek, Ph.D., Director, Center for Circadian Biology & Medicine Charles E. & Emma H. Morrison; Professor of Biology, 2153 N. Campus Drive, Evanston, IL 60208-3520 USA
Telephone: (847) 491-2865, Fax: (847) 467-4065; e-mail: fturek@nwu.edu

Team Lead **Date**

TABLE OF CONTENTS

I. ABSTRACT

The success of human space missions depends on each astronaut remaining alert and vigilant while operating sophisticated equipment and following complex procedures. During long-duration space flight, the space environment affects a number of physiological systems critically involved in human performance, and it is vital to mission success to understand the biological limits of human performance under space flight conditions. This team is focused on these issues and, in particular, is concerned with the following aspects of the space environment: microgravity, altered light-dark cycles, altered or reduced sleep/rest opportunities, high levels of automation, and habitation in a remote, inaccessible location. The primary thrust of this team's research program involves altered circadian organization, sleep disruption and cumulative sleep loss, and the associated neurobehavioral decrements occurring during long-duration space flight.

The goals of the Human Performance Factors, Sleep and Chronobiology (HPFSC) Team are to: (1) Characterize and quantify the adverse effects of long-duration space flight on sleep and circadian rhythms; (2) Characterize and quantify the effect of sleep loss and/or circadian dysfunction on physical and neurobehavioral performance; (3) Understand the basic mechanisms underlying the deterioration of sleep, circadian organization and human neurobehavioral function during space flight; (4) Develop high-fidelity mathematical models of performance based on circadian organization and sleep-wake history; (5) Develop effective countermeasures to optimize sleep and facilitate circadian adaptation in the space environment and thereby maintain optimal neurobehavioral performance; (6) Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight, with possible spin-off applications on Earth.

The team research objectives are driven by the Critical Path Roadmap related to Human Performance Failure because of Sleep and Circadian Rhythm Problems. The current research program involves nine ground-based research projects. Many of the projects impinge on more than one critical risk. The strategy of the Human Performance Factors, Sleep and Chronobiology Team is to develop a synergistic interaction between research projects at the molecular, cellular, organismic, and human levels, and to integrate predictive biomathematical modeling of the sleep and circadian systems.

II. INTRODUCTION

The need for sleep and an entrained circadian pacemaker have a sustained influence over many biomedical systems essential for maintaining astronaut physical condition, mental health, and performance capability. Dysfunction of sleep and circadian systems can adversely affect an organism's ability to respond to environmental challenges and has been linked to physiological and psychological disorders. The success of human space missions depends on each astronaut remaining alert and vigilant while operating sophisticated equipment and following complex procedures. During exploration class space missions, the space environment affects a number of physiological systems critically involved in human performance, and it is vital to mission success to understand the biological limits of human performance under such conditions. It has been demonstrated that both acute gravitational changes and space flight disrupt circadian rhythms and reduce sleep. Since circadian disruption and sleep loss result in both physiological and performance deficits, this team is focused on these issues and, in particular, is concerned with the following aspects of the space environment: microgravity, altered light-dark cycles and altered or reduced sleep/rest opportunities that may involve extended durations of wakefulness. The primary thrust of this team's research program involves altered circadian organization, sleep disruption and cumulative sleep loss, and the associated neurobehavioral decrements occurring during exploration class missions. This area has a high degree of relevance to a number of cardiovascular and immune changes, neurovestibular alterations and nutritional needs, and behavioral and psychological health in space flight.

The Human Performance Factors, Sleep and Chronobiology Team's program addresses risks and hazards in space flight that have been identified in the Human Behavior and Performance Discipline Area of the Critical Path Roadmap Baseline Document (2000). Specifically:

- Human Performance Failure Because of Sleep and Circadian Rhythm Problems (19)
- Human Performance Failure Because Of Human System Interface Problems and Ineffective Habitat, Equipment, Design, Workload, or In-flight Information and Training Systems

Our team has the following three **risk-based goals** for its program:

Goal 1: *Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration.*

Goal 2: *Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.*

Goal 3: *Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.*

The Human Performance Factors, Sleep and Chronobiology Team is focused on developing countermeasures for the sleep loss and circadian dysfunction and associated neurobehavioral and physiological performance decrements that occur during long-duration space flight. These countermeasures may include behavioral, pharmacological, environmental light or other adaptive approaches such as meal timing to maintain function and performance under the adverse conditions of exploration class space missions.

III. RESEARCH PROGRAM STRUCTURE AND DESIGN

The Human Performance Factors, Sleep and Chronobiology Team is focused on developing countermeasures for the sleep loss and circadian dysfunction and associated neurobehavioral performance decrements that occur during long-duration space flight. The team research objectives are driven by the Critical Path Roadmap related to Human Performance Failure because of Sleep and Circadian Rhythm Problems. The current research program involves nine ground-based research projects. The strategy of the Human Performance Factors, Sleep and Chronobiology Team is to develop a synergistic interaction between research projects at the molecular, cellular, organism, and human levels, and to integrate predictive biomathematical modeling of the sleep and circadian systems.

In 2001, the HPFSC Team was substantially restructured. The current team is comprised of nine PIs, six of whom are new NSBRI investigators. Three of these six new NSBRI investigators are new to the space science community, a direct result of the recruitment efforts made within the science community. In order to achieve the goals listed above, the Human Performance Factors, Sleep and Chronobiology Team has identified the following six interrelated themes within this research area:

A. **Effects of long-duration space flight on sleep and/or circadian rhythmicity.** The focus of this theme is to identify and understand the mechanism underlying the effect of long-duration space flight (microgravity, altered light intensity, loss of geophysical cues, isolation, altered physical activity, etc.) on neurobiologic, endocrinological, and behavioral functions (molecular, cellular and organismic) that control sleep and circadian systems.
B. **Effects of sleep loss and/or circadian dysfunction on physical and neurobehavioral performance.** The focus of this theme is to identify and to understand the mechanisms underlying the acute and chronic adverse effects that sleep loss, sleep disruption, and/or circadian dysfunction have on critical physiologic and performance parameters during long-duration space flight (e.g., neurophysiologic function, physiological alertness, vigilance, cognitive performance, mood/morale, problem solving and communication).
C. **Predictive modeling of performance based upon circadian organization and sleep homeostasis.** This theme is concerned with the development of analytical or phenomenological mathematical models that predict individual human performance capability by involving multiple subsystems (e.g., circadian rhythmicity, sleep homeostasis, work-rest schedules, etc.) as an integrated unit across levels of organization, and by estimating the impact of countermeasure use designed to optimize human physical and/or neurobehavioral performance.
D. **Countermeasures to optimize sleep and facilitate circadian adaptation in space and maintain optimal neurobehavioral performance**. The research program of this team will not only define the impact of the space environment on sleep and circadian rhythmicity and the effects of the sleep loss and circadian dysfunction on performance but also will develop methods to counter the adverse physiological and behavioral events. These countermeasures may include behavioral, pharmacological, environmental light or other adaptive approaches to maintain function and performance under the adverse conditions of long-duration space flight.
E. **Monitoring and assessment during space flight.** This theme deals with the development of methods for monitoring the status of sleep, sleep homeostasis and circadian organization, as well as technologies that monitor ambient lighting conditions on space shuttle and ISS and assess and update the current functional status or performance capability of the individual

The Human Performance Factors, Sleep and Chronobiology Team is focused on developing countermeasures for the sleep loss and circadian dysfunction and associated neurobehavioral and physiological performance decrements that occur during long-duration space flight. The initial strategic research program for the Human Performance Factors, Sleep and Chronobiology Team involves nine research projects that collectively address the five research themes described above. The schematic of the circadian and homeostatic regulation of sleep and alertness and physiological functions shown in Diagram 1 illustrates the relationships between the nine current ground-based experiments that comprise the NSBRI Human Performance Factors, Sleep and Chronobiology Team, with the principal targets of each project indicated. This diagram illustrates the interrelated nature of these projects, designed to fill critical gaps in knowledge that need to be filled in order to develop effective countermeasures for long-duration space flight. Each of the individual projects is summarized below and in Table 1, including which goal(s) are addressed and countermeasure targets.

Brainard et al.: Optimizing Light Spectrum for Long Duration Space Flight
The physiological changes caused by disturbed circadian rhythms and altered sleep-wake patterns can result in decrements in alertness, concentration, and performance. This project addresses these risk factors, which threaten the safety of personnel and the objectives of space missions as stated in Goal 3.
Countermeasure targets include:
1. Identification of the optimum spectrum for photic resetting of the circadian pacemaker.
2. Design specifications for space suit visors and the windows used in space vehicles and habitats;
3: Engineering parameters for the ideal spectral distribution for illumination of general living quarters during space exploration.

Czeisler et al.: Circadian Entrainment, Sleep-Wake Regulation & Performance during Space Flight
The intent of this project is to develop countermeasures to facilitate adaptation of the human circadian pacemaker to the 24.65-h day length of Mars, which is outside the range of entrainment of the human circadian pacemaker given the weak synchronizing stimuli within the Martian habitat. This project applies to Goal 3.
The primary *countermeasure target* is to evaluate the efficacy of intermittent bright light pulses as a treatment to reduce the risk of the misalignment of circadian phase, sleep disruption, associated decrements in neurobehavioral performance and reduction in nocturnal growth hormone secretion experienced by individuals exposed to the 24.65h Martian day.

Dinges et al.: Countermeasures to Neurobehavioral Deficits From Partial Sleep Loss
Using a response surface experimental paradigm (RSM), this project seeks to reduce neurobehavioral deficits and fatigue due to inadequate sleep in astronauts by investigating how variations in sleep duration and its circadian placement relate to the return of performance per time invested in sleep. This project applies to Goal 2.
Countermeasure targets include determination of the amount of naptime necessary to compensate for interrupted nocturnal sleep periods for the prevention of cumulative sleepiness and performance deficits.

Fuller et al.: Primate Circadian Rhythms in the Martian Environment
This project is focused on the ability of the circadian time system to synchronize to the Martian photic (spectrum and period) by examining the effects of 1.0, 1.5 and 2.0G on the period of the circadian pacemaker. A G vs. period model will be developed to predict the effect of the 0.38 G Martian environment on the period of the circadian pacemaker. Long-term (4 months) physiological and behavioral responses will be examined.
Countermeasure targets include the use of timed bright light pulses on circadian entrainment. This program will develop a primate model to evaluate physiological and behavioral consequences of long-term exposure of males and females to altered lighting and gravitational environments. This project applies to Goals 1 and 3.

Jewett et al.: Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure
The intent of this project is to further develop and refine our mathematical dynamic stimulus processing model so that it can accurately predict the phase and amplitude of the human circadian system under any lighting system especially those which are in space. The mathematical Neurobehavioral Performance model validated against performance data collected will result in the development of a user-friendly Performance Simulation Software program. This project applies to Risk-based goals 1 through 3 and Non-Risk-Based Goal 4 (see below).
Countermeasure targets include the design of shift schedules to allow astronauts to receive available bright light at appropriate times for proper circadian alignment with their sleep/wake schedules.

Menaker et al.: A Model of Circadian Disruption in the Space Environment
This project proposes to evaluate the effects of "constant" conditions and shift work schedules on the maintenance of circadian rhythmicity when the central and peripheral structures are abnormally phased. The resulting abnormal circadian organization is "dysphasia." This project applies to Goal 1.
Countermeasure targets include an evaluation of meal timing, melatonin administration, forced exercise, and short pulses of complete darkness as a treatment to reduce the risk of circadian dysphasia.

Morin et al.: Circadian and Vestibular Relationships
This project seeks to determine the route by which a correlate of the non-photic stimulus, i.e., locomotion, might gain access to the circadian rhythm system and shift rhythm phase. It has also opened the possibility that the vestibular system is a specific route by which sensory information related to head movement might gain access to the circadian system. This project applies to Goal 1.
Countermeasure targets include an evaluation of a non-locomotor, non-photic three-dimensional motion stimulus to activate functionally the vestibular and circadian systems, laying the groundwork for the future development of novel approaches for the treatment of space motion sickness and for resetting circadian phase.

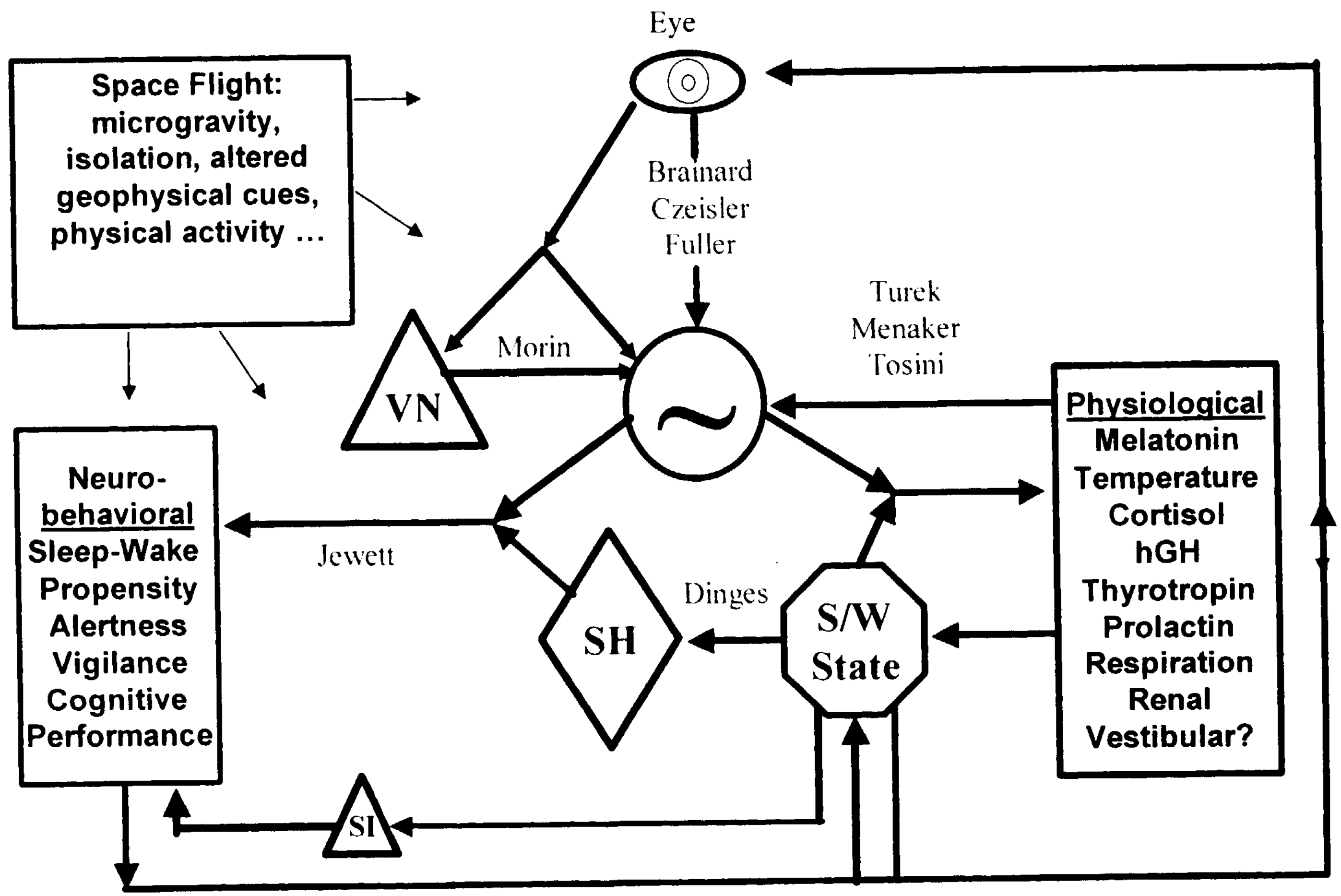
Tosini et al.: Long-Term Exposure to Dim Light Desynchronizes the Circadian System of Rats

The goal of this project is to understand the mechanisms responsible for the desynchronization of circadian rhythm in locomotion and the enzymes responsible for the production of melatonin. Investigating the effect that internal desynchronization has on the immune response and motor and cognitive performances. This project applies to Goal 2.
Countermeasure targets include an evaluation of the use of melatonin as a pharmacological agent to counteract desynchronization of the circadian rhythms.

Turek et al.: Animal Model for Sleep Loss and Circadian Disruption

This project will focus on determining the effects of 12 hours of imposed wakefulness on circadian rhythms, sleep-wake cycles, neurobehavioral and motor performance measures during normal active and inactive periods. This project applies to Goals 1 and 3.
Countermeasure targets include treatment exercise and with either physiological or pharmacological dose of melatonin reduce the effects of circadian disruption and sleep loss as well as alleviate the adverse effects associated with work at different times of day.

Diagram 1. Description of Current (2001) Program for Human Performance Factors, Sleep and Chronobiology. This diagram illustrates the relationships between the different physiological systems investigated by the different projects on the team. Illustrated is the influence of the retinal light exposure on the human circadian clock (circle with the oscillator symbol ~) and the influence on the sleep-wake state (S/W), and their effect on a number of physiological variables (melatonin, temperature, etc.). A combined influence of the circadian clock and sleep-wake is exerted on neurobehavioral variables (sleep-wake propensity, alertness, etc.). The sleep-wake state influence is illustrated via the intermediary of the sleep homeostat (SH), and sleep inertia (SI). The global influence of factors associated to Space Flight (micro gravity, isolation, etc.) on the sleep and circadian systems is also represented. The interaction of the Vestibular Nucleus (VN) and its output pathways with the circadian pacemaker is being investigated by one project.



HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BRAINARD/Optimizing Light Spectrum for Long Duration Space Flight	Goals 1, 3	Optimum light spectral distribution	Healthy male and female human subjects	Develop melatonin fluence-response curves below 440 nm and above 600 nm in human subjects. Develop action spectrum between 400 and 700 nm in subjects with dilated and undilated pupils	Identification of optimum light spectral characteristics for maintaining or adjusting circadian phase and sleep-wake cycle in astronauts and ground control workers. Preliminary test of monochromatic stimuli for phase shifting human circadian rhythms	Assist in designing a novel light panel for circadian stimulation. Assist in developing protocols for comparing head mounted light therapy devices
CZEISLER/Circadian Entraining, Sleep-Wake Regulation & Performance During Space Flight	Goals 1, 2	Intermittent bright light pulses	Healthy male and female human subjects scheduled to non-24-hour day lengths in an environment shielded from periodic, 24-h time cues	Quantification of the intrinsic period and the limits of entrainment of the human circadian pacemaker; investigation of the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function	Preliminary evaluation of the efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars	Full-scale clinical trial of age and gender matched astronaut surrogates living for extended durations on a non-24-hour work schedule while exposed to intermittent bright light at the most effective wavelength
DINGES/Countermeasures to Neurobehavioral Deficits from Partial Sleep Loss	Goals 1, 2, 3	Naps and split sleep schedules	Healthy male and female human subjects	Mathematically track neurobehavioral performance deficits associated with chronic sleep restriction. Examine sleep efficiency and architecture during restricted sleep periods at different circadian phases	Develop response surface map paradigms to further understand the interaction between sleep duration, sleep-wake placement and neurobehavioral functioning	Development of optimal sleep-wake schedules (including main and supplementary sleep episodes) to ensure maintenance of high level neurobehavioral functioning

Note:
Goal 1: Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration.
Goal 2: Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.
Goal 3: Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.

FULLER/Primate Circadian Rhythms in the Martian Environment	Goals 1, 2	Bright light pulses	Rhesus monkeys as human surrogates. Large-diameter centrifuge to produce altered environment. Controlled lighting period, intensity and spectra. Long duration exposure in controlled animal facilities.	Determine the effect of altered gravity on primate circadian rhythms, principally the endogenous clock period.	Enhance entrainment response to low light (ISS, Martian habitat), reddish light (Mars), and non-24 hour schedules by means of exposure to light pulses. Definition of bright light source for light pulses. Studies will address timing and efficacy of bright light exposure.	Projected application of bright light pulses to prevent loss of circadian entrainment, sleep and rhythm disturbances, performance decrements.
JEWETT/Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure	Goals 1,2	Design of rest/work and sleep/wake schedules	Previously collected human data;	Determine the nature of amplitude recovery dynamics of human circadian system.	Design shift and sleep schedules for proper circadian alignment. Validate refined circadian amplitude dynamics of light model with data from new human phase shifting experiments	Incorporate refined light model into circadian components of neurobehavioral performance model and predict the performance in human phase shifting experiments
MENAKER/ A Model of Circadian Disruption in the Space Environment	Goals 1,2	Coupling between multiple circadian oscillators	Transgenic rat incorporating a circadian luciferase reporter gene	Description of system disintegration under simulated space flight conditions	Repair system disintegration with timed application of light, food and melatonin	Transfer working countermeasures to humans
MORIN/Circadian and Vestibular Relationships	Goals 1,2	Anatomical & functional issues linking the vestibular & circadian systems	Anatomical tract tracing using retro and anterograde transport of labels. Study of brain regions for stimuli responses known to alter vestibular functions. Phase shifts in circadian rhythms	Understanding the basic anatomical & functional pathways linking vestibular & circadian systems	N/A	N/A
TOSINI/Long-term Exposure to Dim Light Desynchronizes the Circadian System of Rats	Goals 1,2	Coupling between central and peripheral oscillators	Measuring expression of gene in peripheral tissues	Identification of the effects on the circadian system of prolonged exposure to constant conditions	Use of melatonin as synchronizing agent	
TUREK/Animal Model for Sleep Loss and Circadian Disruption	Goals 1, 2	Exogenous melatonin administration and exercise	Mice	N/A	Testing of the effectiveness of countermeasures (melatonin, exercise) using a mouse model	N/A

In addition to the focus of the Human Performance Factors, Sleep and Chronobiology Team on achieving Risk-based Goals, there are also a number of important, **non-risk based goals** that the team is targeting, as follows:

Goal 4: *Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight.*
To achieve this goal, current studies are being conducted to assess the potential of using the Actiwatch-L (a wrist-worn light and actigraphy recording device already approved for space flight) to monitor sleep and light exposure of individual crew members while in space. This device could replace more extensive polysomnography devices used in more recent studies of sleep in space. Studies are also underway that compare the wrist-level Actiwatch-L light recordings with eye-level light measurements. Work is progressing on the use of the Actiwatch-L measurements as inputs to a mathematical model that can then predict the level of sleep homeostasis, phase of circadian rhythmicity and relative neurobehavioral performance levels.

Goal 5: *Develop new methods for monitoring ambient and retinal light exposure (illuminance/photopic lux, broadband visible irradiance, and circadian effective illuminance/circadian lux) on board space shuttle and ISS during space flight and on planetary habitats.*
For measurement of retinal light exposure in space, please see Goal 4 above. For ambient light exposure, wall-mounted ambient light recording devices have been tested aboard the Space Shuttle in the Neurolab flight. The team's current studies will help determine the circadian effective illuminance and irradiance levels, and then these recording devices can be refined to measure circadian-activating light levels more precisely.

Goal 6: *Develop Earth-based applications of technologies for non-invasively monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance for industrial and medical use.*
The polysomnography device that was developed for the recording of sleep in space in the Neurolab Shuttle flight have become a useful, wire-free device for recording polysomnography in lab-based and home-based basic science and clinical studies. This technology has the advantage of being appropriate for use when ambulatory, and straight-forward enough for a trained person to apply to themselves.
The use of salivary melatonin as a marker of circadian phase has been applied in both space and on Earth and is a technology that allows the validation of experimental and modeling results in field studies in which plasma melatonin measurements would not be possible.
Mathematical models that are developed to predict neurobehavioral performance in space are also being used to determine appropriate shift scheduling, light exposure, sleep timing, and countermeasure applications for shift workers, pilots, military and medical personnel, and transportation workers who also face the challenges of restricted sleep and circadian misalignment here on Earth. Neurobehavioral test batteries that are developed for these projects are useful for the validation of mathematical models in field and laboratory studies as well.

Goal 7: *Develop Earth-based applications of high-fidelity mathematical models of performance based on circadian organization and sleep-wake history for industrial and medical use.*
The mathematical models of performance that are being developed in this project can be applied to any Earth-based situation in which it would be helpful to know the effects of a sleep/wake

schedule and a light exposure pattern on resulting neurobehavioral performance (e.g., shift workers, pilots, military and medical personnel, and transportation workers). Therefore, the mathematical models developed here have been programmed into user-friendly simulation software that can be used by anyone to predict neurobehavioral performance given light exposure levels and sleep/wake history. This software is updated with model revisions and user-interface improvements on a regular basis.

Goal 8: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment.*
The studies conducted here improve our understanding of the effects of light on the human circadian system, and the role that the circadian system plays in neurobehavioral performance. These findings are incorporated into our mathematical models on an ongoing basis. This allows us to then determine the best light schedule and intensities to reduce the risk of performance failure by appropriately aligning the circadian system with the work/rest schedule. This technology is already currently in use in transportation, military and industrial settings here on Earth.

Goal 9: *Develop Earth-based application so technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to acute a chronic degradation of sleep quality or quantity.*
Our projects will help determine the amount and timing of sleep that best allows people to work extended and/or misaligned shifts with the least risk of performance failure. These findings will also be incorporated into the mathematical model being developed here. The model can then be used to help schedule rest/nap/sleep times so that they are the most effective in improving performance levels.

Goal 10: *Develop Earth-based applications to technologies developed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work.*
Studies investigating the effects of extended duration work schedules in these projects allow us to determine the best timing of countermeasures (light exposure, naps, melatonin, etc.) to improve performance. These findings are completely applicable to any extended duration work schedules used here on Earth.

Goal 11: *Integrate research and analysis*
Our goal is to integrate research within the Human Performance Factors, Sleep and Chronobiology Team, with other teams, and with work being done by Team investigators not directly supported by NSBRI.

IV. RESEARCH PROGRAM ACCOMPLISHMENTS

The program accomplishments of each of the individual projects is summarized below:

Project 1: <u>Optimizing Light Spectrum for Long Duration Space Flight</u>

PI: *George Brainard, Ph.D.*
Thomas Jefferson University

Research Focus: Use of light spectrum and light visor design

Specific aims:

Test the hypotheses that:
1. Wavelengths of light below 440 nm and above 600 nm are active in regulating melatonin secretion via measurement of fluence response curves in humans;
2. There will be a loss of sensitivity to monochromatic light when the eyes are not pharmacologically dilated during the melatonin suppression test;
3. There will be a shift in spectral sensitivity of light regulation of melatonin secretion when the eyes are not pharmacologically dilated.
4. Improve light treatment, identify optimal spectral transmission characteristics for visors and windows, and engineer the ideal spectral distribution for illumination of living quarters.

Research Progress 11/1/2001-10/31/2002:

The long term goal of our research is to determine the best wavelengths of light for use as a countermeasure during long duration space flight, as well as for adjusting circadian and sleep disruption in civilians. A preliminary key finding is that the fluence-response relationship between 420 nm exposure and melatonin suppression is univariant with wavelengths between 440 and 600 nm. This finding has practical importance to astronauts in long duration space flight since 420 nm irradiance is greatly increased outside the earth's atmosphere (e.g. Space Shuttle and International Space Station).

Another preliminary key finding is that there appears to be a loss of sensitivity to 460 nm light for melatonin regulation when the pupils are free to respond to light stimuli. Further investigation is needed to specifically quantify how much loss is due to pupil regulation. It will be important to further characterize both wavelength and intensity responses in freely constricting eyes in order to practically utilize action spectrum data in optimizing light as a countermeasure to circadian disruption during long duration space flight. In most cases, astronauts' eyes will be freely reactive during long duration space flight.

The above progress can be used to optimize the total lighting environment of astronauts on long duration space exploration missions. These data can be used to 1) improve light treatment as a countermeasure for circadian and sleep-wake disruption in space flight, 2) identify the best spectral transmission for space suit visors and the windows used in space vehicles and habitats, and 3) engineer the spectral distribution for illumination of general living quarters during space exploration.

According to the Critical Path Roadmap Baseline Document: A Risk Reduction Approach for Human Spaceflight (December, 2000), our project status is currently at a Countermeasure Readiness Level of 4. Once the concept formulation component of determining the countermeasure for sleep disturbance and circadian disruption has been completed, a progression to concept testing (Countermeasure Readiness Level 5) will ensue. The five year research strategy (2002–2006) for this project will include the initial determination of feasibility and efficacy of implementing study findings in the context of manned space flight missions. General lighting systems for astronauts for manned space programs and space stations are often comprised of light sources which provide wavelengths and intensities for optimal vision in space vehicles (Man-Systems Integration Standards, NASA-STD 3000, 1995). For example, the specification on Lighting Intensity Design (8.13.2.1 A) reads: "Light level or intensity should be sufficient to allow the crew members to perform their visual tasks efficiently...[for most nominal work and living space areas]." Although it is obviously useful to optimize visual stimulation of astronauts with the best intensities and wavelengths for photopic vision, those lighting characteristics are not necessarily optimal for reinforcing circadian entrainment.

Our progress to date on this project has resulted in three peer-review publications, one book chapter and ten abstracts which reference NSBRI support. Understanding the relative potency of different wavelengths for circadian stimulation is a critical step towards optimizing light as a specific countermeasure and a general illuminant in all long duration space exploration facilities.

Project 2: <u>Circadian Entrainment, Sleep-Wake Regulation & Performance during Spaceflight</u>

PI: Charles Czeisler, Ph.D, M.D.
Brigham and Women's Hospital/Harvard Medical School

Research Focus: Synchronization to Mars' day with two brief light pulses

Specific aims:
Test the hypotheses that:
1. Synchronization of the human circadian pacemaker to a sleep-wake and light-dark schedule with an imposed period ~4% longer than its intrinsic period will be disturbed.
2. This disturbed circadian synchronization will disrupt sleep, endocrine function, and impair waking alertness and performance.
3. Two relatively brief (45 minute) daily exposures to evening bright light (~10,000 lux) will establish a normal entrained circadian phase in subjects on such a schedule, resulting in improved sleep consolidation, undiminished growth hormone and cortisol secretion and enhanced daytime alertness and performance.

Research Progress 11/1/2001-10/31/2002:

During FY03 we completed five 65-day studies. This effort amounts to 325 subject test days in the laboratory. Originally we proposed to complete 260 subject test days per year and are thus ahead of schedule. Since FY01, we recruited 11 healthy volunteers (9 males, 2 females), completed physical and psychological screens on all volunteers recruited, and completed ten 65-day studies. Among, the first ten studies completed, 4 subjects were exposed to brief bright light pulses as a countermeasure to circadian misalignment associated to living in a non-24-h day, and 6 subjects were exposed to dim light as controls. Data collected include: 15,600 hours of core body temperature data, ~16,000 blood samples (for melatonin and growth hormone levels assessment), urine samples, ~10,000 hours of sleep and waking EEG recordings, subjective sleep quality by means of daily post-sleep questionnaires, ~15,6000 hours of actigraphy, light intensity, neurobehavioral performance and mood assessment. The successful collection of these data will allow us to test hypotheses 1, 2, and 3 of the project. Data analyses are currently in progress.

The physiological data collected during the first three years of funding demonstrated the need to develop effective and attainable countermeasures to prevent circadian misalignment during an exploration class mission to Mars (Wright PNAS). Indeed, we have demonstrated that a scheduled dim light-dark rest-activity cycle, with a dim ambient light intensity similar to that used aboard the space shuttle middeck, is able to entrain most, but not all human subjects to a scheduled 24-hr day, whereas none of the human subjects scheduled to a 24.6-h day (the period of the axial rotation of Mars) were entrained to this weak synchronizer (see preliminary results). Circadian phase misalignment to the 24.6-h day resulted in sleep disturbance (reduced sleep efficiency), endocrine disturbance (secretion of the sleep-promoting hormone melatonin during the waking day, reduced nocturnal growth hormone secretion and reduced cortisol levels), and impaired daytime alertness and neurobehavioral performance (reduced vigilance). The degree of circadian misalignment to the 24.6-h day was found to be strongly dependent upon the period of each subject's circadian pacemaker, such that subjects with periods shorter than 24.0 hr demonstrated the greatest degree of circadian misalignment to the 24.6-h day.

If the results from our current study show that circadian entrainment to a non-24-h sleep-wake/dark-light cycle is achievable by means of intermittent bright light pulses, then we will have successfully developed a countermeasure to prevent circadian misalignment during an exploration class mission (to Mars for example). To further refine and improve the efficiency of the countermeasure, additional research will be necessary to determine by what mechanism circadian entrainment is being maintained and also to determine the stability of entrainment under these dim light conditions.

Project 3: <u>Countermeasures to Neurobehavioral Deficits From Partial Sleep Loss</u>

PI: *David F. Dinges, Ph.D.*
University of Pennsylvania

Research Focus**:** The use of naps to ameliorate the affects of chronic sleep restriction

Specific aims**:**

1. Establish Response Surface Map to determine how to best use anchor and nap sleeps to promote neurobehavioral performance and alertness at an adverse circadian phase for waking;
2. Identify the optimal diurnal anchor sleep and nocturnal nap schedule to maintain neurobehavioral function when work is initiated with abrupt circadian displacement;
3. Determine how diurnal anchor sleep times and nocturnal nap sleep affect sleep physiology and circadian adjustment across a chronic schedule of simulated night operations.

Research Progress 11/1/2001-10/31/2002:

This project specifically addresses the following questions in the Human Performance Factors, Sleep and Chronobiology research area:
1. How do task characteristics; operator environments; human-machine interactions; daily, weekly and long-term work-rest schedules; and recovery sleep/naps alter the effects of sleep loss and/or circadian disruption on human performance? (NASA/NSBRI Critical Path question 6.10.)
2. How does space flight or exposure to chronic sleep restriction and/or circadian disruption affect sleep- and circadian-mediated neuroendocrine and autonomic functions, particularly those relevant to risk mitigation (e.g., growth factors, glucocorticoids, monoamines) during extended-duration missions?
3. Which behavioral, physiological, pharmacological and/or environmental countermeasures will help crew members reduce disturbances of circadian rhythmicity; sleep disturbances, or homeostatic sleep drive, thereby reducing the associated performance deficits? (NASA/NSBRI Critical Path question 6.06.)
4. What are the long-term consequences of the use of countermeasures designed to mitigate performance decrements associated with sleep loss and/or circadian disturbances? (NASA/NSBRI Critical Path question 6.07.)

To date we have completed the study of N=37 subjects in this protocol. Analysis of the polysomnographic, neurobehavioral and neuroendocrine data is underway on the data collected from the completed subjects, so that we may integrate this data into our existing response surface models. In experiment 1 we have been using a response surface experimental approach to systematically determine the chronic (10-day) effects of 18 sleep schedule conditions that involve restricted nocturnal anchor sleep alone and in combination with varying durations of restricted diurnal naps on performance, mood, sleep, circadian physiology and hormones. The resulting preliminary response surface maps (RSMs) derived from this dose-response experiment indicate that total sleep time per 24hr is a prime determinant of cumulative neurobehavioral deficits, and that combining a restricted nocturnal anchor sleep with a midday nap can attenuate cumulative deterioration in performance. In order to complete our understanding of how to optimize performance in the face of restricted sleep in space flight, in the current experiment we have reversed the circadian placement of these 18 anchor sleep + nap sleep conditions (i.e., diurnal anchor sleep alone and in combination with varying durations of restricted nocturnal naps), in order to (1) establish the RSMs during simulated night operations; and (2) by comparison with the RSMs for the study currently being completed, to determine the role of initial circadian phase of sleep on the cumulative rate of impairment from chronic sleep restriction.

Project 4: <u>Primate Circadian Rhythms in the Martian Environment</u>

PI: *Charles A. Fuller, Ph.D.*
University of California, Davis

Research Focus: Bright light pulses, Period vs. Gravitation

Specific aims:
Test the hypotheses that:
1. Rhesus macaques will not entrain to the Martian solar day when exposed to ambient light available on Mars, resulting in performance decrements and sleep and circadian dysfunction;
2. Some, but not all rhesus macaques will be able to entrain to a Martian solar day under a lighting environment proposed for the Martian Habitat;
3. The rhesus circadian period will change as a direct function of G level in hypergravity;
4. Daily evening pulses of bright light will synchronize all rhesus monkeys to the proposed Habitat environment

Research Progress 11/1/2001-10/31/2002:

1. Effect of Gravity on the Circadian Period of Rhesus Monkeys

During this period we performed the necessary setup and experiment preparations. These activities included training six male rhesus to use the Psychomotor Test System (PTS), followed by surgical implantation of telemetry transmitters. The use of telemetry allows us to record brain temperature, activity and sleep parameters from unrestrained subjects. We have partially completed this series of studies. Six males were studied in 1G in a non-entraining 28-h LD cycle. This is an adaptation of the forced desynchrony method previously used with humans and rodents to determine the period of the circadian pacemaker. In 1G, the intrinsic period of the rhesus circadian clock was on average 24.5 hours (range 24-25.3 h), or a little longer than the period seen in human studies or by us in preliminary rhesus studies.

We have acclimated these animals to 1.5G and have nearly completed a second forced desynchrony study at this G level. Although our conclusions are preliminary, it appears that circadian period in rhesus may be slightly shorter in 1.5G. We will need to complete 2G studies to address our hypotheses fully.

2. Acclimation to Martian Day Length and Altered Lighting Environments

Six female rhesus monkeys have been trained in the use of PTS and the first telemetry surgery has been completed. We are setting up a second facility to allow us to perform the lighting studies in parallel with the centrifuge studies. Females serving as subjects in the lighting studies will be examined later in the centrifuge facility.

Significance of Findings

The responses of the rhesus monkey's circadian clock to light are very similar to those of humans. We also see similarities in the range and variation of circadian periods, which are shorter than those of New World primates and much closer to those of humans. Rhesus monkeys are also suitable subjects for long-term centrifugation studies and offer distinct advantages over humans. We anticipate that the changes in circadian period seen in altered gravity in rhesus monkeys will add a new predictive element to models of circadian responses to space flight and low-gravity environments.

Project 5: <u>Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure</u>

PI: *Megan E. Jewett, Ph.D.*
Brigham and Women's Hospital/Harvard Medical School

***Research Focus*:** Use of light and performance mathematical models in schedule design

***Specific aims*:**
1. Further develop and refine the dynamic stimulus processing model by using data from existing four studies;
2. Perform validation analyses on the revised models;
3. Incorporate these refinements into models of neurobehavioral performance;
4. Develop a user-friendly predictive performance software program that can be used in-flight as a self-directed countermeasure.

Research Progress 11/1/2001-10/31/2002:

Specific aims proposed in this project are : Aim 1: To further develop and refine our Light Model using data from four studies of the effects on the human circadian system of different stimulus cycles of brief or extended and bright- or moderate-intensity light pulses. Aim 2: To validate the Light Model refined above in Aim 1 using data from four different studies of the effects on the human circadian system of single-cycle patterns of brief or extended bright light pulses and of sleep-wake/light-dark schedules with a wide range of periods. Aim 3: To incorporate the Light Model into our Neurobehavioral Performance Model and validate this model using data from the above 8 studies. Aim 4: To develop a user-friendly Circadian Performance Simulation Software (CPSS) for field applications.

We have been focusing on refinement of model as well as development of User friendly software during the last 12 months. To refine our pacemaker model as specified in Aim 1 we performed statistical time series analysis of one of the markers of circadian clock, Core Body Temperature (CBT) collected under Constant Routine conditions, as mathematical model consisting of a circadian signal and thermoregulatory noise. Signal in the model is represented as the solution of Light model and noise as Autoregressive process. We also used six different "Two Harmonic" models (TH) directly to fit CBT data with and without noise component with dependent and independent growth factors for each harmonic. Our model successfully extracted the low amplitude circadian signal from the noisy CBT data and allowed us to study the amplitude recovery dynamics observed in CBT data. Further this model could represent both the statistical and dynamical characteristics observed in CBT data. When we analyzed the TH models without AR processes we found the best fit to the data when the two harmonics had independent exponential factors, suggesting that that there is a dominant second harmonic component in the CBT data that must be taken into account in these models. These findings will be used to refine the current light model.

We have just released a greatly enhanced version of our Circadian Performance Simulation Software (CPSS 1.2). In CPSS 1.2 we redefined the phase relationship between the Light Model's state variables and the CBT so that the predictions are more stable over a wider range of operating conditions. We have incorporated many new graphical user interface enhancements within the software, including displaying a graphical representation of the protocol prior to simulating and allowing the user to manipulate simulation output graphs. This makes CPSS 1.2 an even more user-friendly simulation software package for the prediction of circadian phase and neurobehavioral performance.

Project 6: A Model of Circadian Disruption in the Space Environment

PI: *Michael Menaker, Ph.D.*
University of Virginia

***Research Focus*:** The effect of meals, melatonin, exercise, and dark pulses dysphasia

***Specific aims*:**
1. Evaluate the effects of constant conditions and of shift work schedules on both the maintenance of circadian rhythmicity in central and peripheral structures, and on temporal synchrony among them in a transgenic rat model system;
2. Ameliorate or prevent dysphasia by manipulating meal timing, melatonin administration, forced exercise and short pulses of darkness.

Research Progress 11/1/2001-10/31/2002:

Food-anticipatory activity (FAA) is the increase in locomotion and core body temperature that precedes a daily scheduled meal. It is driven by a circadian oscillator but is independent of the suprachiasmatic nuclei. Recent results that reveal meal-entrained clock gene expression in rat and mouse peripheral organs raise the intriguing possibility that the digestive system is the site of the feeding-entrained oscillator (FEO) that underlies FAA. We tested this possibility by comparing FAA and Per1 rhythmicity in the digestive system of Per1-luciferase transgenic rat. First, rats were entrained to daytime restricted feeding (RF, 10 days), then fed ad libitum (AL, 10 days), then food deprived (FD, 2 days). As expected, FAA was evident during RF and disappeared during subsequent ad lib feeding, but returned at the correct phase during deprivation. The phase of Per1 in liver, stomach and colon shifted from a nocturnal to a diurnal peak during RF, but shifted back to nocturnal phase during the subsequent ad libitum and remained nocturnal during food deprivation periods.
Second, rats were entrained to two daily meals at zeitgeber time (ZT) 0400 and ZT 1600. FAA to both meals emerged after about 10 days of dual RF. However, all tissues studied (all 5 liver lobes, esophagus, antral stomach, body of stomach, colon) showed entrainment consistent with only the nighttime meal.
These two results are inconsistent with the hypothesis that FAA arises as an output of rhythms in the GI system. The results also highlight an interesting diversity among peripheral oscillators in their ability to entrain to meals and the direction of the phase shift after RF ends.
In the course of doing these experiments we looked for effects on rhythms in isolated femoral arteries and found that these rhythms were completely unaffected by food restriction, in contrast to rhythms in "digestive" organs. We have now looked at a number of arteries and veins—all are rhythms with characteristic phases. We think the contrast between the digestive and the circulatory system in response to food is likely to be important and are now putting a large effort into understanding circulatory system responses to light and food.

These results have important implications for understanding the interaction of the mammalian circadian pacemaker with oscillators in peripheral tissues. It could ultimately lead to the development of countermeasures involving the timing of meals to facilitate circadian adaptation to both phase shifts and entrainment to non-24-hour day lengths.

Project 7: Circadian and Vestibular System Relationships

PI: Lawrence P. Morin, Ph.D.
State University of New York, Stony Brook

Research Focus: Three dimensional motions to stimulate the vestibular and circadian system

Specific aims:
1. Identify efferent and afferent anatomical connections between the vestibular nuclei and the intergeniculate leaflet;
2. Test the hypothesis that patterned moving light (an optokinetic stimulus) will functionally activate the vestibular and circadian systems;
3. Test the hypothesis that a non-locomotor, non-photic three-dimensional motion stimulus will functionally activate the vestibular and circadian systems, as measured by FOS induction in the IGL and circadian phase shifts.

Research Progress 11/1/2001-10/31/2002:

Interactions between the circadian and vestibular systems: We have hypothesized that angular and linear acceleration data is transmitted from medial vestibular nuclei afferents to the IGL and the SCN, and are capable of acting as non-photic modulators for circadian behaviors. If true, this hypothesis would imply the existence of a vestibular-circadian psychophysical function which could help develop techniques for amelioration of chronobiological upsets such as jet lag or insomnia via specific vestibular stimulation. To examine these hypotheses, we are carrying out neural tract tracing studies looking for afferent and efferent interconnectivity between vestibular and circadian control nuclei, as well as examining FOS expression in these nuclei after different types and degrees of vestibular stimulation in a nocturnal rodent with a well-studied circadian system, the Syrian hamster (Mesocritus aureus).

Choleratoxin/PHAL tracing of vestibular projections: We have examined anatomical patterns of afferent and efferent connectivity between vestibular and circadian systems using anterograde choleratoxin (CTX) and retrograde phaseolus vulgaris leucoagglutinin (PHAL) neural tract tracers. To date, 57 Syrian hamsters have had these tracers iontophoresed into the medial vestibular nucleus (MVe). Immunohistochemistry and image analysis have demonstrated the clear presence of monosynaptic afferent pathways from the MVe to the IGL, confirming earlier work with retrograde tracer injection into the IGL.

Green-fluorescent protein conjugated pseudorabies virus tract tracing (GFP-PRV):
GFP-PRV is a fluorescently-tagged modified herpes virus which infects neighboring neurons in a strictly retrograde fashion from the point of injection. Using focal injection of GRP-PRV in the SCN, we are able to examine visualize the entire SCN input pathway in a retrograde manner. Of 22 hamsters injected to date, 4 had clear focal injections strictly limited to the SCN; about 10 others were in surrounding nuclei and provide excellent controls. Pressure injections in the SCN, shows robust label of infected cells in the ipsilateral IGL, and to a lesser extent the contralateral IGL. Labeled cells were also observed in the oculomotor complex, the MVe, and cells of the solitary nucleus ipsilateral to the primary IGL label. This technique confirms the interconnectivity of the vestibular and circadian systems. As injection precision improves, we

will be able to examine the issue of whether this connectivity is restricted to specific domains within the target structures.

FOS expression following vestibular stimulation: The FOS protein is a well studied marker for neuronal activation and has been used in numerous circadian and vestibular studies. To date, 52 hamsters have been subjected to linear (anterior-posterior or lateral shaking) or angular (rotation through the inter-aural axis) vestibular stimulation under dark conditions. Differential FOS expression was noted among the vestibular nuclei based on stimulus condition. Animals subjected to linear acceleration at rates >1.0 Hz (>1 G at endpoints of movement) showed FOS expression in the SCN and IGL bilaterally. Animals subjected to angular acceleration at rates >60°/sec showed lateralization of FOS expression in the MVe and IGL, and approximately symmetrical distribution of FOS label in the SCN. Number of cells in the target nuclei displaying FOS expression under both conditions was positively correlated with magnitude of angular acceleration, although we have not yet determined the saturation plateau. Control (restrained) animals and animals subjected to low levels of angular or linear stimulation showed little or no FOS expression. These findings raise the questions of whether there is a "threshold" function for modulating circadian behavior based on vestibular-GHT input to the SCN, and whether there are modality-specific processing regions within the IGL.

Project 8: Long-Term Exposure to Dim Light Desynchronizes the Circadian System of Rats

PI: *Gianluca Tosini, Ph.D.*
Morehouse School of Medicine

Research Focus**:** Use of melatonin to synchronize rhythms

Specific aims**:**

1. Determine the effect of long-term exposure to constant conditions on circadian rhythms.

Research Progress 11/1/2001-10/31/2002:

The current levels of monetary support of our project is very limited (we have been awarded a grant for 50,000 $ total equal to 36,000 $ direct) and therefore our research activity and progress are limited (5% of my time and 20% of Dr. Fukuhara's time). In addition, the reduction of our budget (26%) has further reduced our efforts. The main aim of our research is to investigate how long term exposure to constant conditions (dim light at the intensity of 0.5-1 lux) affects the circadian organization of the rat.

We have held animals (36 wistar rats for each of the three experimental groups) in a room with constant dim illumination (< 1 lux) and monitored the locomotor activity for each animal by a computerized system. Then after 0, 5 and 60 days, we have sacrificed the experimental subjects by decapitation at six different times of the day (CT 4, 8, 12, 16, 20 and 24). Tissues (SCN, pineal, retinas, lung, liver, and skeletal muscle) were collected from each animal, immediately frozen and then stored at – 80 oC. mRNA levels, in the SCN were determined by quantitative in situ hybridization, while mRNA level in the other tissues, were determined by real time quantitative PCR. The expression of the gene Period1 was used as a marker of the phase of the circadian clock, while the expression of the arylalkylamine N-acetyltransferase (AA-NAT) gene was used as a marker of the phase of melatonin synthesis.

All the animals tested showed a clear circadian rhythm in locomotor activity for the whole duration of the experiment. In the SCN Period1 mRNA expression was rhythmic in 12L:12D, after 5 or 60 days in red dim light. Also in the retina Period1 and AA-NAT mRNA levels were rhythmic in 12L:12D and after 5 days. However, after 60 days in red dim light the rhythmicity was less clear. In the pineal gland Period1 and AA-NAT mRNA levels were rhythmic in 12L:12D and after 5 days in constant red dim light. After 60 days in constant dim light, in some animals, the expression of these genes was altered and out of phase).

Unfortunately, on May 21st the Neuroscience Institute at Morehouse School of Medicine was destroyed by a fire. As consequence of such an event some samples have been destroyed (all the lung, liver and skeletal muscle samples), and thus we will need to repeat the sampling in the next year. In conclusion, the experiments that we have performed during the last year have expanded and confirmed our preliminary results demonstrating once again that internal de-synchronization may occur in some animals (20-30%) when exposed to constant dim light. In addition, our data support the idea that locomotor activity is not a complete indicator of the circadian status and, therefore, indicate that internal desynchronization may occur also in individual that show a normal pattern of activity.

Project 9: Animal Model for Sleep Loss and Circadian Disruption

PI: Fred W. Turek, Ph.D.
Northwestern University

Research Focus: The effect of melatonin on circadian phase

Specific Aims:

1. Determine the effects of 12 hours of imposed wakefulness during the normal active and inactive periods on circadian rhythms, the sleep-wake cycle and neurobehavioral and motor performance measures in the mouse;
2. Treatment with either a physiological or pharmacological dose of melatonin at the beginning of the imposed period of wakefulness will alter the effects of this temporal desynchrony on the circadian clock, the sleep-wake cycle and/or neurobehavioral and motor performance measures;
3. Access to a wheel (exercise) when in the home cage, will alter the effects of the imposed periods of wakefulness on the circadian clock, the sleep-wake cycle and neurobehavioral and motor performance measurements.

Research Progress 11/1/2001-10/31/2002:

Our project addresses risk based goals one and two of the Human Performance Factors, Sleep and Chronobiology Team. Our progress in the past 12 months has placed us in an excellent position to move forward with examining the impact of both chronic partial sleep loss and circadian disruption on performance using our animal model. Data collection and analysis for specific aim one is underway.

During the past year we have set up and expanded the facilities and equipment for data collection. The current system will allow us to simultaneously measure sleep-wake and circadian variables in mice during a protocol that will result in circadian disruption and chronic partial sleep deprivation. Two animal rooms have been dedicated to this project, one with the capacity to record sleep in 16 animals and activity and core body temperature in a total of 28. In addition, an adjacent room has been equipped for neurobehavioural and motor performance testing.

In addition to ongoing data collection and analysis for specific aim one we have conducted a series of pilot studies to test the system. The first pilot study was to determine how much sleep the animals are able to achieve while in the slowly rotating wheel. These studies indicate that at 1 revolution per minute an animal is able to enter NREM sleep about 8-10% of the time but that they have no REM sleep. The second pilot study was to determine the pattern of sleep recovery during chronic partial sleep loss animals were subjected to 8 days of chronic partial sleep restriction. Specifically animals had a 20-hour period/day of imposed wakefulness, and the opportunity to sleep for only 4-hours per day during the light phase. Sleep was recorded for eight consecutive days during the 4-hour recovery period. The pattern of sleep during recovery changed across consecutive days of sleep restriction in particular the %NREM sleep while initially high after one day of restriction steadily declined over the next two days to be similar to baseline levels of %NREM sleep. While in comparison %REM sleep stayed elevated across consecutive days of sleep restriction. This pilot study indicated that animals change their strategy for sleep recovery depending on how many days they have been sleep deprived. This pilot data will help us determine which days to focus on for scoring and analyzing sleep records. The third pilot study was to determine strain difference in rotarod performance. In the current project we proposed to use two different inbred strains of mice, the C57BL6/J (C57) and B6C3F1/J (C3H). It has been hypothesized that the accelerating rotarod should not require any preliminary training to obtain satisfactory measures of performance. However, our data suggest that there are differences between our two strains of mice in both neuromuscular function and motor learning. In a small pilot study, C3H mice showed greater improvement over four consecutive days of testing and were able to stay on the rod longer than C57 mice. This difference in rotarod performance will prove to be an important consideration in future studies.

In summary, during the past year we have shown that animals can be successfully sleep deprived using a slowly rotating wheel and that animals will alter their strategy for recovery sleep during consecutive days of chronic partial sleep deprivation. Finally, we have shown that there are strain differences at baseline in both neuromuscular function and motor learning in the mice stains we will be using.

V. FUTURE PROGRAM DIRECTIONS

The Human Performance Factors, Sleep and Chronobiology Team has nine ground-based projects currently funded until 2003. In addition to the progress toward countermeasure development anticipated from the currently funded research projects, it is anticipated that the following four research questions which are not being addressed by the current research program will be addressed in the coming years:

Physical effects. Research is needed to determine how space flight or exposure to chronic sleep restriction and/or circadian disruption affect sleep- and/or circadian-mediated neuroendocrine, metabolic, neurologic or autonomic functions, particularly those relevant to risk mitigation (e.g., growth factors, nutrition, glucocorticoids, monoamines) during extended duration missions.

Monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and/or neurobehavioral performance during space flight. Research is needed to to validate methodologies that are portable and non-intrusive in the space flight environment to assess sleep and/or circadian rhythms.

Novel countermeasure development. Research is needed to determine how recent advances in the neurobiology of sleep and/or circadian rhythms (orexin/hypocretin system, circadian photoreception, output pathways that regulate sleep or circadian rhythms) can be used to develop countermeasures to adapt to and thereby maintain optimal neurobehavioral performance during exploration class space missions.

Age, gender and inter-individual differences. Research is needed to determine how age, gender and individual biological and behavioral characteristics alter sleep- and/or circadian-mediated physiologic responses to, and risk mitigation for, prolonged space flight.

William T. Shearer, M.D., Ph.D.
Team Leader

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
ANNUAL PROGRAM REPORT 2002

TEAM NAME: **Immunology, Infection, and Hematology Team**

TEAM LEADERS:

William T. Shearer, M.D., Ph.D., Team Leader
6621 Fannin, MC 1-3291, Houston, TX 77030
832-824-1274 (Telephone) / 832-825-7131 (Fax)
E-Mail: wtsheare@TexasChildrensHospital.org

Janet S. Butel, Ph.D., Associate Team Leader
One Baylor Plaza (MS: BCM-385), Houston, TX 77030
713-798-3003 (Telephone) / 713-798-5019 (Fax)
E-Mail: jbutel@bcm.tmc.edu

Gerald Sonnenfeld, Ph.D., Associate Team Leader
720 Westview Drive, S.W., Atlanta, GA 30310-1495
404-752-1586 (Telephone) / 404-752-1179 (Fax)
E-Mail: sonneng@msm.edu

TEAM PROJECTS AND PRINCIPAL INVESTIGATORS:

1. **Space Flight Immunodeficiency – William T. Shearer, M.D., Ph.D.**

2. **Viral Infections and Mucosal Immunity – Janet S. Butel, Ph.D.**

3. **Suspension, the HPA Axis, and Resistance to Infections – Gerald Sonnenfeld, Ph.D.**

4. **Human Hematopoietic Pleuripotential Stem Cells – Alan M. Gewirtz, M.D.**
   421 Curie Blvd (Rm. 713 BRB II/III), Philadelphia, PA 19104
   215-898-4499 (Telephone) / 215-573-2078 (Fax) / E-Mail:
   gewirtz@mail.med.upenn.edu

5. **Endogenous Opioid-Mediated Fas Expression in Stress-Induced Apoptosis –**
   Yufang Shi, D.V.M., Ph.D., 661 Hoes Lane, Piscataway, NJ 08854
   732-235-4501 (Telephone) / 732-235-5223 (Fax) / E-Mail: shiyu@umdnj.edu

6. **Microorganisms in the Spacecraft Environment - George E. Fox, Ph.D.**
   Department of Biology and Biochemistry, Houston, TX 77204-5001
   713-743-8363 (Telephone) / 713-743-8351 (Fax) / E-Mail: fox@uh.edu

SIGNATURE: William T. Shearer
William T. Shearer, M.D., Ph.D.

11-02-02
Date

TABLE OF CONTENTS

PAGE(S)

William T. Shearer, M.D., Ph.D.
Team Leader

I. ABSTRACT

In Fiscal Year 2 (2001-2002) of the current 3-year NSBRI grant cycle, the 6 projects of the Immunology, Infection, and Hematology (IIH) Team have come together in a powerful reinforcing manner to forge a unified program with significant discoveries and clear vision of where the team needs to go in the future. We have addressed each one of our goals and are anxious to move on with implementation of the countermeasures designed to achieve them. In essence, our team's goals are to: 1) reduce the risk of space flight conditions on bone marrow stem cells, and myeloid and lymphoid differentiated cells, 2) reduce the risk of astronauts developing new and reactivated viral infections, early cell death, and malignancy, and 3) reduce the risk of superstrains of microorganisms in space.

A year ago, we determined that the major gap in our team research program was the absence of experiments with the space flight conditions of radiation and microgravity. We have moved aggressively to fill that gap with experimental data that have been published in the peer-reviewed literature and accepted in competitive national meeting presentation formats. For example, we have published information describing enhanced morbidity and mortality of bacteria in small animals subjected to hindlimb-unloading model of microgravity. In preliminary work, we believe that this enhanced pathogenicity of bacterial challenge may be due to an effective loss of specific antibodies. In radiation-exposed animals, the amount of radiation (protons or γ- rays) absorbed by an astronaut going to Mars (3 Gy) acutely depresses both immune cells (myeloid and lymphoid cell types) and immune responses and alters the cytotoxic cytokine profile to render animals at risk of opportunistic infection. The mechanism for this loss of infection-fighting cells is likely due to apoptosis (early cell death). We have begun to examine the DNA and gene microorganism patterns taken from animals subjected to these conditions of microgravity and radiation to determine if their resistance has been enhanced—creation of super bugs.

Our next experiments will include evaluation of a direct countermeasures component of adding specific anti-microbe IgG antibodies to mice suspended in microgravity conditions and in animals exposed to space radiation to determine if this added component of immunity can counteract the loss of specific antibody function experienced by irradiated mice. Our plans for Fiscal Year '03 include the extension of the radiation to heavy metal ion (^{56}Fe) with the collaboration of Dr. Marcello Vazquez at Brookhaven National Laboratories. Also, we plan to evaluate a general countermeasure of nutritional supplements in animals subjected to conditions of microgravity and radiation on the premise that nutritional status deteriorates under the stressors of these conditions and that additional high-quality nutrients will boost immune responses. All of the team project leaders are being urged to submit competitive renewal applications for NSBRI funding early next spring to keep the momentum of the team accelerating and on its present course.

We expect that our experiments will both more clearly define more clearly the risks of immune compromise, infection, and cancer and result in very effective countermeasures to these serious risks. We want to enlarge the team membership with scientists in radiation immunology, microbiology, virology, and nutrition. We plan to extend our present collaboration with the NSBRI radiation, bone metabolism, and human performance teams.

II. INTRODUCTION *(modified from Strategic Plan, May 2, 2002)*

Background

Conditions of space flight pose a potential threat to an astronaut's immune system. These conditions include isolation, containment, weightlessness, increased radiation exposure, and enhanced microbial contamination. In all human and animal subjects flown in space, evidence of immune compromise, reactivation of latent virus infection, and development of a pre-malignant or malignant condition exists. Moreover, in all ground-based space flight model investigations, evidence of immune compromise and reactivation of latent virus infection is also observed. Studies are in progress to determine whether malignancy, too, will be observed in these experimental animals. All of these symptoms are similar to those found in a wealth of human pathological conditions where the human immune system is compromised, such as with stress, immunosuppressive drugs, infection, and radiation, and where reactivated, chronic virus infections and cancer appear as a natural consequence. Two examples where these clinical conditions are readily observed are Epstein-Barr virus (EBV)-driven lymphomas in transplanted patients and Kaposi sarcoma in acquired immunodeficiency syndrome (AIDS) patients. Given these known risks to the immune system, it is highly appropriate, indeed imperative, that NSBRI researchers carefully investigate the effects of space flight conditions on human immunity, infection rate, and cancer rate.

Risks

We have chosen to define the risks of spaceflight in terms of the IIH Team's research plans:

Risk 1: Radiation Damage to Stem Cell and Immune System
Risk 2: Microgravity and Stress Effects on Immune System and Resistance to Infection
Risk 3: Reactivated Latent Infections
Risk 4: Malignancy
Risk 5: Altered Microbes

In all of the risks proposed for the Immunology, Infection, and Hematology Team, the principal focus must be the underlying stem cell damage that produces the immunological deficits that create the observed risks (e.g., infections on space flights occur because of underlying immune damage).

Goal 1: *Reduce risk of space flight conditions (isolation, containment, stress, microgravity, and radiation) damaging the human bone marrow stem cell and differentiated immune cells.*

Goal 1 covers Risks 1 and 2.

Goal 2: *Reduce risk of astronauts developing new and reactivated infections, premature immune cell death, and malignancy.*

Goal 2 covers Risks 3 and 4.

Goal 3: *Reduce risk of space flight-induced development of superstrains of microbial organisms.*

Goal 3 covers Risk 5.

III. RESEARCH PROGRAM STRUCTURE AND DESIGN
(modified from Strategic Plan, May 2, 2002)

Historical Basis

The IIH Team seeks to reduce the risks defined above. The first step in this direction is to firmly establish the molecular and cellular consequences of exposure of the human stem cell and differentiated immune cells (peripheral blood, tissue, mucosa) to the conditions of space flight. Knowing the precise damage to the human immune system will greatly facilitate the development of a countermeasures program. A recent example of the team's progress will illustrate this concept. For 25 years, it has been known that humans in space and in the space-equivalent model of the Antarctic winter display weak, delayed-type hypersensitivity skin reactions to recall antigens. This skin test is a very crude method of assessing immune system deficiencies. Our team has greatly advanced knowledge of the precise molecular events taking place in the human immune system in response to space flight equivalent conditions by determining recently that TH2 $CD4^+$ T-cells reduce the output of the proinflammatory cytokine interleukin-10 (IL-10) in humans in the Antarctic winter. We plan also to define the early cellular changes in reactivated viral infections and the role of the stress (hypothalamic-pituitary-adrenal axis) system in creating secondary immunodeficiency, enhanced infection rates, and development of malignancy. In addition, we will strive to understand the potential for the emergence of superstrains of bacteria, viruses, and fungi in irradiated hosts. With this new information, we will be able to much better plan for an effective countermeasures program involving shielding (structural, chemical) for radiation, stress-reduction programs, nutritional, pharmacologic and immunologic prevention and treatment programs (for example, gene or cell inhibitors, immunizations and antibody, cytokine, or stem cell therapy), and a microbiocidal program for prevention of opportunistic infection.

Following the award of the present three-year cycle of grant support that began in September 2000, the Immunology, Infection, and Hematology Team was reconstituted with six projects that possessed a cohesive critical mass of investigators and projects (see **Table 1**). The principal focus of five of the projects is the harm to the human immune system that might result from immunosuppressive factors in long-term space flight. These factors include deep space radiation, microgravity, physical and psychological stress, isolation and containment, microbial contamination, altered microbial virulence, and sleep deprivation. All of these factors have produced alterations in immune responses of humans and animals flown in space or their counterparts using earth-bound space-equivalent models. There is collaboration of investigators within a project and between projects. The leadership of the team (Drs. William T. Shearer, Janet S. Butel, and Gerald Sonnenfeld), for example, participate in certain aspects of many of the projects (see **Table 2**). Projects 1-5 deal with uncovering the pathogenic mechanisms of risk factors, whereas Project 6 concerns the detection system for pathologic microbes, currently bacteria, but in the future viruses and fungi, that would cause immunosuppression.

Selection of Team Projects

In terms of an overall **team selection of priorities** for a cohesive research program for the **risk-based goals**, we have decided to focus on two types of immunosuppresive factors—radiation and microgravity, using: 1) radiation viral, and immune studies and 2) anti-orthostatic (microgravity) model and microbial monitoring studies, respectively. All of the six projects will support these two team studies.

Team Project 1: Radiation, Viral, and Immune Studies

In the **first of these team projects**, the co-investigators will include Drs. Shearer, Butel, Ling, Conner, Reuben, and Rosenblatt, members of the NSBRI Immunology, Infection and Hematology Team from Baylor and Dr. Daila Gridley from Loma Linda University (LLU). Selected strains of mice (e.g., BALB/c, C57 black) will be exposed to proton and gamma ray radiation and subsequently to murine viruses (e.g., gamma 68, polyomavirus), in an attempt to determine the combined effects of space radiation and latent virus infection on the immune function of study animals. This first approach will examine the simultaneous effects of radiation and infection and will then be followed by a sequential approach of infection first and radiation second, the likely scenario for human space travelers to Mars. The dose of radiation that will be utilized initially (3Gy, the estimate of radiation received by astronauts on a Mars Mission) will be that used by Dr. Gridley and her colleagues who have demonstrated rapid and profound alterations in immune cells and immune responses in murine subjects. Replicate and controlled experiments will be performed by both the LLU site and the Baylor site to insure that the same methods are followed at both sites and that the results of the experiments at Baylor confirm those of LLU. If gamma radiation proves to be equivalent to proton radiation in terms of effects upon the immune system (e.g., spleen cell T-cell response to non-specific stimuli and specific antigen stimulation; plasma antibody formation to neoantigen; spleen lymphocyte subset distribution), it may be possible to avoid transfer of mice between institutions, as Baylor has a source of gamma radiation.

In addition to examination of the effects of radiation and latent virus infection on immune cells and immune responses, study animals will be evaluated for the development of tumors and blood malignancies. This will be carried out with the assistance of Dr. Cory Brayton, a veterinary pathologist at Baylor, who has agreed to collaborate on this project.

Also, Dr. Alan Gewirtz at the University of Pennsylvania has begun collaborative NSBRI studies with Dr. Elizabeth Sutherland at the Brookhaven National Laboratory (BNL) with bone marrow-derived human stem cell lines. These cell lines were exposed to heavy metal ion (Fe^{56}) radiation and subsequently tested by standard hematologic assays for ability to form colonies of cells in the myeloid series: granulocytes, erythroid cells, and platelets. In the future, similar experiments will be performed at LLU, where the effects of proton and gamma radiation will be evaluated in these same assays. Because the preparation of human stem cells from donor bone marrow also yields precursor cells in the lymphoid system, it will be possible to simultaneously evaluate the effects of the various types of radiation on the development of T- and B-cells. Similarly, macrophages, monocytes, and stromal cells could be evaluated. The methods of analysis of these various types of immune cells could include measurement of cell growth factors (e.g., IL-3, IL-6, IL-7, TGF-β), apoptosis gene regulation (e.g., gene array assay), and cell repair pathways. These studies would include the collaboration of Drs. Gewirtz, Reuben, Rosenblatt, and Gridley.

Also, peripheral blood human stem cells will be harvested by pheresis in subjects given granulocyte-monocyte colony-stimulating factor (GMCSF) to increase the number of circulating stem cells at the M.D. Anderson Cancer Center. Dr. James Reuben will utilize these cell harvests in similar radiation studies and evaluate dendritic cell (#1 and #2 types) function in the presentation of antigens to lymphocytes.

In both bone marrow and peripheral blood stem cell preparations, evidence of genetic damage will be investigated by examination of progenitor cells for chromosomal breaks. These measurements will yield important information on the possibility that radiation of human stem cells might result in leukemogenesis and tumorigenesis.

Future collaborative studies have been proposed for the Radiation Team, in which the use of surrogate markers could be used to assess the risks of tumor development in irradiated animals. Surrogate markers would greatly reduce the time needed to evaluate tumorigenesis and to observe exposed animals for cancer development. For the current Fe^{56} irradiated rat breast tumor model, one such surrogate marker might be the appearance of epithelial cells in the peripheral blood that herald the development of breast cancer. In addition to the detection of epithelial cells, it might be possible to examine the gene imprints of these cells by gene array assays. Such studies might yield a characteristic dysregulation of normal gene activation that would be predictive of breast cancer in this animal model.

This first team project addresses Goals 1 and 2 (space flight conditions damaging immune cells and development of new or reactivated infections, premature immune cell death and malignancy, respectively), but with the assistance of Project 6 we will also be addressing Goal 3, the detection of genetically altered (possibly supervirulent) strains of environment or host microorganisms with the use of DNA probes (see Section 4.5 and Table 1). Originally designed to develop genetic probes of spacecraft bacterial contaminants, Project 6 will adapt the genetic probes to detect contaminating viruses and to detect the emergence of both bacteria and viruses made more virulent by exposure to spaceflight conditions, principally radiation.

Team Project 2: Anti-Orthostatic (Microgravity) Model and Microbial Monitoring Studies

The second of the team projects will involve the anti-orthostatic (AOS) (hind-limb suspension) model and addresses Goals 1 and 2. The subgroup on hind-limb suspension felt that it was important that standardized procedures be used by the group to allow for comparison of results across projects. The exact caging and suspension techniques do not have to be identical, but the parameters used for setting up the suspension should be uniform. In the future, all suspension will be set up with uniform parameters. Suspension will be carried out with a 15 to 20 degree head-down tilt. The tilt will be measured at the body axis of the animal. Controls for all experiments will consist of at least vivarium controls in standard housing and restraint controls with animals in suspension hardware but with all four paws on the ground and bearing weight. Additional controls may be added at the investigator's discretion. Vivarium controls will be in individual cages, not housed with multiple animals per cage. All hind-limb suspension experiments will commence in the morning between 9 and 11 AM. Dr. Sonnenfeld has already had remarkable success with these procedures in demonstrating an at least two-fold increase in death in AOS mice challenged with *Klebsiella pneumoniae*.

We plan to examine changes in differential gene expression in the immune system using commercially available low-density nylon-based gene array technology. Each blot contains 23 specific and two housekeeping genes. Arrays are available that can detect specific sets of genes that are grouped based on their association with known signal transduction pathways. Once changes in particular pathways are identified, pathway-specific gene arrays are available to elucidate changes in expression of pathway-specific genes. In addition, arrays are available to detect changes in gene expression of mouse cytokines, interleukin receptors, chemokines, chemokine receptors, inflammatory cytokines, T-cell activation markers, and B-cell activation markers. The approach is to catalog global changes in the immune system (cell distributions, cytokine production, gene expression) utilizing the AOS mouse model, and then to determine any additive effects of concomitant virus infection and/or proton irradiation on those patterns. This comprehensive approach will provide new insights into mucosal and systemic host immune functions. Additionally, comparison of the results from the animal model and human studies should provide directions for future studies.

William T. Shearer, M.D., Ph.D.
Team Leader

National Space Biomedical Research Institute
IMMUNOLOGY, INFECTION AND HEMATOLOGY

Table 1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BUTEL/Viral Infections and Mucosal Immunity	1-5	Pharmacological Agents	AOS; IR; Humans	Detect immune damage; Measure infection	Formulate antiviral reagents	
FOX/Microorganisms in the Spacecraft Environment	3-5	Pharmacological Therapy	Microbes	Develop microbe detection system	Perfect microbe detection system	Flight test detection system
GEWIRTZ/Effect of Deep Space Radiation on Human Hematopoietic Stem Cells	1,3,4	Stem Cell Therapy, Cancer Chemotherapy	In Vitro Stem Cells	Detect damage to stem cells	Formulate autologous stem cell transplant	Test stem cell Transplantation in space
SHEARER/Space Flight Immunodeficiency	1,3,4	Antibody Therapy, Stem Cell Therapy	IR; Humans	Measure apoptosis in thymocytes	Adapt Earth Rx strategies	Perform Rx in space
SHI/Endogenous Opioid-Mediated Fas Expression in Stress-Induced Lymphocyte Apoptosis	1,2,4	Cytokine Therapy	AOS, IR	Measure HPA in AOS, IR	Formulate drug treatment program	
SONNENFELD/Suspension, the HPA Axis and Resistance to Infection	2-5	Pharmacological Therapy	AOS, IR	Determine role of different stressors on immune responses	Formulate anti-stress program	Test program in space

Risks Key: 1) Radiation damage to stem cell and immune system; 2) Microgravity damage to immune system; 3) Reactivation of latent viral infections; 4) Malignancy; 5) Altered microbes

Definitions: AOS, anti-orthostatically suspended murine model; IR, irradiated mice; Humans, humans exposed to Antarctic winter or isolation in capsules; Microbes, microbial detection systems; HPA, hypothalamic pituitary axis; Rx, treatment

William T. Shearer, M.D., Ph.D.
Team Leader

National Space Biomedical Research Institute
IMMUNOLOGY, INFECTION AND HEMATOLOGY PROGRAM

Table 2. Integration Activities

	BUTEL	FOX	GEWIRTZ	SHEARER	SHI	SONNENFELD
Internal Communication (E-mail, telecons, retreats, scientific meetings for all projects)	• Shearer • Sonnenfeld • Fox • Gridley (LLU) • Lugg (ANARE) • Pierson (NASA) • Larina (IBMP)	• Butel • Sonnenfeld	• Shearer • Shi • Sutherland (BNL)	• Butel • Gewirtz • Fox • Shi • Sonnenfeld • Gridley • Lugg • Pierson • Dinges (Psych)	• Sonnenfeld • Butel	• Shearer • Butel • Vazquez (Rad)
Integrated Experiment Development	Model Radiation and AOS Studies • Shearer • Gridley • Reuben • Sonnenfeld • Pierson • Larina • Lugg • Fox	Collaborative Gene Probe Studies • Butel • Sonnenfeld	Model Radiation Studies • Reuben • Shearer	Model Radiation and Human Exposure Studies • Butel • Reuben • Lugg • Gridley	Model AOS Studies • Gewirtz	Collaborative Gene Probe Studies • Butel • Fox
Sample Sharing	Blood, Urine • Shearer • Reuben • Larina	Microbes • Butel • Sonnenfeld	Stem Cells • Reuben • Shearer	Blood • Butel • Reuben • Dinges	Blood • Sonnenfeld • Butel	Blood • Vazquez
Synergistic Studies of Opportunity	Antarctic Winter • Shearer • Lugg • Pierson	Radiation, AOS • Butel • Sonnenfeld	Radiation • Reuben • Shearer • Kennedy (Rad. Team)	Antarctic Winter, Sleep Deprivation • Butel • Dinges • Lugg	Radiation • Sutherland • Kennedy	Radiation, AOS • Butel
Development of Computer Model of Integrated Human Function						

Definitions: ANARE, Australian National Antarctic Research Expedition; NASA, National Aeronautics and Space Administration; IBMP, Institute for Biomedical Problems, Moscow; LLU, Loma Linda University; Psych, Psychosocial Team; Rad, Radiation Effects Team; BNL, Brookhaven National Laboratory; AOS, Antiorthostatic Suspension

IV. RESEARCH PROGRAM ACCOMPLISHMENTS

Team Project 1: Radiation, Viral , and Immune Studies

a. The Effect of Irradiation on Murine Polyomavirus Replication and Persistence in Mice. *JS Butel, S Zhang, BN Lee, DY Shen, JM Reuben, WT Shearer*

Rationale: There is concern that long-duration, deep space flight will alter the human immune response, leading to "space flight immune deficiency", reactivation of latent viruses, and increased viral infection and disease, including cancer. The specific agents being studied are the polyomaviruses, small DNA viruses with strong oncogenic potential that are known to establish persistent infections and to undergo reactivation when the host immune system is compromised, leading sometimes to viral disease and cancer. Murine polyoma virus (PyV) is a naturally occurring polyomavirus of mice that is genetically related to the human polyomaviruses. Another major risk to the success of space missions is chronic exposure to ionizing radiation, which can damage host cells and immune function.

Methods: Six- to 8-week-old BALB/c mice are used; some are given 3 gray whole-body gamma irradiation. Mice are inoculated intraperitoneally with different amounts of PyV (25–128 hemagglutinating units). At different times postinoculation, tissues are collected, weighed and DNA extracted. Virus is detected using a specific PCR method (1–2 μg DNA/reaction).

Results: We monitored virus replication in 8 tissues (salivary gland, kidney, liver, lung, spleen, mammary gland, skin and bone) at different time points after infection (days 3, 7, and 20) of normal mice. Length of persistence of virus in different tissues was dependent on the dose of virus inoculated. Some tissues retained virus at detectable levels for up to 20 days, whereas other tissues had cleared the virus by day 20. Having established the parameters of virus infection and replication in normal animals, experiments have been initiated to evaluate the effect of gamma irradiation on host control of viral infection. In preliminary experiments, we have found that gamma irradiation delayed the clearance of virus infection, with persistence of virus being observed in kidney, liver, spleen and salivary gland at least through day 31. Immune function assays are in progress in collaboration with Dr. J. Reuben to correlate immune status with virus detection. Follow-up long-term experiments will examine the effect of gamma irradiation on reactivation of latent viral infections and tumor development.

This mouse model will allow targeted studies of the effects of irradiation on host immune function, virus infection, and tumor development. Such data will help define the potential risk of these combined factors to long-duration space flight and will allow tests of countermeasures.

b. The Effect of Gamma Irradiation on the Immune Responses of Mice with Polyoma Virus Infection. *JM Reuben, JS Butel, BN Lee, S Zhang, DY Shen, WT Shearer*

Background: There is concern that protracted space flight may adversely affect the human immune response by altering the delicate balance between Th1 (IL-2, IFN-g, and TNF-a) and Th2 (IL-4 and IL-5) cytokines to a level that may result in the reactivation of latent viruses, and increased viral infection and disease, including cancer. The specific agents being studied are the polyomaviruses, small DNA viruses with strong oncogenic potential that are known to establish persistent infections and to undergo reactivation when host immune system is compromised, leading to viral disease and cancer. Murine polyoma virus (PyV) is a naturally occurring polyomavirus of mice that is genetically related to the human polyomviruses. Another major risk to the success of the space missions is chronic exposure to ionizing radiation, which can damage host cells and immune function.

Methods: We used seventy 6-8 week old Balb/c mice to study the effects of gamma irradiation and PyV infection on T-cell proliferation and cytokine production. Of the 70 mice studied, 48 mice received 3 Gy of gamma irradiation on Day 1 (Groups B and D). The 22 non-irradiated mice were split into 2 groups; 12 were inoculated intraperitoneally with PyV on day 3 (Group C) and 10 were not inoculated with PyV (Group A). Among the 48 irradiated mice, 36 were inoculated intraperitoneally with PyV on day 3 (Group D) whereas the other 12 mice were not inoculated with PyV (Goup B). Mice were sacrificed on days 3, 7, 12, 17, 24, and 31, spleen cells harvested and activated in vitro with Conanavalin A (Con-A) to assess the proliferation and the production of Th1 (IL-2, IFN-g, and TNF-a) and Th2 (IL-4 and IL-5) cytokines by T cells.

Results: Compared with non-irradiated mice (Groups A and C), Con-A-stimulated spleen cells of irradiated mice (Groups B and D) produced significantly lower levels of IL-2 ($P = 0.001$), IFN-g ($P = 0.001$), TNF-a ($P = 0.001$), IL-4 ($P = 0.001$), and IL-5 ($P = 0.003$) on day 3, prior to inoculation with PyV. Similarly, the proliferation of Con-A-stimulated spleen cells of irradiated mice was significantly less than spleen cells of non-irradiated mice ($P = 0.001$).

PyV infection of irradiated mice did not adversely affect the immune function up to day 12 post-infection; however, on day 31, post infection with PyV infection, spleen cells of irradiated mice (Group D) produced significantly lower levels of IL-2 ($P = 0.01$), IFN-g ($P = 0.01$), TNF-a ($P = 0.01$), and IL-5 ($P = 0.019$) than spleen cells of irradiated mice without PyV infection (Group B). Group D mice produced significantly less Th1 cytokines, IL-2 and IFN-g, than non-irradiated mice that were inoculated with PyV (group C) at all time points tested.

Conclusions: We have established a mouse model system to study the combined effects of radiation and virus infection on the host immune system and virus infection. Our preliminary data suggest that there are potential risks for the host from the combined exposure to gamma irradiation and infection with virus that suppresses Th1 cytokine production.

c. Effect of Deep Space Radiation on Human Hematopoietic Stem Cell Function.
M Stanislaus, P Bennett, P Guidal, G Danet, J Luongo, B Sutherland, A Gewirtz

Astronaut flight crews on long-term missions in deep space will be exposed to cosmic radiation consisting of high energy particles (predominantly $Fe56^+$), and high doses of low energy transfer (LET) elements. The effect of this environment on DNA damage and stem cell function is presently unknown, and important to define. We initially investigated the biologic consequences of exposing human hematopoietic stem and progenitor cells (HSC; HPC) to Fe26+ particles generated by the Relativistic Heavy Ion Collider at BNL, and for more repetitive, confirmatory, experiments, to gamma-radiation imparting similar amounts of energy, using a Cs 137 source. Normal marrow mononuclear cells (MNC) were exposed to gamma-irradiation ranging from 15 cGy to 140 cGy. Effects on HPC were assessed by colony forming unit (CFU) assays, and HSC by long-term cultures (LTCIC) and SCID mouse repopulation assays. A 15 cGy exposure resulted, respectively in a 19%,24%,25% and 33% decline in CFU-GM, BFU-E, CFU-Meg, and CFU-GEMM, while a 140 cGy exposure resulted, respectively, in 67%,84%,98% and 93%

colony declines. Effect on HPC proliferative capacity was assessed by counting cell s/colony in CFU-GM and BFU-E. BFU-E, not surprisingly, were more severely effected manifesting a 82% decrease in cells/colony compared to 61% in CFU-GM. Gamma-radiation also had a substantial effect on LTCIC with 48% and 99% decreases with 15 cGy and 140 cGy doses respectively. These results are consistent with an experiment performed on MNC exposed to BNL generated $Fe56^{+}$. Effect of these doses on SCID repopulating cells (5 mice/group) is being evaluated. Ionizing radiation (IR) also induces difficult to repair clusters of complex DNA damages consisting of oxidized bases, a basic sites, and breaks on opposing strands within a few helical turns. In whole cells, even low doses of IR resulted In complex damages accounting for -30% of al I damages found. These results suggest that: I] human HPC and HSC are very sensitive to even low doses of radiation of the type to be anticipated in travel away from earth orbit, and 2] further studies are needed to both quantitate the risk to flight crews on deep space voyages, and to develop effective countermeasures.

d. Antarctica Winter Isolation Alters the Pro-Inflammatory: Anti-Inflammatory Cytokine Balance in Humans Experiencing Reactivation of Latent Viruses: Implications for Chronic Viral Infection and Development of Malignancy.
WT Shearer, DJ Lugg, HM Rosenblatt, BN Lee, SG Cron, EO Smith, PM Nicholis, RM Sharp, K Rollings, JM Reuben

Background: Space flight conditions of stress, isolation, containment, microbial contamination, microgravity, and radiation weaken immune responses and predispose to infection and cancer. Pro-inflammatory cytokines such as IFN-γ and anti-inflammatory cytokines, such as IL-1αRA, and IL-10 are frequently measured in suspected pathological conditions where the balance between TH1 and TH2 cytokines is thought to exert an important immunoregulatory function. Since the 8-month Antarctic winter-over presents several conditions of space flight that might alter immune balance of latent virus infection, we measured pro- and anti-inflammatory cytokines in human volunteers during the Antarctic winter.

Methods: Human volunteers (adult males 24-45 yr) were stationed at the Australian Antarctic outposts of Davis (n=10) and Casey (n=11), serving as experimental subjects, and on the supply station of Macquarie Island (n=7), serving as control subjects. In April 1999 the experimental subjects were isolated by ice, whereas control subjects still had access to the mainland. Monthly plasma specimens were collected, stored at -70°C, and later packed on dry ice and airlifted to Houston. An enzyme-linked immunoassay (ELISA) was used for the determination of cytokines. Statistical analysis of data utilized an analysis of covariance for repeated measures for the change of plasma cytokine concentrations with respect to time and students T-test for the significance of cytokine values between experimental and control values at individual time points.

Results: There was a significant time-dependent decrease ($P = .042$) in the plasma levels of IL-10 in study subjects (Davis and Casey) during the period of isolation in comparison with the control subjects stationed on Macquarie Island. Bimonthly comparisons between study and control subjects revealed significant differences from March through September ($P \leq .036$). For example, the adjusted value (mean ± SEM) in September for the study subjects (6.22 ± 0.31 pg/mL) was 18% lower than that for the control subjects (7.59 ± 0.53 pg/mL). Study subjects exhibited a time-dependent decrease in plasma IL-1RA levels in comparison with control subjects ($P = .053$). Bimonthly comparisons of study and control subjects' values revealed statistically significant differences in the isolation period ($P \leq .034$). The adjusted value (mean ± SEM) in September for the study subjects 24.1 ± 1.01 pg/mL) was 42% lower than that for the control subjects (42.8 ± 1.06 pg/mL). During the period of isolation, there was a significant time-dependent difference in the plasma level of IFN-γ between the study subjects and control subjects ($P = .039$). Bimonthly comparisons of study and control subject values revealed statistically significant differences in the isolation period ($P \leq .045$). The adjusted valued (mean ± SEM) in September for the study subjects (11.6 ± 1.05 pg/mL) was 43% higher than that for the control subjects (8.09 ± 1.10 pg/mL).

Conclusion: IL-10 and IL-1RA are potent anti-inflammatory cytokines that are capable of shifting the balance of pro-inflammatory and anti-inflammatory cytokines. We conclude that the Antarctic winter-over model of space flight demonstrated a tipping of the cytokine balance toward a pro-inflammatory profile—findings consistent with latent virus activation of T-cells.

e. **Polyomavirus JCV Reactivation and Shedding in Healthy and Immunocompromised Hosts: Implications for Space Travel.** ***JS Butel, JA Lednicky, RA Vilchez, F Visnegarwala, DE Lewis, CA Kozinetz, WA Keitel***

Background: Space flight is known to affect the immune response, and weakening of normal immunity can have a major impact on the host's ability to control infections. An important issue is how serious a medical risk infectious diseases pose to the success of long-duration space flight. Because all humans are infected for life with latent and persistent viruses, we are interested in whether space flight-induced immune deficiency may allow reactivation of latent viruses, leading to viral disease and malignancies. We have used polyomavirus JC virus (JCV) as a representative persistent virus and HIV-infected subjects as models of individuals with immunodeficiency. We determined the pattern of JCV shedding over time in healthy adults and the frequency of virus reactivation among individuals with impaired immune responses.

Methods: We performed two prospective human cohort studies: (1) Shedding of JCV was monitored longitudinally in 30 healthy adults over 14 months; and (2) Reactivation of JCV was determined in single samples from 70 HIV-infected patients receiving highly active antiretroviral therapy (HAART), compared to 68 HIV-uninfected individuals serving as controls. Samples of blood and urine were collected and analyzed by polymerase chain reaction and sequence analysis using JCV-specific primers against different regions of the virus genome.

Results: JCV viruria over time among the 30 healthy adults was 46.7% (≥1 positive urines over 14 months) with shedding occurring more often in persons ≥40 years of age ($p<0.03$). The urinary excretion of JCV among healthy volunteers was more common in the fall and winter months ($p=0.05$). In the HIV-infected cohort study, JCV shedding was more common in HIV-positive patients but not significantly different compared to the HIV-negative group (22/70, 31% vs. 13/68, 19%; $p=0.09$). HIV-positive individuals did not display the age-related pattern of JCV shedding ($p=0.13$) typical of the control group ($p=0.01$). Among HIV-infected patients, JCV excretion was significantly correlated with lower CD4 cell counts ($p=0.03$). No JCV sequences were detected in the blood of any of the patients in the two cohort studies.

Conclusion: These results suggest that the reactivation of JCV over time varied among individuals and by season. JCV shedding among patients with partial immune function (HIV-infected patients receiving HAART) was increased in patients with modest reduction in immune capacity. These findings support the potential for virus reactivation as a result of space flight-induced immune suppression.

Team Project 2: Anti-Orthostatic (Microgravity) Model and Microbial Monitoring Studies

a. Suspension, the HPA Axis, and Resistance to Infection. *G Sonnenfeld*

1) The hypothesis bring tested is: antiorthostatic (AOH or hindlimb) suspension of mice, a model for some of the effects of space flight on the immune system, results in altered resistance to infection with pathogens. Testing of this hypothesis will provide data to allow development of future studies to determine if space flight affects resistance to infection and if countermeasures can be developed to prevent any detrimental effects.

The specific aims of the study are:

A) to expand the range of infections altered by AOH suspension. We have already shown that resistance to some infections that are not likely to be risks during space flight has been altered by AOH suspension and we now wish to determine if infections that could be a risk during space flight are affected by the suspension model.

B) to determine the mechanism of alteration of resistance to infection induced by AOH suspension. Although previous studies have shown that immune responses are altered by space flight, we now wish to extend these studies to determine the role of neuroendocrine system in regulating infections. This will be carried out using two approaches. The data obtained from experiments using both approaches will be integrated to allow for development of a model for the mechanism(s) of the effects of hindlimb suspension on resistance to infections.

2) We have completed our study on the effects of hindlimb unloading suspension on resistance to infection with *Klebsiella pneumoniae*. We have found that suspension enhanced mortality of infected mice significantly compared to controls. We also found that suspended mice had impaired ability to clear the *K. pneumoniae*. We also carried out a study to determine the effects of hindlimb suspension on infection of mice with *Pserudomonas aeruginosa*. We found that suspension resulted in enhanced mortality of mice infected with *P. aeruginosa*. It also appears that production of specific IgM and IgG antibodies directed against *P. aeruginosa* was significantly inhibited in the suspended mice.

We received a contract from a Japanese corporation, the Amino-Up Chemical Company, to test the effects of a nutritional supplement, AHCC, in our model. Our results show that pretreatment with continued treatment of mice throughout the suspension period resulted in protection of hindlimb-suspended mice from infection with *Klebsiella pneumoniae*.

We also continued our studies on the effects of catecholamines on bacterial growth a virulence. We were able to show that growth of anaerobic bacteria was affected by treatment with catecholamines. Treatment of bacteria with the hormone DHEA inhibited bacterial growth. Therefore, we will be exploring use of hormones and nutritional supplements as countermeasures.

In collaboration with Drs. Fox and Willson, we have begun studies using array analysis to determine the proteins that are enhanced when gram-negative bacteria have growth enhanced by catecholamines. We are also about to begin studies with Dr. Butel on the effects of catecholamines on growth of viruses.

Finally, we have agreed with Dr. Vazquez of the Radiation team to look at cytokine profiles of mice he currently is exposing to radiation.

3) The results of the current research are very much inline with the proposed studies described in the original proposal. We will continue in the next year with the work as outlined in the original proposal.

4) We will, in the next year, expand our studies with suspension to include gram positive bacteria. We will study the mechanisms involved in the effects of suspension on resistance to infection and the effects of catecholamines on bacterial growth. We will also look at the practicality of expanding development of countermeasures that we have uncovered

b. Apoptosis in Thymocytes in Anti-Orthostasis. ***Y Shi***

The funding for our project was started on April 1, 2002. In the last few moths, we have established the mouse antiorthostatic suspension model. We have identified several potential variables and now stabilized our experimental system. We have found that suspension could induce significant reduction in both thymocytes and splenocytes. Flow cytometrical analysis revealed that immature $CD4^{+}CD8^{+}CD3^{low}$ thymocytes are most sensitive to suspension-induced reduction. Significant reduction could be observed as early as 2 days after suspension. Mature $CD4^{+}CD8^{-}$ and $CD4^{-}CD8^{+}$ cells are also being affected, though longer suspension is required. In the spleen, the changes varies in different populations. $CD4^{+}$ T cells showed a sharp reduction at 2 days after suspension while $CD8^{+}$ T cells and $CD19^{+}$ B cells showed a gradual reduction from day 2 to day 7. It should be point out that the changes in different populations of lymphocytes does not exactly correlate with the published data obtained from rats flew to the space. Different variables in the two systems will be analyzed in our future experiments.

We have found that suspension could increase the expression of Fas expression on splenocytes. Interestingly, suspension-induced reduction in the splenocytes could be blocked by administration of antibody to FasL (60% vs. 13%). Interestingly, stress-induced thymocytes reduction could not be affected by anti-FasL, indicating that in response to suspension stress, splenocytes and thymocytes die via different mechanisms. We also found that opioid receptor antagonist, neltraxone, could also effectively block suspension-induced reduction in splenocytes, bout not in thymosytes.

Although our data from the anti-FasL experiment clearly indicate that Fas-mediated apoptosis is involved in the splecocytes, we also found that suspension also induced some increase of $CD4^{+}$ cells in bone marrow, indicating that except apoptosis, lymphocyte redistribution may also contribute to the reduction in the splenocyte of mice subjected to antiorthostatic suspension.

Our studies have clearly demonstrated that the Fas-FasL interaction is critical for splenocytes apoptosis in suspended mice. Since it has been reported that free radical reactive species are also important in stress-induced lymphocyte death, we tested whether there is an interaction between reactive species and Fas. We found in an in vitro experiment that Fas and H2O2 could synergistically induce apoptosis in freshly isolated splenocytes. The effects of glutathione, a free radical scavenger, are now being evaluated in the rescue of lymphocyte apoptosis in the mouse antiorthostatic suspension model.

We have also studied the effect of anti-orthostatic suspension on T cell proliferation induced by anti-CD3 stimulation. At different time after suspension, splenocytes were isolated and equal number of live cells were activated and their proliferation was assay by [3]H-thymidine incorporation. We found that the most significant reduction in cell proliferation was at 2 days after suspension. Interestingly, this reduction was blocked by anti-FasL. Therefore, the Fas and FasL interaction also plays an important role in activation-induced cell proliferation. We have also established that Fas-mediated apoptosis play a critical role in the differentiation of Th1 and Th2 cells. The aspect of Th1 and Th2 differentiation will be examine in suspension-induced modulation of the immune system.

Early work has begun with the RANKL (Receptor activator of NF-kB ligand) expression in lymphoid tissue in stressed mice treated with steroids. This new member of the TNF family has been shown to be important in osteoclast formation and function. We have found that this molecule could be induced in lymphocytes by TCR ligation and treatment with dexamethasone. Since steroid hormones are released during stress, their role through RANKL in the communication between the skeletal and the immune systems will be further investigated.

c. Microbial Monitoring. *GE Fox, R Willson*

Probes: We have completed development of a set of 16S rRNA probes that can be used with similar efficiency at a single hybridization temperature. These probes will target major problem and indicator organisms in water samples. We also completed the development of a computational algorithm that allows identification of short 16S rRNA subsequences that are highly characteristic of various phylogenetic groupings. In principle, an array of appropriately designed probes based on these signature sequences could be used to determine the genetic affinity (nearest known relatives) in the absence of any prior knowledge of what the problematic organism might be. In practice, the signature sequences themselves tend to be short (15 nucleotides or less) and hence not ideal for use in arrays. Most recently, we discovered a way to extend the algorithm that will allow us to identify very long (30-60 nucleotides) signature fragments whose sequences, despite occasional mismatches, are highly characteristic of various phylogenetic groupings. We are currently identifying a number of useful sequences of this type and have arranged a collaboration with Xeotron Inc. to construct and test a prototype signature array.

Detection:

<u>**Mass Spectrometry:**</u> Our studies of signature sequences made it clear that many short oligonucleotide sequences are in fact highly characteristic of specific organisms or groups of organisms. A portion of these signature sequences can be readily liberated from RNA samples by a very simple one step experimental procedure, enzymatic digestion with a specific endonuclease such as ribonuclease T1. These RNAs are sufficiently small that they might be readily identified by their mass (and implied composition) in a MALDI-TOF mass spectrometer. This approach is especially promising because several groups are developing mass spectrometry instruments for

use in space. Because the University of Houston is in the process of purchasing state of the art mass spectrometry equipment that will be available to us, we have decided to pursue this approach. Initial experiments with a control RNA were successfully completed recently and we are now in the process of examining digestions from a single organism.

Beacons and NASBA: Several probes for organisms of primary interest have been successfully implemented in beacon format. "Red-shifted" beacons have minimized contributions from sample autofluorescence. A new collaboration with the Ellington group at the University of Texas will implement some of our beacons in the context of the UT "Electronic tongue" biosensor device.

The major difficulty in applying beacons to microbial detection is sensitivity; organisms of interest are sometimes present at concentrations too low to be quantified by beacon fluorescence. RT-PCR amplification is one solution to this problem, but we have been exploring an alternative amplification method which may be much more compatible with spacecraft operation. NASBA is an isothermal, multi-enzyme amplification cascade compatible with RNA samples and not requiring the energy-intensive heating and cooling cycles characteristic of PCR. We have achieved NASBA amplification of segments of rRNA, and are now exploring its use with viral samples. In each case, beacon detection of the amplicons will be possible, allowing specific and convenient homogeneous detection.

Microgravity Studies: There is preliminary evidence that the microgravity environment seen in space effects bacteria in non-obvious ways with such possible outcomes as altered drug resistance or pathogenicity. In order to explore this possibility further, we are collaborating with Dr. Duane Pierson of JSC to examine the response of *E. coli* cells grown in simulated microgravity. In order to do this, we are using modern proteomics technology to examine the expression levels of each and every gene in *E. coli* when cells are grown in a rotating bioreactor. Although this portion of the project was delayed by the inability of the manufacturer to deliver the arrays on a timely basis, we are now making good progress. Various kinetic controls have been completed and several control hybridizations have now been completed. In the future, it is likely that in addition to examining mRNA levels it will be useful to use two-dimensional protein gels to examine the actual levels of various gene products. We are currently developing this capability, which will also benefit from the new mass spectrometry facilities as well.

Sample Processing: Most recently, we have been addressing the problem of probe/beacon target accessibility in rRNA, especially large and highly structured 16S rRNA. Early experiments with unfolding-promoting oligonucleotides designed to hybridize to core structural elements have been promising. More directly, we have been exploring fragmentation of rRNA using cleavage by controlled heating in high [Mg+2] buffers, or by ribonucleases. Each of these approaches has been shown to enhance the hybridization signal obtained with beacons.

Collaborations with Other NSBRI Team Members: In collaboration with Dr. Janet Butel, we are examining the historical relationship between sequenced strains of the SV40 virus in order to better understand the significance of cases where SV-40 has been isolated from humans. Our contribution is to the bioinformatics component of the project. We are also beginning to collaborate with Dr. Butel on viral detection using NASBA is an isothermal, multi-enzyme amplification cascade compatible with RNA samples and not requiring the energy-intensive heating and cooling cycles characteristic of PCR. NASBA would be combined with beacon detection of the amplicon.

In collaboration with Dr. Gerry Sonnenfeld, we are building on his group's observation that human stress hormones stimulate the growth of several strains of bacteria at physiologically-relevant concentrations. Dr. Sonnenfeld's postdoc will come to Houston in September so that we may conduct collaborative experiments using macroarrays to determine the effects of hormone exposure on gene expression *in E. coli.*

Team Publications/Manuscripts (2001 – 2002)

- Aviles H, Belay T, Fountain K, Vance M, **Sonnenfeld G**. Increase susceptibility to *Pseudomonas aeruginosa* infection under Hindlimb unloading conditions, submitted

- Belay T, Vance M, Fountain K, **Sonnenfeld G**. Hindlimb suspension decrease resistance of mice infected with Klebsiella pneumoniae (abstract). *Gravit Space Biol Bull* 15:58, 2002.

- Belay T, **Sonnenfeld G.** Differential effects of catecholamines on *in vitro* growth of pathogenic bacteria. *Life Sci* 71:447-456, 2002.

- Belay T, Aviles H, Vance M, Fountain K, **Sonnenfeld G.** Effects of the hindlimb-unloading model of spaceflight conditions on resistance on mice to infection with Klebsiella pneumoniae. *J Allergy Clin Immunol* 110:262-268, 2002.

- DeWalt B, Murphy JC, **Fox GE, Willson RC**. Compaction agent clarification of microbial lysates. *Protein Expr Purif,* in press, 2002.

- Kourentzi KD, **Fox GE**, **Willson RC**. Microbial Identification by immunohybridization assay of artificial RNA labels. *J Microbiol Methods* 49:301-306, 2002.

- Larios-Sanz M, Kourentzi KD, Murphy JC, Maillard KI, **Pearson DL**, **Willson RC, Fox GE**. "Monitoring microbial populations in space environments. In SA de CV, ed., Dianostico Molecular, JGH: Mexico City, in press, 2002.

- **Lednicky JA**, Havorson SJ, **Butel JS**. PCR detection and DNA sequence analysis of the regulatory region of lymphotropic papovavirus in peripheral blood mononuclear cells of an immunocompromised rhesus macaque. *J Clin Microbiol* 40:1056-1059, 2002.

- **Lednicky JA**, **Vilchez RA**, Keitel WA, Visnegarwala F, White ZS, Kozinetz C, Lewis DE, **Butel JS**. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy, submitted, 2002.

- Murphy JC, **Fox GE**, **Willson RC**. Structured RNA isolation and fractionation with compaction agents. *Anal Biochem* 295:143-148, 2001.

- Murphy JC, Jewell DL, White KI, **Fox GE**, **Willson RC**. PCR product purification using immobilized metal affinity chromatography spin columns. *BioTechniques,* in press, 2002.

- Murphy JC, **Fox GE**, **Willson RC**. Compaction agents enhance anion-exchange Adsorption of nucleic acids. *J Chromatography,* in press, 2002.

- O'Sullivan CE, Peng RS, Cole KS, Montelaro RC, Sturegeon T, Jenson HB, **Ling PD.** Epstein-Barr virus and human immunodeficiency virus serological responses and viral burdens in HIV-infected patients treated with HAART. *J Med Virol* 67:320-326, 2002.

- **Shearer WT,** Lee B-N, Cron SG, **Rosenblatt HM**, **Smith EO**, **Lugg DJ**, Nickolls PM, Sharp RM, Rollings K, **Reuben JM**. Suppression of human anti-inflammatory plasma cytokines IL-10 and IL-1RA with elevation of proinflammatory cytokine IFN-g during the isolation of the Antarctic winter. *J Allergy Clin Immunol* 109:854-857, 2002.

- **Shearer WT**, **Sonnenfeld G**. Alterations of immune responses in space travel. In Hans M, ed. Encyclopedia of Space Science and Technology. New York: John Wiley & Sons, in press, 2002.

- **Shearer WT**, **Lugg DJ, Rosenblatt HM,** Nickolls PM, Sharp RM, **Reuben JM,** Ochs HD. Antibody responses to phiX-174 in human subjects exposed to the Antarctic winter-over model of spaceflight. *J Allergy Clin Immunol* 107:160-164, 2001.

- **Shearer WT, Reuben JM,** Mullington JM, Price NJ, **Lee B-N, Smith EO,** Van Dongen HPA, Szuba MP, **Dinges DF**. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 107:165-170, 2001.

- **Shearer WT.** Contamination of the spacecraft environment: immunologic consequences. *Gravit Space Biol Bull* 14:7-14, 2001.

- **Shi YF**, Devadas S, Greeneltch KM, Yin DL, Mufson RA, Zhou JN. Stressed to Death: Implication of lymphocyte apoptosis for psychoneuroimmunology. *Brain Behav Immun,* in press, 2002.

- **Sonnenfeld G**. The Immune System in Space and Microgravity. *MSSE* in press, 2002.

- **Sonnenfeld G**. Animal models for the study of the effects of spaceflight on the immune system. *Adv Space Res,* in press, 2003.

- **Sonnenfeld G**, **Shearer WT**. Immune function during space flight. *Nutrition* 18:899-903, 2002.

- Starikov D, Boney C, Medelci N, Um JW, Larios-Sanz M, **Fox GE,** Bensaoula A. Experimental simulation of integrated optoelectronic sensors based on III nitrides. *J Vac Sci Technol,* in press, 2002.

- **Vilchez RA**, Madden CR, Kozinetz CA, Halvorson SJ, White ZS, Jorgensen JL, Finch CJ, **Butel JS**. Association between simian virus 40 and non-Hodgkin lymphoma. *Lancet* 359:817-823, 2002.

- **Vilchez RA, Lednicky JA**, Havorson SJ, White ZS, Kozinetz CA, **Butel JS**. Detection of polyomavirus simian virus 40 tumor antigen DNA in AIDS-related systemic non-Hodgkin lymphoma. *J Acqu Immune Defic Synd* 29:109-116, 2002.

- Zhang XR, Zhang L, Li L, Glimcher LM, Keegan AD, **Shi YF**. Reciprocal expression of TRAIL and CD95L in Th1 and Th2 cellss: role of apoptosis in T helper subset differentiation. *Cell Death Differ*, in press, 2002.

- Zhang Z, **Willson RC, Fox GE**. Identification of characteristic oligonucleotides in the 16S ribosomal RNA sequence dataset. *Bioinformatics* 18:244-250, 2002.

<u>Team Presentations (2001 – 2002)</u>

- Cano T, Murphy JC, **Fox GE, Willson RC**. "Conformational Control as a Tool in Plasmid Purification", (Oral Presentation-Abstract 534956) 224th National Meeting, American Chemical Society, Boston, Massachusetts, August 18-22, 2002.

- Larios-Sanz M, Kourentzi K, Warmflash D, **Willson RC, Pierson DL, Fox GE**. "Microbial Contaminants in Crew Habitat Modules During Exploration Class Human Space Missions: Monitoring Potential Pathogens", (Panel Presentation) 73rd Annual Meeting, Aerospace Medical Association, Montreal, Canada, May 5-10, 2002.
- **Shearer WT**. Team Report: Immunology, Infection, and Hematology. National Space Biomedical Research External Annual Retreat, Montgomery, TX, January 13-17, 2002.
- **Shearer WT**. Team Report: Immunology, Infection, and Hematology. National Space Biomedical Research External Advisory Council Meeting, San Jose, CA, March 12-14, 2002.

- **Shearer WT**. Compromise of the Human Immune System in Interplanetary Space Travel. XV Mexican Congress of Clinical Immunology, Ixtapa-Zihuatanejo, Mexico, May 1, 2002.

- **Shearer WT**. Challenges to the Human Immune System During Space Travel. University of North Carolina – Chapel Hill 2002 Cellular and Molecular Biology Program Symposium: Space: Challenges for Human Physiology, Chapel Hill, NC, May 3, 2002.

- **Shearer WT**. Risk Factors for Human Immunology in Space. National Space Biomedical Research Institute Summer Teachers Program, Houston, TX, June 7, 2002.

- **Sonnenfeld G**. Space Flight, Immune Responses and Resistance to Infection. Invited Seminar, Medical Division, Brookhaven National Laboratory, 2001.

- **Sonnenfeld G**. Stress, Space Flight, and Resistance to Infection. Amino Up Chemical Company Seminar, Sapporo, Japan, 2002.

- **Sonnenfeld G**, Aviles H, Belay T, Vance M, Fountain K. Stress, Suspension, and Resistance to Infection. 8th European Symposium on Life Sciences Research in Space and 23rd Annual International Gravitational Physiology Meeting, Stockholm, Sweden, 2002.
- **Sonnenfeld G**. Space Flight and Immune Responses of Rhesus Monkeys. Karolinska Institute Symposium on Space Research in Non-Human Primates, Stockholm, Sweden, 2002.

- **Sonnenfeld G**. Animal Models for the Study of the Effects of Spaceflight on the Immune System. Invited Lecture – COSPAR/World Space Congress, Houston, TX, 2002.

- **Sonnenfeld G**. Space Flight, the Immune System, and Resistance to Infection. Invited Symposium on the Role of Infection in Chronic Disease, German Clinical Research Group and German Research Centre for Biotechnology, Braunschweig, Germany, 2002.

- Starikov D, Boney C, Medelci N, Um JW, Bensaoula A, Larios-Sanz M, **Fox GE**. Development of Integrated Multifunctional Optical Sensors Based on III Nitrides. (Oral Presentation, Session PH-ThA4, Photonic Materials: Applications and Processing). American Vacuum Society 48th International Symposium, San Francisco, CA, October 28-November 2, 2001.

- Warmflash D, Larios-Sanz M, **Fox GE, Willson RC**, McKay DS. Technologies for Microbial Detection to Support Both Vehicle/Habitat Medical Monitoring and Planetary Astrobiology During Human Surface Exploration of Mars (Panel Presentation). 73rd Annual Meeting, Aerospace Medical Association, Montreal, Canada, May 5-10, 2002.

- Warmflash D, Larios-Sanz M, **Willson RC, Fox GE**, McKay DS. Progress in the Use of Rapid Molecular Techniques to Detect Life Forms in Soil: Implications for Interplanetary Astrobiology Missions. 33rd Lunar & Planetary Science Conference, Houston, TX, March 11-15, 2002.

Team Grants (2001 – 2002)

- **Janet S. Butel, Ph.D., PI** - Hamster Model for AIDS Lymphomas: National Institutes of Health, 09/01/02 – 08/30/04 / Total Costs: $301,000

- **George E. Fox, Ph.D., PI** - The Origins of Translation and Early Life: NASA Exobiology Program, 07/01/02 – 06/30/05 / Total Costs: $343,177.00

- **Paul D. Ling, Ph.D., PI** - Epstein-Barr Virus Leader Protein Function: American Cancer Society, 01/01/03 – 12/31/06 / Total Costs: $791,000

- **James M. Reuben, Ph.D., PI** - Effects of Radiation on Human Peripheral Blood Dendritic Cells: NASA, 10/01/02 – 09/30/05 / Total Costs: $471,658

- **Gerald Sonnenfeld, Ph.D., PI** – Nutrition and Immunity: Amino-Up Company, 2002-2003 / Total Costs: $70,000
- **Regis A. Vilchez, Ph.D., PI** - The Pathogenesis of Polyomavirus SV40 in Non-Hodgkin's Lymphoma: Leukemia & Lymphoma Society, 11/01/02 – 10/31/05 / Total Costs: $360,860

- **Richard C. Willson, Ph.D., PI** - Competitive Ion-Exchange Adsorption of Proteins: National Science Foundation Separations Program, 09/01/01 – 08/31/04 / Total Costs: $343,177.00

Muscle Alterations and Atrophy Team 2002 Report

Team Leader:
Kenneth M. Baldwin
Dr. Kenneth M. Baldwin
Department of Physiology and Biophysics
University of California, Irvine
Irvine, CA 92697
Phone: (949) 824-7192
Fax: (949-824-7192
Email: kmbaldwi@uci.edu
Project Title: Role of Muscle Loading on Mechanisms of Protein Translation and Their Impact on Unloading -Induced Atrophy

Co-Team Leader:

Dr. Alfred Goldberg
Department of Cell Biology
Harvard School of Medicien
Boston, MA 02115-6092
Phone: (617) 432-1855
Fax(617) 432-232-0173
Project Title: The Activation of Protein Breakdown in Muscle Upon Unloading and Possible Countermeasures

Principal Investigators and Project Titles:

Parker Bruce Antin; Ph.D.
Department of Cell Biology and Anatomy
College of Medicine
University of Arizona
888 N. Euclid. #510
P. O. Box 3308
Tucson, AZ 85722-3308
Phone: (520) 621-5993
Fax: (520) 626-2097
Email: pba@u.arizona.edu
Project Title: Calpains in Simulated Microgravity-Induced Muscle Atrophy

Marc. T. Hamilton; Ph. D.
Department of Veterinary Sciences
College of Veterinary Medicine
University of Missouri, Columbia
Columbia, MO 65211
Phone: (573) 882-7011
Fax: (573) 884-6890
Email: HamiltonM@Misssouri.edu
Project Title: Genomics of Human Skeletal Muscle During Bedrest and Exercise

Susan C. Kandarian, Ph.D.
Department of Health Sciences
Sargent College
Boston University
881 Commonwealth Ave
Boston, MA 02215
Phone: (617) 353-5169
Fax: 617-353-7600
Email: skandar@bu.edu
Project Title: Gene Expression Profiling of Unloaded Skeletal Muscle

Susan C. Kandarian, Ph.D.
Department of Health Sciences
Sargent College
Boston University
881 Commonwealth Ave
Boston, MA 02215
Phone: (617) 353-5169
Fax: 617-353-7600
Email: skandar@bu.edu
Project Title: Gene Expression Profiling of Unloaded Skeletal Muscle

Michael B. Reid, Ph.D.
Department of Medicine
College of Medicine
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030
Phone: (713) 798-7224
Fax: (713) 798-3619
Email: reid@bcm.tmc.edu
Project Title: Redox Modulation of Muscle Function in Microgravity

Shantanu Sinha;, Ph. D.
Brain Research Institute
School of Medicine
University of California, Los Angeles
P.O. Box 951761
Los Angeles, CA 90095-1761
Phone: (310) 825-2320
Fax: (310) 794-6613
Email: ssinha@mednet.ucla.edu
Project Title: In Vivo Stress Strain Dynamics in Human Muscle

Robert W. Wiseman, Ph. D.
Departments of Physiology and Radiology
Michigan State University
East Lansing, MI 48824
Phone: (517) 355-6475
Fax: (517) 355-5125
Email: rwiseman@msu.edu
Project Title: Calcium Homeostasis and Muscle Phenotype: Role of Cellular Energetics

P. Bryant Chase, Ph.D.
Department of Biological Science
Florida State University
Tallahassee, FLA32306
Phone: (850) 644-0056
Fax: (850) 644-0392
Email:chase@bio.fsu.edu
Project Title: Cell and Molecular Biomechanics: Cardiac and Skeletal Muscle

Martin Kushmerick, M.D., Ph.D.
Department of Radiology, Bioengineering, and Physiology
University of Washington
Seattle, WA 357115
Phone☹206) 543-3762
Fax☹206) 221-6515
Email:kushmeri@u.washington.edu
Project Title: Human Muscle Energetics and Mechanics

Table of Contents:

I. Abstract.

The research mission of the Muscle Alterations and Atrophy Team (MAAT) is to ascertain the underlying mechanisms associated with the loss of muscle mass, strength, and endurance that are the cornerstones of the structural and functional deficits that occur when individuals (human and animal) are subjected to prolonged states of inactivity or skeletal muscle unloading. A key element of this research mission is to, over time, elucidate countermeasures that can effectively ameliorate these deficits using a variety of strategies such as exercise, nutritional and pharmacological interventions, as well as evolving the unique strategy of human powered artificial gravity (assuming that both NASA and the NSBRI becoming truly committed to exploring the modality as a countermeasure strategy). In the past fiscal year significant progress has been made in gaining a better understanding of 1) the factors that induce/affect muscle atrophy, 2) the key genes that are impacted by muscle unloading stimuli, 3) the functional consequences of the atrophy process, and 4) the efficacy of using a) relatively common therapeutic agents and b) a simple isometric resistance training program to significantly reduce the atrophy response in rodent skeletal muscle. This latter observation has the potential to be translated to human experimentation as a potential countermeasure

II. Introduction

In the Fall of 2000, the National Space Biomedical Research Institute's (NSBRI) Muscle Alterations and Atrophy Team (MAAT) began its second three-year funding cycle on research dealing with the structural and functional deficits of the skeletal muscle system in response to prolonged exposure to space flight or the environment of microgravity. Of the eight original projects that were selected in the first period of funding (1997-2000), only one project was selected for continuation. The PI for the project was Dr. Alfred Goldberg, Harvard Medical School; and Dr Ken Baldwin, University of California, Irvine served as a co-investigator on that original project.

In the Fiscal-Year 2000-2003 funding cycle, seven new projects were selected for funding in addition to Dr. Goldberg's project. Two projects were selected for a funding cycle that started on October 1, 2000. These selections involved projects headed by Dr. Baldwin and Dr. Goldberg, respectively, who now serve as the Team Leader and Co-Team Leader for the MAAT. The remaining six projects were recently initiated in funding cycles at different starting dates in the 2001 calendar year. These projects are defined in the next section, Program Structure and Design. During Fiscal Year 2001-2002, two additional projects from the Integrated Function Team were reassigned to the MAAT such that there are now a total of ten research projects that define this team.

The research mission of the MAAT is to ascertain the underlying mechanisms associated with the loss of muscle mass, strength, and endurance that are the cornerstones of the structural and functional deficits that occur when individuals (human and animal) are subjected to prolonged states of inactivity or skeletal muscle unloading. A key element of this research mission is to, over time, elucidate countermeasures that can effectively ameliorate these deficits using a variety of strategies such as exercise, nutritional and pharmacological interventions, as well as evolving the unique strategy of human powered artificial gravity (assuming that both NASA and the NSBRI becoming truly committed to exploring the modality as a countermeasure strategy).

Muscle Deficits and Critical Concerns to Be Addressed by the Muscle Team.

The following deficits/concerns have been identified in the critical pathway of understanding astronaut health and safety during prolonged spaceflight. These include:

1. Reduced muscle mass (atrophy), which is thought to be due to an imbalance in protein synthetic to protein degradation activity within targeted fibers. The mechanism(s) for such a response is largely unknown.

2. Reduced muscle strength leading to a decrease in physical activity performance and high power output capacity. Deficits in strength often exceed the loss in muscle mass suggesting that more complex mechanisms are responsible for the reduced performance.
3. A slow-to-fast shift in the contractile protein phenotype, e.g., shifts to expression of faster myosin heavy chain (MHC) and calcium cycling proteins. These alterations induce the muscle fibers to become less economical in sustaining force output and locomotor activity.

4. A decreased resistance to fatigue, (which could have functional implications in the performance of extra vehicular activity in space and in performing emergency egress activity upon space craft landing.) This problem is relevant to the other deficits outlined above.

5. A proneness to muscle injury, which is due to the atrophy and loss of strength. An additional outcome of the muscle weakness could cause increased susceptibility to accidents that, in turn, could cause damage to other systems, e.g., bone fractures.

6. Changes in muscle properties are closely linked to changes in the ability of nervous system to accurately control movements; and thus such changes affect safety when performing any type of work.

III. Research Program Structure and Design

Listed below are the research topics and the associated Principal Investigators that form the backbone of the MAAT Strategic Plan. These include:

- Role of Muscle Loading Conditions on Mechanisms of Protein Translation and Their Impact on Unloading-Induced Atrophy -(PI: K. M. Baldwin; University of California, Irvine). This project addresses Concerns #1 and #2.

- The Activation of Protein Breakdown Upon Unloading and Possible Countermeasures—(PI: A.L. Goldberg; Harvard Medical School). This project addresses Concern #1.

- Calpains in Simulated Microgravity-induced Muscle Atrophy -(PI: P. B. Antin; University of Arizona). This project addresses Concern #1.

- Genomics of Human Skeletal Muscle During Bedrest and Exercise --(PI; M. Hamilton; University of Missouri, Columbia). This project addresses Concerns #1-4.

- Gene Expression Profiling of Unloaded Skeletal Muscle -(PI; S. Kandarian: Boston University). This project is also linked to Concerns #1-4

- In Vivo Stress Strain Dynamics in Human Muscle -(PI:S. Sinha; University of California, Los Angeles). This project addresses Concerns #4-6

- .Redux Modulation of Muscle Fatigue and Atrophy Processes in (Simulated) Microgravity -(PI; M. Reid: Baylor College of Medicine). This project addresses Concern # 2 and 4.
- Cell and Molecular Biomechanics: Cardiac and Skeletal Muscle-(PI; P. B. Chase: Florida State University). This project addresses concerns #4-6.

- Calcium Homeostasis and Muscle Phenotype -(PI: R. Wiseman: Michigan State University). This project addresses Concerns #3 and 4.

- Human Muscle Energetics and Mechanics-(PI; M. Kushmerick: University of Washington). This projects addresses Concerns #4-6.

IV. Research Program Accomplishments

Key Findings From the Baldwin Team:

The major goal of our project is to identify the key molecular events that occur to control net protein balance when muscles are manipulated to either hypertrophy or atrophy. Additional studies are designed to determine what types of resistance training are more effective in reducing muscle atrophy in models of muscle unloading (simulated events that mimic microgravity).
In FY 01-02 we demonstrated that a daily resistance training program consisting of isometric contractions (3-4 sets; five 1 sec contractions per set; spaced with appropriate rest intervals) is effective in retarding the atrophy and net total protein loss that occurs in a mix-fibered rodent muscle (medial gastroc) in response continuous hindlimb unloading. This retention of muscle mass was associated with signals that indicated that the muscle was attempting to turn pathways on that normally are indicative of a hypertrophy response. The significance of this observation is that if this type of intervention is extended to astronauts, it would appear that a relative simple resistance training paradigm

that can be performed in a minimal time frame may be effective in retaining muscle mass during prolonged space flight.

In an additional study we observed that one of the early signaling processes important for muscle hypertrophy and a positive protein balance involves an increase in the ribosomal RNA pool, which is needed for the general translation of muscle protein. The significance of this response is that this adaptive process may be a good predictor of the net protein balance in the muscle that can be achieved, because additional observations by our group indicates that the early stages of atrophy cause an opposite response, e.g., an decrease in ribosomal RNA concentration and content. This adaptive response may serve as a good predictor of whether a given activity pattern may result in muscle protein deficits or muscle protein gains.

Publications:

- Adams, G. R., V. J. Caiozzo Cellular and molecular responses to increased skeletal muscle loading after irradiation. Am. J. Physiol Cell Physiol. 283: C1182-C1195, 2002.

- Baldwin, K. M. and F. Haddad. Skeletal Muscle Plasticity: cellular and molecular responses to altered physical activity paradigms. Am. J. Physical Med. 81: 000-000, 2003.

- Baldwin, K. M., V. R. Edgerton, and R. R. Roy. Muscle Loss in Space: Physiological Consequences . Encyclopedia of Space Science Technology. John Wiley and Sons, Hoboken, New Jersey. p. 1-10, 2003.

- Haddad, F. R. R. Roy, V. R. Edgerton, and K.M. Badlwin. Atrophy responses to complete muscle Inactivity I: Cellular markers of protein deficits. (submitted)

- Haddad, F. R. R. Roy, V. R. Edgerton, and K.M. Badlwin. Atrophy responses to complete muscle Inactivity II: Molecular markers of protein deficits. (Submitted)

Key Findings From the Goldberg Team.

Muscle unloading (e.g., in space and bed-ridden individuals) and a wide variety of disease states (such as cancer cachexia, sepsis, or renal failure) cause a rapid loss of muscle protein and functional capacity due primarily to activation of the ubiquitin-proteasome pathway. In an effort to establish a comprehensive picture of the transcriptional adaptations that occur during muscle wasting and underlie the excessive proteolysis, we have been using cDNA microarrays to analyze skeletal muscle undergoing atrophy. Initially, we compared the transcriptional profile in gastrocnemius muscles from normal mice with ones from mice fasted for one or two days. We then studied whether similar adaptations occurred in rodent muscles atrophying due to cancer cachexia, diabetes, chronic renal failure, and unloading. Expression of the vast majority (>95%) of the genes represented on the microarray did not change. However many of the mRNAs which increased markedly were previously uncharacterized (ESTs), including atrogin-1, the new ubiquitin ligase (E3), whose expression was induced 7-10-fold in all types of atrophying muscle examined. Related work has shown that this enzyme rises prior to the onset of atrophy (Gomes, et al., PNAS, 2001) and that lack of atrogin-1 decreases the muscle weight loss upon denervation or unloading (Bodine, et al., Science, 2001). Additionally, among the known, differentially expressed genes on the microarrays, certain patterns emerged: 1) only a small decrease in expression of mRNAs encoding proteins of the myofibril (which comprise most of proteins lost during atrophy), except for a large decrease in one component, myosin-binding protein H; 2) an increase in mRNAs encoding polyubiquitin and many (but not all) 20S and 19S proteasome subunits. 3) a coordinate decrease in mRNAs for glycolytic enzymes and a large increase in mRNA for PDH kinase, which are likely to contribute to decreased glucose utilization and increased use of fatty acids for energy production in muscle during fasting and cachexia. A number of genes whose differential expression may provide important clues to the atrophy process were also identified (such as decreased expression of the growth-factor binding protein and increases in the stress-protein metallothionein). These findings demonstrate the utility of microarrays for analysis of atrophying muscles. Aside from discovering some disease-specific transcriptional changes in muscle, we have helped to clarify the common transcriptional response that generates enhanced proteolysis during rapid atrophy. Present efforts are focusing on attempts to understand the mechanisms that activate this response and agents that may inhibit it and help prevent atrophy.

Publications:

Jagoe, RT, Lecker, SL, Gomes, M, and Goldberg, AL. Patterns of gene expression in atrophying skeletal muscles: the response to food deprivation. FASEB Journal 2002, 16: 1697-1712.

Lecker, SL, and Goldberg, AL. Slowing Muscle Atrophy: Putting the Brakes on Protein Breakdown. J. Physiol., 2002 (In Press).

Key Findings From the Antin Team:

Calpains in Simulated Microgravity Induced Muscle Atrophy. Therefore, the objective is to test the hypothesis that inhibition of calpain activity in skeletal muscles can reduce myofibril degradation and muscle atrophy. This is being accomplished through over expression of the calpain inhibitor calpastatin in transgenic mice, and assessing its effects on muscle atrophy in the hindlimb unweighting model.

An important initial goal of this project has been to generate and characterize a transgenic mouse model for regulated over expression of transgenes in skeletal muscles. We have utilized the benefits of an optimized tet-on system and a modified muscle creatine kinase (MCK) promoter to generate a skeletal muscle-specific, doxycycline (Dox) controlled over-expression system. A DNA construct was generated in which the codon optimized reverse tetracycline transactivator (rtTA) was placed under control of a skeletal muscle-specific version of the mouse MCK promoter. Transgenic mice containing this construct expressed rtTA almost exclusively in skeletal muscles. These mice were crossed to a second transgenic line containing a bi-directional promoter centered on a tet responder element (TRE) driving both a luciferase reporter gene and the calpain inhibitor calpastatin. Dox treated compound hemizygous mice showed high level, muscle-specific luciferase activity often exceeding 10,000 fold over non-muscle tissues of the same mouse. Similar muscle-specific induction was observed with the tagged calpastatin protein on western blots. These findings demonstrated the effectiveness and flexibility of the tet-on system to provide a tightly regulated over-expression system in adult skeletal muscle. Experiments are now underway to assess the potential protective effects of calpastatin over expression on hindlimb unweighting-induced muscle atrophy.

Identifying the molecular pathways regulating muscle atrophy is an important aspect of the muscle team strategic plan, because understanding how muscle atrophy is regulated will enable the design and implementation of effective countermeasures. Experiments in this proposal are designed to determine the involvement of calpain proteases in muscle atrophy; results may suggest direct pharmacological targets for inhibition of atrophy during extended space travel..

Publication:
Grill, M.G., Bales, M.S., Garriock, R.J., and Antin, P.B. (2002) Development of an Inducible System for Muscle-specific Gene Expression in Transgenic Mice: Transgenic Res: In press.

Key Finding From the Sinha Team.

Muscle atrophy can result from a variety of clinical conditions such as micro-gravity or immobilization. To address this problem, an advanced high-resolution magnetic resonance imaging (MRI) was developed to determine the complex biomechanical interactions of tendons, aponeurosis and muscle fascicles which underlie everyday movements and investigate how these alter under conditions of atrophy.

We determined the strain distribution parameters in the triceps surae muscle complex of the lower leg, in-vivo, during isometric contraction, in both normal control subjects, in subjects one of whose legs was atrophied by suspension for four weeks, and at different time points during a period that these subjects were undergoing rehabilitative physio-therapy.

Significant Findings/Accomplishments: Velocity/strain (primary measure) and muscle volume data (secondary measure) were acquired at baseline, mid- and termination of suspension of one leg, in six normal (4 male and 2 female) subjects (after IRB approval) for a 4 week period. At the end of the suspension period, each was given standard physio-therapy. In terms of changes of muscle volume, different muscle groups decreased to different extent. The medial gastrocs decreased by a average of 9% (in four weeks) while the lateral gastrocs had a greater variation between subjects, ranging from 4 to 0.4%. In terms of Maximal Voluntary Contraction (MVC) a significant drop of 40%

(mean) was observed across subjects. Fig. 1 shows the extent and pattern of traversal of different pixel along the S/I axis, in this case near the junction of the medial and lateral gastrocs and the aponeurosis through the different phases of the

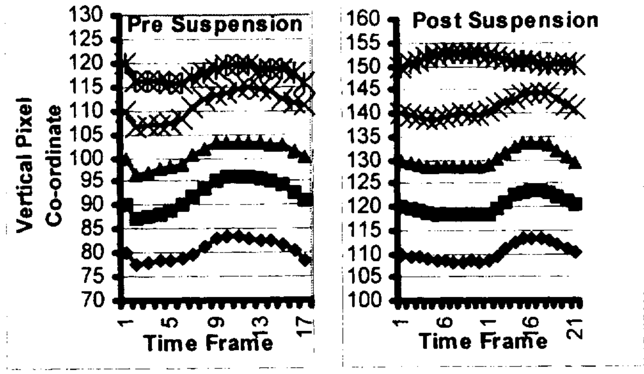


Fig. 1. Extent of Tissue Movement at Medial Gastroc, before and after atrophy, through Contraction Cycle.

contraction cycle. It is clearly obvious that the extent of strain at different points of different muscle groups change significantly with the onset of atrophy. In fact, equivalent points in the muscle experience a decrease in strain by as much as 40%. Further, and not evidenced in the figure above, upon onset of atrophy different muscle groups are recruited at different levels, that is, there is re-distribution of strain for the same isometric contraction. This suggests that in the atrophied state, more volume of muscle must be used to generate the same amount of torque as the un-atrophied muscle.

Publications:

Sinha S, Hodgson JA, Finni T, Lai A, Grinstead J, Edgerton VR. A comparison of muscle kinematics quantification using phase-contrast and spin tagging methods of visualizing motion. Submitted for publication.

Finni T, Hodgson JA, Lai A, Edgerton VR, Sinha S. Non-uniform behavior of human triceps surae aponeurosis-tendon complex during submaximal voluntary contractions in vivo. Submitted for publication.

Key Findings From the Kandarian Team.

The overall aim of the proposed work is to delineate cellular mechanisms involved in unloading-induced skeletal muscle atrophy.

As a first step in elucidating these mechanisms we have analyzed global gene expression patterns in rat soleus muscles using Affymetrix GeneChips at 1, 4, 7, 14 days of biomechanical unloading. Temporal analysis of the parallel expression of ~8000 gene products has served as a window into the signaling networks that underlie the atrophy process. Microarray data analysis software has been used to segregate gene expression changes based on involvement in known functional groups, regulatory and signaling pathways. Clustering algorithms have been used to elucidate sets of co-regulated genes with similar temporal expression patterns. We are currently in the process of testing candidate genes that may be involved in the progression of atrophy using overexpression systems in both cell culture and in whole muscle.

Summary of Significant Accomplishments: Physical inactivity is characterized by profound skeletal muscle wasting, increased morbidity and compromised quality of life. We have used Affymetrix GeneChips to analyze the early time course of regulatory gene expression changes that occur during muscular inactivity. Soleus muscle was isolated from rat hindlimbs suspended for 1, 4, 7, and 14 days and time matched controls. Alterations were seen that suggest a decrease in translational activity and an increase in protein degradation. Novel findings include the activation of two ubiquitin-protein ligases not previously characterized with atrophy (Nedd4 and Mdm2), tight co-regulation of proteasome subunits and differential expression of several serine proteases, serine protease inhibitors and tissue inhibitor of metalloproteinase 1. K-means clustering revealed distinct relationships and co-regulation between growth, signaling, and transcription factors as evidenced by different activation times, magnitudes and durations. Possible relationships were identified among genes related to phosphoinositide signaling, IGF-I, Jak-Stat, myogenic, notch, TGF-B, and mechanotransduction signaling, as well as cell cycle regulators. For instance, one cluster included an early and sustained co-regulation of MyoD, Cited2, Igfbp5, and PI4K. A late but transient upregulated cluster included p21, Follistatin, Stat5b, c-Jun, and C/EBP delta. Carp, Homer2, and CaMKII, genes not previously characterized with respect to atrophy, were co-regulated in a cluster markedly decreasing over the course of unloading.

The present work has uncovered several novel relationships and patterns of differential gene expression that provide insight into the parallel pathways that regulate skeletal muscle wasting and suggest new avenues for study. This work is currently being considered for publication. An avenue that we are currently pursuing is the expression of NEDD4 in C2C12 muscle cell line. We have constructed a NEDD4 overexpression clone in a conditional (tetracycline) expression system that is commercially available. We obtained a muscle specific transactivator plasmid from Parker Antin (also on the muscle team). We have optimized all conditions for transient overexpression of NEDD4 to determine if it is sufficient to induced atrophy in this cell line. We have also confirmed that NEDD4 is expressed by C2C12s. The reporter plasmid, which expresses EGFP, indicates that our transfection efficiency is 15-20% (using effectamine). The level of inducible expression obtained in the presence of tetracycline (dox) is 20-fold. This latter result was obtained using the same conditional expression system but with the luciferase reporter rather than the EGFP reporter in the plasmid. We are currently testing for the level of NEDD4 expressed in cells that took up plasmid using westerns and immunocytochemistry..

Key Findings From the Bryant Project.

The overall goal of this project is to produce a muscle cell model (digital muscle cell) that will: explain biomechanical adaptations that occur with alterations in muscle protein isoforms due to changes in activity level; predict bioenergetic changes associated with changes in activity level; be integrated into computational models of human limb and heart. To accomplish our goal of constructing a digital muscle cell, we will: (1) identify contractile protein composition of skeletal and cardiac muscles from high- and low-activity rats; (2) characterize contractile properties (phenotype) of selected muscles containing unique mixtures of protein isoforms, as identified in Aim 1; and (3) in parallel with Aims 1 & 2, develop the "digital" cell biomechanical model.

We have made significant progress looking at myosin isoform dependence of ATP hydrolysis product inhibition of cellular biomechanics. To correctly model the interaction between cellular energetics and biomechanics (chemo-mechanical transduction) in muscles with heterogeneous fiber populations we measured the product inhibition (inorganic phosphate, Pi) of force development in chemically demembranated single muscle cells from rat and rabbit muscle. Increased cellular levels of Pi are implicated as a mechanism of fatigue in both high intensity and chronic exercise. The relationship between [Pi] and maximum force production was determined in muscle fibers from five different muscles of rat: adductor mangus, gracilis, TFL, psoas and soleus muscles. We also measured this relationship in rabbit psoas and soleus muscle fibers to investigate possible species differences in muscle fiber chemo-mechanical properties. Muscle fiber myosin isoform was determined by gel analysis Results from these studies indicate differences in the Pi-sensitivity of force between different muscle types and between similar muscles of different species. The data were modeled with a kinetic model of chemo-mechanical transduction for muscle acto-myosin crossbridges that is based on mass action principles. This model could successfully predict the Pi-force relationships for all the muscle fiber types used in experiments. Importantly, the predictions of the model were sensitive enough to determine the affects of accumulating Pi at the levels likely to be seen during fatiguing exercise. This supports the utility of this model as a valid component of the digital cell in predicting functional alterations that occur with alterations in muscle use.

Publication:
An abstract has been submitted based on this work (Fredlund, Regnier and Chase, 2003, *Biophys. J.* 84: In press).

Key Findings From the Reid Team.

Description: This project is testing reactive oxygen species as mediators of muscle wasting, weakness, and fatigue in microgravity and is evaluating antioxidants as putative countermeasures.

Progress: In studies of cellular mechanism, we have demonstrated that 1.) gravitational unloading by hindlimb suspension increases oxidant activity within skeletal muscle fibers and 2.) reactive oxygen species activate nuclear factor-κB (NF-κB), a transcription factor known to mediate muscle catabolism. 3.) We have established that oxidative stress increases ubiquitin conjugating activity in muscle, an essential step in protein breakdown. 4.) We also have identified a novel regulatory protein that is upregulated by NF-κB. This protein, UbcH2, is a ubiquitin conjugating enzyme that is highly expressed in striated muscle and responds to catabolic stimuli, mediating the rise in ubiquitin conjugation that follows.

Operational Relevance: 1.) In evaluating countermeasure strategies, we have demonstrated that NF-κB signaling in skeletal muscle can be inhibited by bouts of muscle contraction, a response demonstrated in humans and in excised rodent muscle. This represents a novel mechanism by which exercise may inhibit disuse atrophy. 2.) We have also established that the dietary supplement curcumin inhibits NF-κB signaling in skeletal muscle. However, in these animal studies, curcumin did not inhibit atrophy of antigravity muscles caused by unloading. 3.) In a separate study, dietary supplementation with the antioxidant allopurinol was found to partially inhibit contractile dysfunction induced by unloading, blunting the overall decrement in soleus force; this was not associated with less atrophy; rather, force-per-area was protected by allopurinol. 4.) The antioxidant N-acetylcysteine (NAC), a reduced thiol donor, was not found to alter the response of murine soleus to prolonged unloading: atrophy and weakness were unaffected by NAC. 5.) However, NAC has been shown inhibit acute muscle fatigue in a variety of conditions. We currently are conducting studies of NAC effects on handgrip fatigue in human volunteers, assessing this compound as a potential oral countermeasure for use in EVA.

<u>Key Findings From the Hamilton Team.:</u>

This goal of this project is to identify candidate genes and clusters of related genes that are differentially expressed during unloading of skeletal muscle, and the impact of exercise as a countermeasure on the global gene expression pattern. This potentially has impact in providing basic insights for other microgravity researchers to base novel hypotheses and interpret their work in the context of global genomic influences of simulated microgravity and exercise. This may also have high impact in understanding the genomic influences responsible for the common and unhealthy responses to reduced muscle use during physical inactivity on earth.

The team has been focusing on analysis of gene expression in human muscle biopsies and comparative studies in rodents using microarrays. Recent revolutionary scientific advances have lead to our ability to examine almost the entire genome (~495,000 probes for ~35,000 genes). We have recently completed the first year of this project. Our laboratory has been utilizing a series of experimental designs and different bioinformatics approaches to determine the changes in gene expression involved in unloading (simulated microgravity) and exercise. A translational approach of complementary and comparative studies in humans and rodents is being performed to help point ourselves and other researchers towards the most robust and promising novel genes that cause deleterious muscle alterations during microgravity in space or physical inactivity on earth. A major goal of this work is to identify novel candidate genes implicated in the induction of the responses to simulated microgravity and activity-dependent countermeasures. In doing so, we have sought to determine the relative sensitivity of the key genes that are responsive to the loading/activity status. We aim to have established the relative degree of robustness for these responses (e.g. high level of responsiveness to short-term periods of inactivity/activity, reproducible with large sample size, statistical significance, generalized differential expression patterns in both human and rat skeletal muscle types, confirmation with alternative methodologies).

One major recent advancement has been our ability to develop objective analytical criteria for establishing the differential expression of microgravity responsive genes. Results reveal that there is indeed a small set of transcripts (< 0.03% of the genome) that are significantly impacted before the muscle is largely remodeled or atrophied, increasing the likelihood that these gene expression changes have a causal role in the initiation of adaptive responses to unloading rather than only secondary responses following the remodeled and atrophied tissue. Importantly, many of the identified genes have never been studied before in the context of muscle physiology but have been documented as master regulators of the phenotype in non-muscle tissues. Some of these are associated with the regulation of transcription, protein turnover, cell signaling, cellular transport, and lipid or glucose metabolism. These studies seeking discoveries at the global genomic level in concert with colleagues investigating different aspects of muscle plasticity are expected to lead to novel and systematic approaches of preventing the negative cascade of muscular responses caused by unloading.

Key Findings From the Wiseman Team.

In the Past Year (Year 01) our research goals were two-fold: First, to understand the role of ATP homeostasis in altering calcium handling properties of muscle cells, and secondly, to evaluate the transcriptional responses to the resulting calcium signaling patterns. In the first year, we have successfully identified and characterized an energetically challenged model to being testing our hypotheses. The progress in defining the energetics is described briefly in the following paragraphs. Calcium measurements are currently ongoing in both wild type and our model and will be completed before subsequent goals relating these changes to transcription factor responses can begin.

We explored the energetics of a known genetic defect in ATP handling, a transgenic mouse deficient in creatine kinase, a promising way to perturb the early events of calcium and ATP homeostasis. This enzyme is important in initial events of nucleotide handling (ADP buffering) and also potentially in calcium handling because the kinetics of sarcoplasmic reticular ATPase activity (calcium pumping) depends critically on adenine nucleotides. The results show that while there was no difference in resting PCr/ATP ratio in control vs. MMKO muscles the relative PCr changes after 2 s bursts of contractions at 5 Hz is quite dramatic (Figure 1) where the initial rate of PCr hydrolysis was decreased by over 75% in MMKO vs. control muscles. Concurrently peak twitch force after 2 s of 5 Hz stimulation was 95.6 ± 1.6 % of initial in control muscles vs. 70.9 ± 1.9 % in MMKO muscles thereafter the steady state approached a similar level (Fig. 2). The increase in estimated ADP associated with this deficit may explain the rapid decrease in twitch force observed at the onset of stimulation in MMKO muscle. This dramatic increase in ADP might alter calcium sequestration and/or release, thereby accounting for the rapid, compensating decrease in twitch force in MMKO muscles. In ongoing experiments we are investigating the changes in calcium homeostasis in fast-twitch, slow-twitch and mixed fiber phenotypes. Further, we have also commenced work on our second goal, to understand how muscles transcriptionally respond to these physiologic challenges.

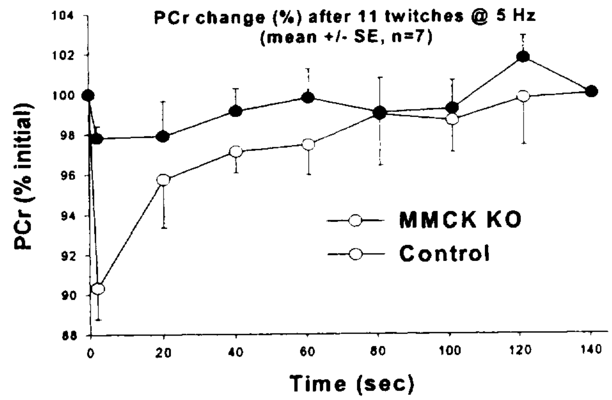
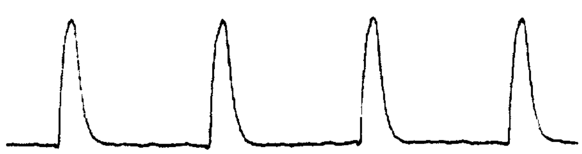
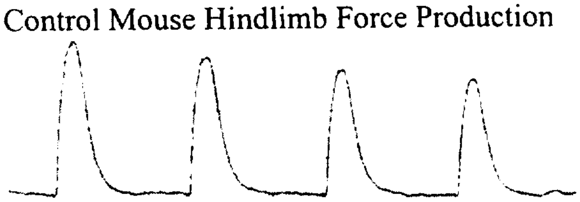


Figure 1. NMR spectroscopic detection of phosphocreatine kinetics in control (open circles) and MMCK KO (closed circles) mouse hindlimb. Note the rapid energetics buffering (rapid PCr hydrolysis) in control animals relative to the MMCK KO muscle cells.



Control Mouse Hindlimb Force Production



MM CK KO Mouse Hindlimb Force Production

Figure 2: Mechanical performance of control (upper trace) and creatine kinase knockout (lower trace) mouse hindlimb exposed to brief energetic challenges using bursts of 5 Hz stimulation. Note the rapid loss of function in the energetically challenged (MMCK KO) animals.

ANNUAL PROGRAM REPORT

NSBRI Team: **NEUROBEHAVIORAL AND PSYCHOSOCIAL FACTORS**

Team Lead:
David F. Dinges, Ph.D.
Professor of Psychology in Psychiatry
Director, Unit for Experimental Psychiatry
University of Pennsylvania School of Medicine
1013 Blockley Hall, 423 Guardian Drive
Philadelphia, PA 19104-6021
phone: 215-898-9949
fax: 215-573-6410
e-mail: dinges@mail.med.upenn.edu

Associate Team Lead:
JoAnna Wood, Ph.D.
Manager, Biobehavioral Laboratory
NASA-Johnson Space Center
2101 NASA Road 1, mail code SK3
Houston, TX 77058-3696
phone: 281-244-5524
fax: 281-244-5734
e-mail: jwood@ems.jsc.nasa.gov

Projects and Principal Investigators:

Project 1. **Individuals and Cultures in Social Isolation**
Principal Investigator: JoAnna Wood, Ph.D. (See address above under Associate Lead)

Project 2. **Psychosocial Performance Factors in Space Dwelling Groups**
Principal Investigator:
Joseph V. Brady, Ph.D.
Professor of Neuroscience
Director, Behavioral Biology Research Center
The Johns Hopkins University School of Medicine
Bayview Medical Center Campus
5510 Nathan Shock Drive, Suite 3000
Baltimore, Maryland 21224
phone: 410-550-2779
fax: 410-550-2780
e-mail: jvb@jhmi.edu

Project 3. **Distributed Team Decision Making for Long Duration Space Missions**
Principal Investigator:
Judith M. Orasanu, Ph.D.
NASA Ames Research Center
IHS, Mail Stop 262-4
Bldg. 262, Room 298
Moffett Field, CA 94035-1000
phone: 650-604-3404
fax: 650-604-3729
e-mail: jorasanu@mail.arc.nasa.gov

Project 4. **Designing a Smart Medical System for Psychosocial Support**
Principal Investigator:
James A. Carter, Ph.D.
Senior Researcher, Interactive Media Laboratory
Dartmouth Medical School
One Medical Center Drive
Colburn Hill, HB 7275
Lebanon, NH 03756

phone: 603-653-1509
fax: 603-653-1515
e-mail: james.a.carter@dartmouth.edu

Project 5. **Optical Computer Recognition of Performance Under Stress**
Principal Investigator: David F. Dinges, Ph.D. (See address above under Team Lead)

Project 6. **Speech Monitoring Cognitive and Personality Alterations**
Principal Investigator:
Philip Lieberman, Ph.D.
Professor
Department of Cognitive and Linguistic Sciences
Box 1857
Brown University
Providence, R.I. 02912-1978
phone: 401-863-2616
fax: 401-863-2255
e-mail: philip_lieberman@brown.edu

Project 7. **Quick Assessment of Basic Cognitive Functions**
Principal Investigator:
Stephen M. Kosslyn, Ph.D.
Professor
Department of Psychology
William James Hall 830
Harvard University
33 Kirkland Street
Cambridge, MA 02138-3846
phone: 617-495-3932
fax: 617-496-3122
e-mail: smk@wjh.harvard.edu

Project 8. **Stress, Performance and Locus Coeruleus**
Principal Investigator:
Gary Aston-Jones, Ph.D.
Professor and Director
Laboratory for Neuromodulation and Behavior
University of Pennsylvania School of Medicine
VAMC Medical Research
University and Woodland Avenues
Philadelphia, PA 19104
phone: 215-573-5200
fax: 215-573-5201
e-mail: gaj@mail.med.upenn.edu

Team Lead 10-31-02
Date

TABLE OF CONTENTS

I. ABSTRACT

The NSBRI Neurobehavioral and Psychosocial Factors Team encompasses the Critical Path Roadmap scientific questions from two of the four areas subsumed under Behavior and Human Performance: (1) Human performance failure because of poor psychosocial adaptation (area 18), and Human performance failure because of neurobehavioral dysfunction (area 21). The Team is charged with conducting research on the development of countermeasures that will ensure that astronaut behavioral health is maintained during prolonged space missions, and that both individual astronaut and crew functioning are effectively optimized. The eight ground-based projects making up the current Team have been underway an average of 19 months. The studies are divided equally between psychosocial and neurobehavioral scientific questions. They cover a considerable breadth of scientific techniques—projects range from studies of humans living in an analog environment to neurobiological studies of rodents performing under conditions of stress. This breadth notwithstanding, the overarching focus of all eight projects is on the impact of stress—individual and interpersonal—on behavioral functions. Collectively, the projects seek to identify (1) the causes of stress, and its consequences for astronaut cognitive, affective and social functioning; (2) techniques to objectively detect stress reactions and performance deficits in individuals and groups in the remoteness of space; and (3) countermeasures to prevent and otherwise mitigate the occurrence of stress reactions and their adverse effects on individual and crew performance. During the past year all projects have progressed to the stage of data acquisition and hypothesis testing. Project 1 (Wood et al.) is studying the role of personality, culture, and group characteristics on both individual and group performance in Antarctica. One important early finding is that female station leaders perceive significantly less social support from fellow expeditioners than do males and female subordinates, or male station leaders, which suggests a need to find flexible approaches to providing support from outside the crew. Projects 2 (Brady et al.) and 3 (Orasanu et al.) have completed development and implementation of their simulated task environments, which are being used to evaluate the factors that promote and degrade distributed team communication and problem solving. Project 4 (Carter et al.) has completed consultation interviews with 11 astronauts who have long-duration space flight experience and numerous ground control personnel, to develop the content needed for a prototypical smart medical system for psychosocial and neurobehavioral support in space flight. Project 5 (Dinges et al.) has completed development of a technique for robust 3-dimensional (3D) tracking of facial expression for the detection of behavioral stress. Project 6 (Lieberman et al.) has also made significant progress in developing and validating a speech-based computer algorithm for detecting cognitive impairment and emotional changes associated with hypoxia and stress in Everest climbers. Project 7 (Kosslyn et al.) has completed development of a set of brief cognitive performance tasks on a hand-held device that can be used to quickly assess cognitive capability in remote locations. Project 8 (Aston-Jones et al.) has established that performance on a target detection task varies markedly under different stress loads, implicating the noradrengeric locus coeruleus in maintenance of stable vigilance performance (and its vulnerability to stress effects), and suggesting that the central noradrenergic system may be a valid target for the development of pharmacological countermeasures to the neurobehavioral effects of stressors. It is anticipated that all projects will complete hypothesis testing during their third year of support.

II. INTRODUCTION

As currently configured, the Neurobehavioral and Psychosocial Factors Team is primarily focused on reducing the risks of human performance failure due to poor psychosocial adaptation (Goal 1) or neurobehavioral dysfunction (Goal 2). Specifically, the Team seeks to counter the development of psychosocial risks (Goal 1) manifested through inadequate leadership; interpersonal strife or social alienation (e.g., due to gender, culture or status differences); poor group teamwork; lack of crew coordination in problem solving; ineffective communications within the team or with ground controllers; and loss of crew morale. In a parallel manner, other projects on the Team seek to counter risks to neurobehavioral health (Goal 2) manifested through stress reactions; anxiety; depression; loneliness; anger; and neurocognitive impairments. Unlike some areas of NSBRI research, where there is a single source for the biomedical problem (e.g., microgravity effects on muscle or bone), there are a considerable number of factors in prolonged space flight that could create or contribute to neurobehavioral and psychosocial dysfunctions (e.g., excessively scheduled activities and work requirements, poor physiological adaptation to microgravity; interpersonal strife; perceived risks to health; loneliness for family; inadequate communication with Earth; habitability constraints; radiation). Consequently, the countermeasures being developed through the research by the Neurobehavioral and Psychosocial Factors Team necessarily must cover an array of issues and approaches. The following are the various categories in which countermeasure development is anticipated from the research on the Team.

1—Selection criteria for optimal crew cohesion, including culture and gender diversity

2—Training for group living; training for flight and ground crew optimal relations

3—Guidelines to optimize communication for crew decisions and problem solving

4—Technologies for monitoring and early diagnosis of cognitive problems, emotional disturbances, and psychosocial dysfunction

5—Behavioral treatments for stress; affective disorders; and for resolving team conflicts

6—Pharmacological treatments for stress; affective disorders and serious neuropsychiatric and neurological reactions

7—Habitability strategies for privacy; and work strategies for motivation and performance

8—Support for relaxation and leisure activity for enhancing quality of life

9—Support for assimilating crews psychosocially and neurobehaviorally after return

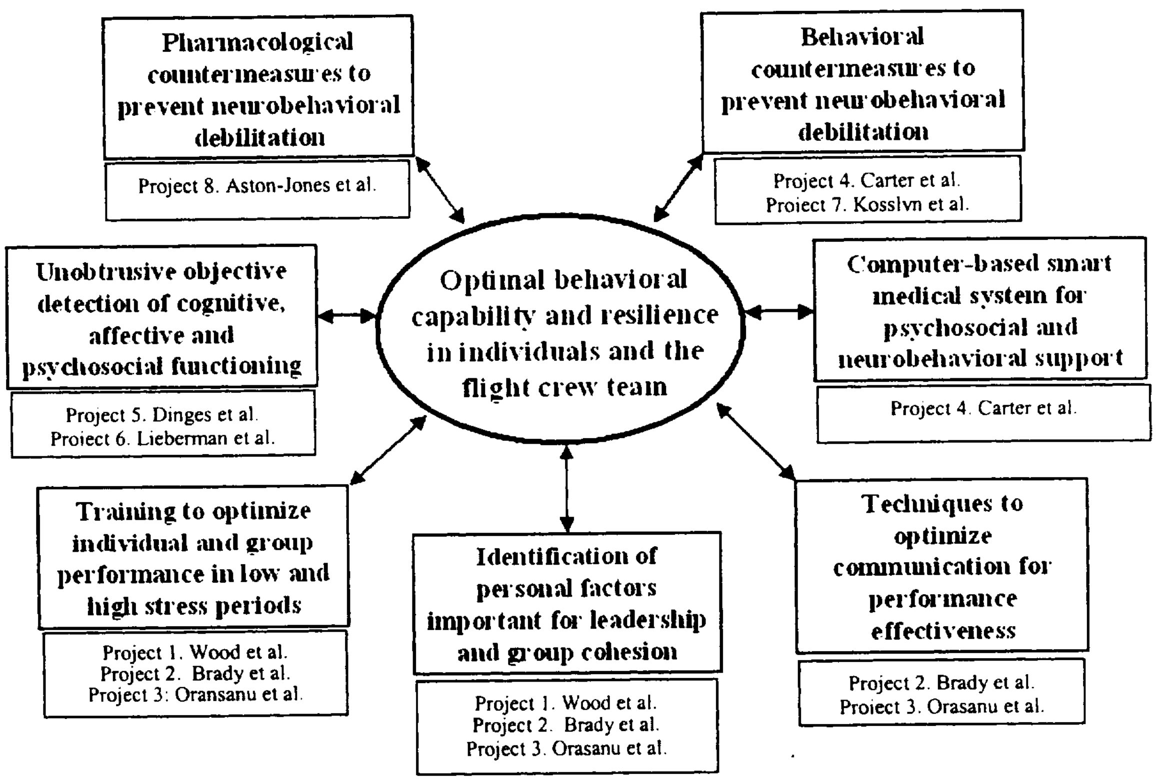
10—Novel countermeasure opportunities identified by NASA and through new scientific efforts

11—Development of a database on the neurobehavioral and psychosocial effects of countermeasures for other biomedical problems in space flight

III. RESEARCH PROGRAM STRUCTURE AND DESIGN

The problems addressed in the Neurobehavioral and Psychosocial Factors research area generally focus on developing countermeasures for severe stress reactions, depression, cognitive dysfunction, and conflict resolution during long-duration space travel. The initial strategic research agenda for the Team involves eight ground-based studies and two as yet unfunded flight experiments (under consideration at JSC) that collectively address four thematically interrelated questions: What are the effects of culture, personality, and leadership on performance, stress, and health in isolated groups? What are the major influences on interpersonal actions, communications, and problem solving in small groups? How can affective, neurobehavioral and neurocognitive dysfunction be objectively detected in remote locations? What neurobiological processes of stress and arousal are the optimal targets for behavioral and pharmacological interventions? Six inter-related themes define the range of factors critical for improving crew health and safety and for optimizing performance capability: (1) Biological mechanisms of neurobehavioral dysfunction; (2) Motivation, cognition and performance; (3) Individual factors in selection, training, performance; (4) Pharmacology in space; (5) Team and interpersonal optimization; and (6) Organizational, cultural and management factors.

The figure below illustrates the Neurobehavioral and Psychosocial Factors Team major research themes and anticipated countermeasure types of the current projects, as well as the projects relevant to each theme. Together the projects address critical complementary components to the maintenance of behavioral and psychosocial health and capability during long duration missions.



The eight ground-based projects making up the Neurobehavioral and Psychosocial Factors Team have been underway an average of 19 months. The projects are described below relative to their respective themes, progress to date and implications. Projects 1 through 4 deal primarily with research questions on "Human performance failure because of poor psychosocial adaptation," which is area 18 from the Critical Path Roadmap. Projects 5 through 8 are concerned primarily with "Human performance failure because of neurobehavioral dysfunction," which is area 21 from the Critical Path Roadmap.

IV. RESEARCH PROGRAM ACCOMPLISHMENTS

For the most part, the projects on the Neurobehavioral and Psychosocial Factors Team have completed the needed technical and preliminary feasibility work for a new area, and are now making progress on data acquisition. As a result, there are still relatively few published findings. Progress on each project during the past year is described below.

Project 1. Wood, J., Helmreich, R., Lugg, D.: Individuals and Cultures in Social Isolation. This project focuses on psychosocial critical path questions. The goal is to increase understanding of the effects of personality, culture, and group characteristics on both individual and group performance in an extreme environment (Antarctica) that parallels many of the conditions likely to occur in long-duration space missions.

Progress: Investigators have nearly completed the second year of the planned two years of data collection. Blood samples to be analyzed for seven neuropeptides will be returned to the U. S. during the austral summer. Preliminary analysis of data from the Helmreich PCI (a personality scale that measures instrumentality, expressivity, and seven other subscales) comparing them to expeditioners from Britain and Norway found that the 3 Antarctic samples were similar to each other on the traits measured by the PCI, despite the fact they are all from different countries. They also scored lower on traits that are generally believed to be undesirable for confined living when compared to students from the U.S. and Norway. Whether these results are due to self-selection (only people with certain traits volunteer) or screening (only people with certain traits are accepted) remains an open issue. These data also support previous research that suggests selection criteria based on scores from the PCI are not likely to favor or disfavor candidates from specific nations. Comparisons of PCI scores with data from the 16PF (another personality scale used to screen potential expeditioners) revealed little overlap, which suggests that the PCI taps different characteristics than does the 16PF.

Data from the first year's administration of the weekly psychological questionnaire have been combined with similar data from previous studies in order to examine group effects and individual differences on several outcome measures. One important finding is that female station leaders perceive significantly less social support from fellow expeditioners than do female subordinates, male subordinates, or male station leaders. In a similar vein, we are developing a multi-level model of interpersonal tensions that includes individual personality traits and station leadership as predictors.

Implications: Although all results are preliminary, these findings have implications for selection and support of crewmembers for long-duration space flight. The PCI may provide valuable information to augment selection and assignment of crews. The findings on social support suggest a need to find flexible approaches to providing support from outside the crew and, perhaps, for additional training for all crewmembers. Findings on interpersonal tensions highlight the multi-causality of most social problems. In addition to their relevance to long-duration space missions, these findings are important for any organization sponsoring the activities of small groups in extreme environments.

Project 2. Brady, J. et al.: Psychosocial Performance Factors in Space Dwelling Groups. This project focuses on psychosocial critical path questions. The goal is to determine the effects of variations in the structure and function of communication channels within and between simulated space-dwelling and Earth-based groups. It addresses the effects on psychosocial performance effectiveness of (1) stressful environmental and behavioral interactions; (2) variations in the appetitive and aversive characteristics of incentive control systems; and (3) selection, training and experience. The research methodology involves development of a distributed interactive multi-person simulation in computer-generated environments as an experimental test bed for modeling psychosocial performances within and between space-dwelling and Earth-based groups. The simulated task environment (STE) provides an automated means of setting the context for the analysis of performance in space-dwelling groups and monitoring the effects of varying experimental conditions on psychosocial interactions.

Progress: The major accomplishments of the project during the past 12 months have included the construction and activation of a dedicated Space Research Laboratory at the Institutes for Behavior Resources as well as the completion and operational testing of the distributed interactive simulation software and hardware systems to study disbursed groups in simulated space environments. It has been the initial objective of this research initiative to provide an STE experimental test bed for modeling the effects of variations in the structure and function of communication channels within and between space flight units and mission operations control centers using the computer-generated simulation methodology as an automated means of electronically monitoring and measuring performance effectiveness.

During the past 12 months professional and technical support staff have been recruited and trained for computer system maintenance as well as screening and assessment of research volunteer participants and the conduct of experimental test sessions. Preliminary testing of the distributed interactive simulation methods and procedures has also been completed to calibrate scenario difficulty, troubleshoot instructions, and refine task effectiveness measures. Recruitment of 3-person simulated spaceflight volunteer experimental crews has also been undertaken during the past several months with the successful result of having thus far enrolled four groups who have agreed to join our 'simulated astronaut corps' with the understanding that they will participate in recurrently scheduled 'flights' and 'missions' over the coming months.

The most salient progress to be reported is the launching of an experimental series of simulated space 'flights' and 'missions' with three different groups of volunteer 'astronauts' over the past several weeks. Each member of the 3-person crews was located at a workstation isolated both physically and acoustically from the others and from a remotely located monitoring center. A computer at each station controlled the simulated performance task and the communication network. The STE performance task scenario for the initial studies focused upon a 3-crew planetary exploration with the primary mission of geologic specimen collection and analysis. The three separate duty stations represented crew positions located in a Rover (sample collection), Lander (sample storage), and Orbiter (sample analysis). The communication network permitted crewmembers to interact via text messages, drawings on a shared 'white board', video of each other, and audio vocal exchanges. Performance effectiveness, based on the crews' collection and analysis of graded value geologic samples varying in density, shape, size, etc. was dependent upon inter-crew communication to solve problems regarding the relationship between relevant sample characteristics and the range of geologic sample grade values.

Implications: The results of these initial studies show that cooperative and productive interactions can be maintained between individually isolated and dispersed members of simulated spaceflight crews communicating and problem solving effectively over extended time intervals. There was a high degree of interchangeability between audio vocal, text messages, and white board modalities suggesting that extended distributed interactive simulation studies might usefully focus upon the development and testing of potential countermeasures to the performance impairing effects of communication system constraints and failures.

Project 3. Orasanu, J. et al: Distributed Team Decision Making in Exploration Missions. This project focuses on psychosocial critical path questions. The goal is to examine how team structure and communication medium affect the nature and quality of small team interaction, distributed decision making strategies, and problem solving under a variety of stressful conditions (i.e., time pressure, risk level, information accuracy/completeness). In addition, autonomic nervous system markers are assessed, and the Specific Affect Coding System technology is used for detecting when crew interactions and decision-making are degrading.

Progress: A new laboratory was established to conduct the research. Four individual computer workstations plus a master control station were connected through a local area network to support team collaboration during a simulated search and rescue task (STE). Physiological monitoring devices (Biologs developed by UFI) available at NASA Ames Research Center have been adapted for use in the experiments. A video camera is installed in each work area to record facial affect while participants engage in the task. Communication switching devices are available to each player for channeling messages to selected recipients. Dependent measures from various sources (i.e., physiological monitors, video-facial affect) will be time-stamped and coordinated to facilitate analysis.

A preliminary study of seven candidate physiological measurements was done to determine which of them were most sensitive to low levels of emotional and mental stress and thus best suited for early detection of stress. We sought to reduce the number of measurements from seven to four in order to minimize subject burden. Another concern was whether physiological measurements taken at alternate locations on the body would provide meaningful data while allowing maximum movement and comfort. Various evaluations resulted in the following measures being chosen for use: ECG (R-R interval, heart rate); EMG (frequency power spectra and the amplitude within the band width of 10-25 Hz); respiration (frequency and amplitude), and skin conductance levels (SCL).

Materials have been developed for use in our study of team interactions during computer-based problem solving. A search and rescue problem set in Antarctica requires four players to develop plans, manage resources, and collaborate in order to find a lost party and accomplish other tasks under complex time-constrained conditions. Four versions of three scenarios have been developed, along with training materials. Two versions of each scenario induce cooperation between team members and will vary in task difficulty (moderate and high). The other two versions induce team conflict (again, one of moderate and the other of high task difficulty). Pilot data are currently being collected on each version.

Implications: Findings on the effects of stressors on team performance in a dynamic challenging task will extend the research base to include problem solving, communication, and cooperation behaviors. The combination of selected physiological measures and facial affect measurements may yield a powerful instrument for assessing low levels of mental and emotional stress. If successful, this tool could lead to early introduction of countermeasures, thus preventing development of high levels of stress and deterioration of space crew performance. Positive stress-coping behaviors will be extracted from the findings and will serve as a basis for developing interactional and strategic behaviors for managing challenging team tasks and interpersonal interactions. Findings developed in the laboratory will be extended to non-laboratory environments, such as simulations of long-duration missions involving multi-cultural crews (e.g., NASDA or ESA studies). A long-range goal is to adapt the tools for use by flight crews as self-monitoring and management systems.

Project 4. Carter, J. et al.: Designing a Smart Medical System for Psychosocial Support. This project focuses on psychosocial and neurobehavioral critical path questions. The goal is to develop a prototypical smart medical system for psychosocial and neurobehavioral support in space flight. The computer-based system will include the systems infrastructure and basic functions of three modules—self-diagnosis of psychological problems, treatment of depression, and conflict management. The prototype will apply IML's Virtual Practicum model, creating an immersive, welcoming environment in which to seek assistance for psychosocial problems. The computer-based system will address neurobehavioral issues, including the assessment of affect and suggested interventions, and provide a training module on interpersonal conflict resolution. The system will be developed and evaluated with experienced users and content experts. If it proves effective, the prototype could be expanded to include additional modules for diagnosis, treatment, patient management, and prevention of any possible psychosocial problems that might arise on space missions.

Progress. Since this project involves interviewing current NASA personnel (astronauts and other operations), it was necessary to secure NASA-JSC CPHS/IRB approval. This was accomplished with some revisions of methods and aims being made in order to accommodate NASA's requirements. In particular the IRB required that the background interview be refocused on consultation about hypothetical problem scenarios instead of asking about actual psychosocial problems that have occurred during space flights. This change will not threaten the original specific aims of the project, and in fact may strengthen the results to the extent that this approach will yield new information on how skillful veteran long duration astronauts would handle various situations relative to novice astronauts.

During the past year, consultation interviews were conducted with two International Space Station flyers, five American Mir flyers, and four Skylab flyers (anticipating at least two additional interviews), plus consultation interviews with long-duration ground crew staff (one flight surgeon and most of the JSC psychosocial support staff). Each interview involved presenting five scenarios to each astronaut dealing with the following topics: Depression; a conflict among space crewmembers; or a conflict between space flight crew and ground crew. Each interview inquired as to what an experienced veteran would do in the situation and what common pitfalls could occur. Astronauts were also asked what other situations would be important for including in training scenarios. These data are being compiled and analyzed.

Strategies for empirically evaluating the completed versions of the depression management and conflict management programs are also being developed in collaboration with two other NSBRI PI's and building on their NSBRI-supported work. Development of all multimedia program designs, content documents, scripts and interactive logic is also underway. These documents relate to both the prototype (which is the scope of the present project) and future completion of the depression and conflict management programs, as well as the overall architecture of the

Psychosocial Support System. If year 03 funding becomes available, these plans will facilitate completion of these programs (although they will also be modified based on evaluation data).

Implications: The interviews conducted with long-duration astronauts provide insights that would otherwise be unavailable to the research team regarding ways of managing psychosocial problems in space flight. They enable the development of more realistic training simulations via incorporation of the responses of experienced veteran astronauts. They also will provide the basis for cataloging best practices for managing psychosocial problems on long-duration space flights from the perspective of astronauts with long-duration flight experience. A secondary benefit of these interviews is to introduce the project to the astronaut community, obtain support, and develop relationships with the astronauts—crucial to the countermeasure's successful completion and implementation. All interviewees have indicated that a smart medical system for psychosocial and neurobehavioral support would be valuable for long-duration space flights.

Project 5. Dinges, D. et al.: Optical Computer Recognition of Behavioral Stress.
This project focuses on neurobehavioral critical path questions. The goal is to determine whether a state-of-the-art optical computer recognition algorithm based on facial expression can be developed that will objectively discriminate when subjects are undergoing behavioral stressors and negative affect. It also evaluates the effects of behavioral stressors on physiological responses (cortisol and heart rate variability), on psychological responses (subjective ratings), and on performance responses, and explores the magnitude of stress responses relative to the accuracy of the optically based computer recognition algorithm of the face, sex, age and ethnicity.

Progress: Significant advances in programming and enhancement of the capabilities of the computer recognition algorithm were completed during the past year, to develop a technique for robust 3-dimensional (3D) tracking of facial expression. Put simply, the new technique, developed by Dr. Metaxas and colleagues, allows the translation of 2D video footage to a form that can be used for tracking the 3D orientation and translation of the face, as well as parameters that describe the movement of eyebrows, mouth, etc. This third generation computer optical mask handles facial and head motion extremely well and provides high spatial resolution around the facial areas where affective expression are most thoroughly communicated.

The paradigms being used to induce low and high behavioral stress have also been markedly refined based on previous repeated work. Preliminary studies revealed that stress induction is best done by a combination of varying performance demands (e.g., high behavioral stress is induced via high workload, task difficulty, time pressure), and by providing subjects with overly positive or negative feedback regarding their performance on the neurobehavioral tasks during the protocol. The latter is done by performance ratings from the experimenter during testing, and on-screen feedback at the end of each performance testing session. In the high behavioral stress condition, subjects are informed on screen and verbally through the intercom that they are not performing as well as most people do on the tasks and should try harder (this information is given not matter how well they perform—a condition approved by the Human Subjects IRB). Data acquisition has been underway for the experiment. It is anticipated that it will be completed on a total of 60 healthy adults (male and female; 22-45 years; ethnic diversity) midway through year 03.

Implications: If optical computer recognition of behaviorally induced stress (with its subjective and physiological concomitants) can be demonstrated to work, then we will have an unobtrusive technique for monitoring stress levels onboard long-duration space craft. Two additional obstacles will need to be overcome to make this feasible in space. The first concerns the edema of the face due to fluid shifts in microgravity, and the second concerns the belief that astronauts are alexithymic (i.e., don't show affect in the face). The former concern will be addressed experimentally in a future study using head down tilt to simulate fluid shifts, while the latter will be addressed experimentally by relating the validity and reliability of optical computer recognition algorithms to alexithymia as measured by a subjective scale being used in the current study.

Project 6. Lieberman, P. et al.: Speech Monitoring, Cognitive and Personality Alterations.
This project focuses on neurobehavioral critical path questions. The goal is to develop a system that will detect cognitive deficits, changes in personality and emotional disturbances by means of acoustic measures of speech. The project utilizes data from studies of speech and behavior of individuals in a space analog environment (Mt. Everest climbers) as well as patients suffering neurodegenerative diseases (Parkinson patients), to develop and verify techniques for analysis of conversational speech for detection of cognitive changes.

Progress: A procedure has been developed to remotely detect impaired decision-making and linguistic ability by means of computer-implemented acoustic analysis of a person's speech. In the past year the approach to acoustic speech measures of cognitive dysfunction has been refined, and the most critical application of this technique–detecting impaired, life-threatening, decision-making ability—has been validated.

The primary space analogue used in this study is evaluation of the speech of climbers ascending Mount Everest, where oxygen deficits adversely affect these neural circuits regulating motor control and others involved in cognition, language and personality changes. Everest climbers are also performing in the presence of life-threatening situations and stress. In the past 12 months we studied 17 climbers ascending Everest. Speech samples were obtained, and cognitive and sentence comprehension tests were administered at Base Camp (5,300 m), and by radio links to Camp 2 (6,500 m) and to Camp 3 (7,200 m). Pulse oximeter data also were obtained.

Validation of the impairment-detection methodology occurred when an profoundly unfortunate incident took place beyond our control. One subject, whose cognitive behavior was unimpaired at Base Camp on everest, showed extreme speech and cognitive deficits two days later at Camp 2. His deficits resembled those of subjects previously tested in laboratory conditions, who had profound damage to the basal ganglia structures of the brain that regulate both motor control and cognition. He was advised of his performance, but insisted that he was fine, an apparent concomitant effect of neural impairment. Weather deteriorated and his teammates descended, advising him to descend. He instead perseverated—a known consequence of basal ganglia dysfunction. He followed his original plan and ascended to Camp 3 where he developed acute mountain sickness. On the following day, he attempted to descend but failed to clip his safety harness to the fixed ropes, falling to his death. (Failure to properly anchor tethers apparently has been a problem on Space Shuttle missions.) Other climbers involved in that episode showed no or only moderate speech motor and cognitive deficits.

Implications: It is anticipated that in long-duration space flight, exposure to cosmic rays may damage the neural circuits that are involved in the speech changes observed with altitude hypoxia. Eye-tracking techniques have also been used during the past year with Parkinson Disease patients to refine measures of language comprehension. The techniques that being developed have found application by the National Transportation Safety Board (NTSB) in investigations of fatal air crashes where hypoxia is a possibility. These procedures also are useful in the evaluation and treatment of Parkinson's and other neurodegenerative diseases and show promise for the diagnosis and treatment of schizophrenia, which appears to involve similar neural circuitry.

Project 7. Kosslyn, S., et al.: Quick Assessment of Basic Cognitive Functions.
This project focuses on neurobehavioral critical path questions. The goal is to develop a set of brief performance tasks on a hand-held device that will be computerized versions of 11 standard tasks from cognitive psychology, which tap the range of basic cognitive abilities. The performance tasks being developed will be very short versions or variants of tasks that will capture the processing differences indicated by scores on the standard tasks and be designed to be self-administered.

Progress: The first year of the project (the period covered by this report) focused on developing the Palm Pilot application, dubbed MiniCog, and in the scripting of a number of short cognitive tasks to be administered by this program. Bay Area Software was commissioned to write the code for both the handheld application and a desktop scripting interface. Bay Area Software is run by Sam Kho, who was the chief programmer for the M100 series of Palm Pilots, and his associate, Jolly Chen, also a programmer for Palm, Inc.

Tasks were scripted using an off-the-shelf HMTL editor, and then converted to a Palm OS compatible format using an interface provided by Bay Area Software. MiniCog is designed to read task scripts, present stimuli for specific amounts of time, and record responses and response times, along with a time-and-date stamp and basic user info (ID, date of birth, sex, and handedness). When a task is complete, users are prompted to enter a password to see a display of their current score (as a function of response time, error rate, or variance, compared to norms). All data are stored for later upload to a desktop computer where more detailed analyses can be performed. The tasks differ only in the instructions (which are presented in initial screens), stimuli, and the number of response keys used.

Based on the literature in cognitive psychology and cognitive neuroscience, the initial tasks selected tap key features of information processing. The specific tasks implemented assess motor control, attention (vigilance, divided attention, and filtering), spatial relations encoding (categorical and coordinate), working memory (verbal and spatial), and problem solving (verbal and spatial). MiniCog is flexible, allowing one to program new tasks quickly and easily as the need arises (e.g., to test a specific aspect of functioning that is needed for a particular real-world application). However, the current version has the following limitations: 1) Only visual stimuli can be presented; 2) the stimuli are presented either in a random order or in a fixed order (adaptive testing is not possible); 3) the responses are limited to key presses (up to 6 keys can be used).

Data acquisition is underway comparing the MiniCog task performance to the longer versions of the tasks, and developing normative data on the MiniCog battery of tasks under both standard laboratory conditions, and under experimental conditions (e.g., stress, sleep-deprivation).

Implications: With the development of the MiniCog platform, other researchers can use the battery to develop their own portable psychological tasks. Both the MiniCog application and the current set of tasks have an advantage over many typical psychological scripting programs and standard tests that they are brief and the method of administration is extremely compact, portable, and inexpensive. This could make the MiniCog practical in a wide range of settings where there are questions of neurocognitive capability.

Project 8. Aston-Jones, G., et al.: Stress, Performance and Locus Coeruleus.
This project is currently the sole basic neuroscience research (i.e., using non-human species) on the Team. It focuses on neurobehavioral critical path questions. The goal is to analyze locus coeruleus (LC) activity during a continuous performance task, to determine the effects of acute and repeated stress on changes in LC function and performance, and identify pharmacological countermeasures to mitigate stress effects on LC activity and attentional function.

Progress: In the last year a target detection continuous performance task was developed that rats can learn rapidly. This task mimics many of the attributes of the target detection task used in previous studies in monkeys in which LC activity appears to play a major role in performance. Rats initiate each trial by pressing one lever, and then must discriminate between two signal lights to determine if the one illuminated is a target or non-target. If the target signal light is illuminated the rat must press a second lever to obtain food reward. If the non-target is illuminated he must withhold responding with no reward and await the next trial. Targets occur randomly on 20% of the trials. This task is the means by which performance abilities and changes are measured in the experiments being performed on stress induction and pharmacologic treatments.

This past year performance on the target detection continuous performance task date was tested under various stressors conditions including acute noise, social deprivation, restraint and restraint coupled with noise. Rats quickly habituate to all but the double stressors (restraint + noise), which yielded promising stress effects on performance. Astronauts are exposed to these stresses in any space mission. Results indicate that double stress during task performance increased (up to 40%) responding to the non-target stimulus (false alarm (FA) error) in this task. The alpha2 adrenoceptor agonist clonidine (which decreases LC-NE transmission) at a very low dose of 1.0 μg/kg reduced the FA error rate seen with the double stress. Higher doses of clonidine (8.0 and 25.0 μg /kg) produced sedation. More study is required to confirm these findings, but they support the hypothesis that an optimum level of noradrenergic tone is necessary for optimal performance on a sustained attention task. If noradrenergic levels become too high because of stress or too low (in the case of high dose of clonidine), then performance declines.

Implications: The present findings are preliminary. Nonetheless, they are promising for the development of countermeasures to stress effects on performance. Specifically, the task being used may serve as a relatively high throughput behavioral assay for testing effects of different pharmacological agents on stress-induced performance impairments in a simple animal model. In addition, the results with clonidine indicate that the central noradrenergic system may be a valid target for the development of countermeasures. These findings are consistent with the initial hypothesis of this project that over-activity of the LC system could underlie at least some effects of stress on performance. This calls for additional work with these and other noradrenergic agents (e.g., beta-receptor antagonists) to tailor pharmacologic countermeasures and limit stress effects on performance in space.

Flight experiments under evaluation at JSC.

The Team has two proposed flight experiments that continue to be evaluated for feasibility at Johnson Space Center. Since these projects are not yet funded or approved for flight, they are listed here only P.I. and Project Title.

Brunner, L., et al.: Effect of Spaceflight on Pharmacokinetics of Psychotherapeutic Agents.
The goal is to determine the effects of space flight on the pharmacokinetics, pharmacodynamics and the underlying physiologic processes (gastric motility and drug absorption), of the anti-anxiety drug, lorazepam (Ativan®), and the anti-depressant drug, venlafaxine (Effexor®).

Kanas, N., et al.: Psychosocial Education (PSE) Training for ISS Missions.
The goal is to evaluate the effectiveness in five International Space Station (ISS) crews and their support personnel of a 5-hour, pre-launch Psychosocial Education (PSE) training program designed to reduce tension and displacement of dysphoria to outside personnel, and to increase cohesion, leader support, expressiveness and personal growth.

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

Research Team Annual Report
November, 2002

Research Team: **Neurovestibular Adaptation**

Team Leader:

Charles M. Oman, Ph.D
Director, Man Vehicle Laboratory
Room 37-219
Massachusetts Institute of Technology
Cambridge, MA 02139 USA
(617) 253-7508; (671) 258-8111 (fax)
cmo@space.mit.edu

Associate Team Leaders:

Conrad Wall, III
Director, Jenks Vestibular Diagnostic Laboratory
Massachusetts Eye and Ear Infirmary
243 Charles Street
Boston, MA 02114

Bernard Cohen, M.D.
Department of Neurology
Mount Sinai School of Medicine
1 East 100th Street
New York, NY 10029

Projects and Principal Investigators

- Context-Specificity and Other Approaches to Neurovestibular Adaptation
  Mark J. Shelhamer, Sc.D., Johns Hopkins University School of Medicine
  (410) 614-6302 mjs@dizzy.med.jhu.edu
- Neuro-Vestibular Aspects of Artificial Gravity Created by Short-Radius Centrifugation.
  Laurence R. Young, Sc.D., Massachusetts Institute of Technology
  (617) 253-7759, lry@space.mit.edu
- Modification of Eccentric Gaze-Holding
  Millard F. Reschke, Ph.D, NASA Johnson Space Center
  (281) 483-7210millard.f.reschke@jsc.nasa.gov
- Visual Orientation and Spatial Memory: Mechanisms and Countermeasures
  Charles M. Oman, Ph.D., Massachusetts Institute of Technology ,
  (617) 253-7508, coman@mit.edu
- Advanced Techniques to Assess and Counter Gait Ataxia
  Conrad Wall III, Ph.D., Massachusetts Eye and Ear Infirmary
  (617) 573-4160, cwall@mit.edu
- Understanding Full-Body Gaze Control During Locomotion
  Jacob J. Bloomberg, Ph.D, NASA Johnson Space Center,
  (281) 483-0436 jacob.j.bloomberg1@jsc.nasa.gov
- Pharmacological Countermeasures for Space Motion Sickness
  John L. Dornhoffer, M.D. University of Arkansas for Medical Sciences,
  (501) 686-5016, DornhofferJohnL@uams.edu

Table of Contents

I. ABSTRACT

The most overt change affecting an astronaut in space flight is the immediate response of the neurovestibular system to changes in gravity. NSBRI's neurovestibular adaptation research program is aimed at developing scientifically-based countermeasures against the vestibular problems associated with space flight. Problems typically arise first when astronauts transition from 1-G to 0-G, unfortunately at a time when their physical and cognitive performance is often critical for mission success and safety. Postflight problems have generally been more severe after 3-5 month Mir and ISS flights than on 1-2 week Shuttle missions, showing that some components of vestibular adaptation to 0-G take place over time scales of months, rather than weeks. Operationally significant vestibular problems are also anticipated when astronauts make the transition from 0-G to partial G, or from 0-G to an artificial gravity environment. NSBRI research is designed to develop countermeasures for a broad set of risks identified by the team and the NASA Critical Path project. These currently are (in priority order): 1. Vertigo on reentry and landing, 2. Acute space motion sickness, 3. Postlanding imbalance, instability, vertigo and orthostatic hypotension or failed landing. 4. Inflight spatial disorientation and frame of reference problems, 5. Chronic space motion symptoms .6. Artificial Gravity related disorientation, nausea, vomiting, and loss of coordination. 7. Peripheral and central vestibular function changes.

The seven projects in the current portfolio have made significant progress since the fall of 2000. Sixty five research publications have issued so far. Results from six of the seven projects will appear in a peer reviewed upcoming special issue of the Journal of Vestibular Research. The Team maintains active collaborations with other investigators at NASA and in the international community, and recently co-sponsored (with NIH) a successful international Space Vestibular Symposium in Portland, Oregon. Proceedings will be published by the Journal of Vestibular Research. In the context of countermeasure development, project highlights of programmatic significance during 2002 include:

1) Relative to postlanding vertigo: Drs. Wall/Oddson delivered a compact, portable balance disturber countermeasure to JSC, where Drs. Bloomberg/Mulavara have established normative data locomotion and dynamic visual acuity for use as a clinical measure of fitness for return-to-duty, and efficacy of rehabiliatative countermeasures.

2) Relative to artificial gravity: Drs. Young/Hecht demonstrated context specific adaptation to Coriolis stimulation, essential if short radius centrifugation is to be used as a countermeasure.

3) Relative to inflight disorientation and frame of reference problems: Drs. Oman/Harris/Taube developed new methods to quantify the "gravitational polarity" of visual scenes useful for design of spacecraft interiors and workspaces, and demonstrated the feasibility of 3D spatial memory training countermeasure. They also showed that animal head direction cells exhibit a distinct "disorientation" response state.

II. INTRODUCTION

The most overt change affecting an astronaut in space flight is the immediate response of the neurovestibular system to changes in gravity. NSBRI's neurovestibular adaptation research program supports research aimed at developing scientifically-based countermeasures against the vestibular problems associated with space flight: spatial disorientation, space motion sickness, oculomotor deficits, postflight postural instability and gait ataxia. Problems typically arise first when astronauts transition from 1-G to 0-G, unfortunately at a time when their physical and cognitive performance is often critical for mission success and safety. Postflight problems have generally been more severe after 3-5 month Mir and ISS flights than on 1-2 week Shuttle missions, showing that some components of vestibular adaptation to 0-G take place over time scales of months, rather than weeks. Operationally significant vestibular problems are also anticipated when astronauts make the transition from 0-G to partial G, or from 0-G to an artificial gravity environment. During the Shuttle/Spacelab era (1980s and 90s), many of NASA's major ground and flight neurovestibular experiments addressed basic issues related to the effects of 0-G vestibular reflexes. NSBRI research is designed to develop countermeasures for a broader set of risks identified by the NASA Critical Path project. In 1997, five principal neurovestibular risk areas were identified (criticalpath.jsc.nasa.gov/main.asp). Since that time, additional information has become available from long duration Shuttle, Mir and ISS flights. Because of NASA's shift in emphasis from exploration (e.g. Mars) missions to long duration ISS long duration flights, the NSBRI neurovestibular team reexamined its critical path risks. In collaboration with colleagues from the JSC Neurophysiology lab, and the JSC Medical Operations branch, the risks were updated and regrouped into seven areas which also define the spaceflight related long term goals of the program. In priority order, these are:

1. <u>Vertigo on reentry and landing</u>, triggered by sudden vehicle accelerations or head movements in a now-unfamiliar gravitational environment, can cause involuntary eye movements (nystagmus), difficulty reading instruments and orientation illusions. Together, these can cause misperception of the attitude, velocity, and acceleration of the vehicle. In critical situations, such as during landing they can lead to involuntary control movements and control errors, resulting in faster and harder landings and potentially in the loss of the vehicle and crew.

2. <u>Acute space motion sickness</u> on insertion into microgravity can produce nausea, vomiting, loss of concentration and inability to follow procedures. The sickness, which can sometimes last for several days, could cause catastrophic failure of EVA suit life support systems and render space suits unreusable, were sickness to occur during EVA. Consideration of this has caused deferment of non-emergency EVAs and Shuttle rendezvous and docking to the fourth day of flight, which has an important impact on Shuttle procedures and crew productivity.

3. Postlanding imbalance, instability, vertigo and orthostatic hypotension have made some crewmembers unable to stand up or walk unassisted after medium and long-duration flights. Associated with this, there is decreased tone in postural muscles, impaired locomotor coordination, instability of vision, difficulty turning corners or negotiating stairs. Any or all of these compromises the ability of crewmembers to egress from the Shuttle rapidly. Potentially, this could lead to injury or death of crewmembers in the event of an emergency or failed landing.

4. Inflight spatial disorientation and frame of reference problems, triggered by 3D body movements as well as inversion and visual reorientation illusions, causing reaching errors and spatial memory problems, difficulty locating emergency egress routes, EVA height vertigo, and operational difficulties during docking and remote manipulation of payloads that could cause dangerous collisions.

5. Chronic space motion symptoms resulting in decreased crew work capacity. Symptoms include fatigue, "space stupids", decreased vigilance, loss of motivation, irritability, gastrointestinal stasis, anorexia, dehydration, weight loss, side effects of anti-motion sickness drugs and changes in sleep-wake cycle.

6. Artificial Gravity related disorientation, nausea, vomiting, and loss of coordination. Symptoms occur in short and medium radius artificial gravity environments due to Coriolis effects on the vestibular semicircular canals, and biomechanical Coriolis forces which disturb normal limb movements. Symptoms necessitate movement restrictions which will compromise crew productivity.

7. Peripheral and central vestibular function changes due to exposure to microgravity, that may contribute to orthostatic intolerance on landing. It is also conceivable that changes in otolith or hair cell function occur after very long duration exposure to weightlessness, or exposure to radiation and environmental ototoxins (e.g. CO) that could cause permanent impairment of balance function. If so, these changes could cause loss of crew productivity when landing on a distant planet or crew injury or death during emergency egress.

III. RESEARCH PROGRAM STRUCTURE AND DESIGN

Design:

The ultimate goal of NSBRI's neurovestibular research program is to develop countermeasures that ultimately will to allow crewmembers to: avoid disorientation, meet the physical requirements of emergencies, treat motion sickness without side effects, and safely control vehicles and systems.

Risk #1 (Vertigo on Rentry and Landing) is believed to represent a serious ("Class I") risk on long duration missions. Though Shuttle pilots are aware of the problem, and voluntarily limit head movements, vehicle accelerations cannot be avoided. Vertigo and nystagmus cause well known difficulties reading flight instruments. Reentry vertigo has been recognized since the earliest days of the Shuttle program, but its operational significance has probably been masked by the traditional "can do" attitude of military-trained pilots who believe they can concentrate on their instruments and "fly through" episodes of vertigo. Flight surgeons report that vestibular disturbances are more severe after long flights. Although the landing vertigo problem has been manageable on 1-2 week flights, it is likely to become a significant problem if shuttle mission duration is extended to 3-4 weeks. McClusky, Clark, Stepaniak 2001 (NASA JSC SD2) found shuttle landing flight technical error (height over threshold, and distance, vertical velocity, and airspeed speed errors at touchdown on 9 missions) correlated with intensity of postlfight neurologic symptoms (9 missions, 8 subjects). Vertigo on short final, flare, or touchdown could cause loss of vehicle control. Vestibular and related somatosensory factors may have contributed to pilot induced oscillations on some Shuttle landings. Additional quantitative data on head movements, vehicle accelerations, and flight technical error are needed. The Shuttle does not have full autoland capability at all likely landing sites. Countermeasures to pre-adapt crewmembers or display/flight control changes and training procedures which reduce disorientation and flight technical error will be required. Providing Shuttle autoland capability will not completely resolve the problem, since pilots must still have sufficient visual acuity to monitor displays used in landing.

Risk #2 (Acute space motion sickness) also represents a Class I risk during EVA, since the Shuttle space suit ("EMU") has no containment bag. In 1980s, Hamilton Standard (P. Heimlich) noted vomitus in the LiOH canister creates exothermic reaction, and shuts down EMU primary vent loop. Frozen vomitus in secondary vent nozzle could shut down the secondary vent loop, leaving only a few minutes of residual in suit O2 remaining. Vomitus is biologically active, so if there is an episode, the suit cannot be reused unless completely refurbished on the ground. Vomitus volume could be somewhat reduced by eating/drinking less frequently, but this is often inappropriate. Modifying the suit to include a vomitus containment receptacle has been considered, but is expensive and may be impractical. Risk is serious if emergency EVA is required. Risk exposure currently is currently reduced by prohibition of non-emergency EVAs before flight day 3. One in-suit vomiting episode has occurred, but before actual EVA began. Acute vomiting episodes – even during IVA – are momentarily disabling. Drug or behavioral countermeasures which reliably and quickly reduce probability of vomiting are needed. Feasibility of EMU modifications to reduce susceptibility or provide containment should be reinvestigated. Opening the early-mission window for EVA by 1-2 days will add useful flexibility in mission planning, and improve overall STS-ISS productivity.

Risk #3 (Postlanding imbalance, instablility, vertigo) remain a concern for all Shuttle crewmembers in the event an emergency requires rapid egress from the vehicle. Although recent cardiovascular and neuromuscular countermeasures have been successful on ISS, neurovestibular balance problems remain a problem for some individuals. Many crew tested cannot run 1000 ft on a treadmill. Countermeasures are needed to pre-adapt returning crewmembers, to mitigate the risk of injury resulting from an accidental fall. It is also important to understand whether there is a vestibular contribution to postflight orthostatic hypotension.

Risk #4 (Inflight spatial disorientation and frame of reference problems) are more significant inside space stations (Mir, ISS) than on Shuttle, due to the complex 3D interior architecture (Richards, et al, 2001), which provides multiple visual frames of reference, and causes visual reorientation illusions. Mental rotation and frame of reference problems have been noted in debriefs of some crewmembers doing ISS robotic ops. Such problems complicated the Mir crew's response to the collison with the Progress spacecraft in 1997. Shuttle crewmembers visiting Mir easily became lost. Mir and ISS crewmembers occasionally report height vertigo when the Earth is in their lower visual field, and for some the experience has been momentarily disabling. The lack of visual references cues during the dark half of each orbit has caused disorientation and concern among some ISS EVA crew. Potential countermeasures include preflight visual orientation training – perhaps using appropriate virtual reality techniques or ground simulators – and improved physiologically based human factors standards for spacecraft architecture and escape path signage.

Risk #5 Chronic space motion sickness symptoms affect 75% of crewmembers to some degree during the first 3-5 days in space, and impair the average physical and mental efficiency of crewmembers, and cause profound somnolence, nausea related inability to follow procedures, and loss of initiative. The impact on operational capability of the crewmember equals or exceeds the somnolence produced by other aberrant circadian cues associated with spaceflight. Though acute space sickness problems are generally confined to the first week, several cases lasting weeks have been described by Russian colleagues, and there is reason to believe chronic low grade symptoms ("sopite syndrome") may persist in some crewmembers for weeks. Existing drugs were developed to prevent and treat acute space motion sickness, and have significant side effects. They may not be the best agents for treating chronic space motion sickness symptoms. Countermeasures include both techniques which accelerate adaptation to weightlessness, and improved anti-motion sickness drugs and other therapies which can be used to block or treat symptoms and signs without unacceptable cognitive or circadian side effects.

Risk #6 Artificial Gravity related disorientation, nausea, vomiting and loss of coordination. Artificial gravity (AG) remains a potentially important multi-system countermeasure for neuromuscular, bone, cardiovascular and neurovestibular dysfunction in 0-G. Large radius AG spacecraft systems are likely at least a decade away, but short radius (2-3 m) systems could be developed now which fit inside Shuttle or an ISS module. As a neurovestibular countermeasure, AG is a double-edged sword: it probably can be used to pre-adapt crewmembers for return to planetary gravity, but if crewmembers move their heads out of the plane of rotation, the resulting vestibular Coriolis stimulus potentially produces complex disorientation and motion sickness. In a rotating artificial gravity environment, with the body's principal oriented perpendicular to the axis of rotation, the direction and magnitude of the vestibular Coriolis effects depend on which way the crewmember happens to be facing. The extent to which a person can adapt in a context specific way to this kind of stimulus is unclear, and requires further research. Establishing the values of AG system radius and RPM, and the duration/repetition rate of AG sessions which are effective for neuromuscular, bone, cardiovascular and neurovestibular therapies remain a NSBRI wide priority.

Risk #7 Peripheral and central vestibular changes due to prolonged 0-G, radiation, or environmental toxins. There is no conclusive evidence that prolonged (months to years) exposure to 0-G produces irreversible vestibular changes, but only half a dozen individuals have yet flown beyond 6-8 months. Anatomical changes have been seen in vestibular sensory epithelia in animals on flights of several weeks and longer, but the functional significance of these changes is unclear. The effects of radiation exposure on the vestibular end organs and central vestibular system (e.g. brain stem, cerebellum, thalamus, hippocampus)has not been established. The effects of gravity on the formation of otolith crystals is not well understood. Loose otoconia will presumably float benignly in 0-G, but returning crewmembers may be more susceptible to disorienting effects (e.g. cupulolithiasis) during landing and postflight. The lack of validated, sensitive instrumentation and methods for early detection of impairment of vestibular reflexes, particularly those associated with response to gravity and linear acceleration is a continuing problem.

In 1999, the NSBRI neurovestibular team held a workshop in Houston to solicit the advice of a panel of outside experts. This group mapped the neurovestibular risks of spaceflight into eight interrelated thematic research areas, and defined a set of critical questions associated with each. These are important, as they formed the basis for the solicitation of the current research program:

1. Sensory-Motor Adaptation

- Can an individual's ability to adapt to multiple gravitational environments be enhanced so astronauts can rapidly transition between 1-G and 0-G, 0-G and partial G, or 0-G and artificial G with minimal performance impairment or motion sickness ? What are the sensory-motor responses that must change in a functionally adaptive manner during prolonged space flight? Does such adaptation take place? How can it be reliably measured?
- Can preflight or inflight training accelerate adaptation ? Can these adaptive responses be trained to be context-specific? What context cues are effective ? Must they be associated with active movement ? How long does context-specific pre-adaptation last ? Does adaptation of eye movements transfer to e.g. arm movement ?
- What is the evidence for and the physiological bases of oscillopsia, disorientation, ataxia, impaired gaze holding, and reduced dynamic visual acuity reported by crewmembers, particularly while making head movements during re-entry and immediately postflight?
- Can long-term exposure to space flight impair sensorimotor plasticity?
- What is the mechanism responsible for postflight sensory flashbacks occasionally reported by some crewmembers ?

- How do countermeasures (e.g., artificial gravity, inflight exercise or preflight training) affect adaptation rates and levels? How do rates and levels associated with physiological (sensorimotor, autonomic, emetic) adaptation to microgravity and 3/8 G on Mars correlate with operational performance changes ?
- What are the appropriate space flight analog environments that can be used as test beds for evaluating neurological adaptation, adverse operational implications, countermeasures and impacts of adaptation on other anatomical and physiological systems?

2. Artificial Gravity

- What are the effects of AG on human eye, head and limb movements ? What are the pros and cons of artificial gravity (AG) as a countermeasure against the effects of 0-G on neurovestibular function ? What are the advantages and disadvantages of large radius continuous AG vs. short radius intermittent AG, and how are these influenced by mission duration and post-landing environment (Mars vs. Earth)?
- Can humans successfully adapt to working perpendicular to the angular velocity vector?
- How can transitions between AG levels be eased?
- What is the maximum tolerable rotation rate for a given G level? What is the best habituation schedule?

3. Visual (Multisensory) Orientation, Spatial Memory, and Navigation

- How do visual and nonvisual cues interact to influence human orientation perception and motor behavior?
- How do visual, vestibular and haptic cues and biases contribute to inversion illusions, visual reorientation illusions, extravehicular-activity acrophobia, disorientation and poor 3-D spatial memory in 0-G?
- What is the neural basis of inversion illusions, visual reorientation illusions, EVA acrophobia, disorientation and 3-D spatial memory problems in 0-G? Does neural coding of place and direction three dimensional, or is it principally two dimensional due to our terrestrial evolutionary heritage ? Does the coding change after adaptation to 0-G?
- Does 1-G training in simulated environments (e.g. using virtual reality or neutral buoyancy techniques) reduce disorientation, and improve 3-D spatial memory and performance in orientation and navigation tasks such as emergency escape ? Can the architecture and layout of spacecraft interiors be improved to minimize disorientation ?
- How can 0-G immersive teleoperation displays be designed to reduce disorientation and/or motion sickness?

4. Vestibular/Autonomic/Emetic Physiology and Countermeasures

- What is the physiological basis for the "sensory conflict" theory for motion sickness ? What is the locus and function of the putative "conflict" signal ? What is the neural or chemical linkage between balance and emetic centers ? What mechanisms establish the threshold for nausea and emesis ? What neurotransmitter and receptor systems are involved ? Is the physiology of space motion sickness fundamentally different from other forms of motion sickness ?

- How do anti-motion sickness drugs affect sensory-motor adaptation and eye movements ?
- Can more effective anti-motion sickness drugs be developed which target emetic centers or the vestibular-emetic linkage ? Drugs must be effective, easily and safely used over days to weeks with minimal side effects and must not impair neurovestibular adaptation.
- Can improved anti-motion delivery systems and dose and side effect monitoring systems be developed? What are the best ground-based techniques for evaluating 0-G pharmacokinetics and for assessing the effectiveness and side effects of drug countermeasures ?
- How does chronic space motion sickness (including sopite syndrome) affect mood, initiative and interpersonal relationships?
- Does the neurovestibular response to weightlessness impair postlanding cardiovascular regulation and contribute to orthostatic intolerance ? How is it mediated ? What is the effective frequency range of compensation ? Can an effective countermeasure (e.g., AG) be developed to exploit this knowledge?

5. Postflight Locomotion and Gaze Assessment

- What causes the profound impairments of posture, gaze and locomotion stability in many returning astronauts (and in vestibular patients), and how can these be quantified?
- What causes the large differences in level of impairment observed among different crewmembers ?
- How do these differences correlate with physiological and operational performance changes?
- How are the multiple, mutually dependent sensorimotor systems responsible for locomotion altered by exposure to space flight? For example, what is the role of the vestibulo-ocular, vestibulo-collic and vestibulo-spinal reflexes in 3-D control of locomotion and gaze while walking, turning or ascending stairs?
- How are target acquisition, smooth pursuit and saccadic mechanisms programmed during locomotion? How do oculomotor and gait control systems interact during locomotion and head turning? How is this interplay affected by space flight?
- What roles do visual cues play in postflight locomotor control?
- In an altered sensory environment, does motor control require increased cognitive resources?
- Does this multi-tasking impair performance? Can a dual-task paradigm be used to monitor adaptation?
- What is the linkage between space flight-induced changes in sensory-motor control and astronaut functional performance?
- What measures represent composite and global indicators of locomotor and/or gaze dysfunction after space flight? What measures are the most efficient and sensitive indicators of changes in locomotion and/or gaze? What is their correlation with functional performance after space flight.

6. Neurovestibular Rehabilitation

- What are the relative contributions of neurovestibular adaptation, neuromuscular deconditioning and orthostatic intolerance to postflight neuromuscular coordination, ataxia and locomotion difficulties?
- Why do certain astronauts recover balance and locomotion function more rapidly than others postflight ?
- What is the effect of cardiovascular, muscle and skeletal rehabilitation therapies on neurovestibular recovery, and the converse ?
- Can preflight or inflight training, balance exercises, sensory aids, prostheses and assessment techniques improve postlanding postural and locomotor control and functional task performance ?
- How should somatosensory information be used to accelerate neurovestibular redaptation?
- Can crewmembers "learn how to learn" by adapting to surrogate sensory-motor rearrangements ?
- How does attention to a new sensory-motor task affect performance of a secondary task?

7. Effects of Stress, Isolation, Immobilization and Diet on Vestibular Function

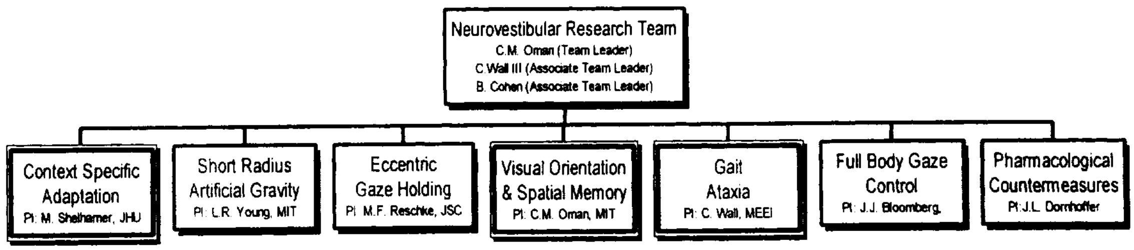
- What are the effect of psychological stress, isolation, immobilization, and diet on vestibular function ? How can they be distinguished from the effects of weightlessness and "normal" physiological variability?
- If there are important effects, what countermeasures can be developed?

8. Potential Mechanisms For and Diagnosis of Irreversible Neurovestibular Changes

- How might very long duration exposure to 0-G or partial G, radiation or environmental toxins such as carbon monoxide or ethylene glycol cause irreversible (pathophysiological) changes in central or peripheral vestibular function or development, or cause acceleration of the normal aging process? What is the likelihood of this ? Would some individuals be more susceptible than others? What is the potential time course? How could such changes be reliably detected at an early stage? What is the best way to non-invasively assess the function of the human otolith end-organs ? How does serum calcium homeostasis impact otoconial turnover?

Current Structure:

NSBRI's neurovestibular research program is led by Dr. Charles Oman (MIT) assisted by Drs. Bernard Cohen (Mt. Sinai School of Medicine) and Conrad Wall (Harvard Medical School/Mass Eye and Ear Infirmary). The current research portfolio of seven projects was selected based on a February, 2000 solicitation (NSBRI 00-01) and independent peer review. Six of the seven are three year projects. Three of the projects (double boxed in the figure below) were initiated in 1997, and competitively renewed in 2000. Several projects will be completed in September, 2003. However, due to NSBRI funding rate problems during GFY 2002, several others have extended their projected completion dates to December, 2002.



The investigators, their institutions, the critical path risks addressed, thematic areas, experimental model, specific aims, countermeasure types and countermeasure development strategy of each of the seven projects are summarized below:

<u>Context-Specificity and Other Approaches to Neurovestibular Adaptation.</u>
PI: Mark J. Shelhamer,
CoIs: Minor, Zee, Angelaki, Zhou, Wu.
Institutions: Johns Hopkins U. School of Medicine, Washington U., U. Mississippi Med Ctr.
Critical path risks addressed: 1. Vertigo on rentry and landing., 3. Postlanding imbalance and vertigo.
Thematic area: Sensory Motor Adaptation
Experimental models: Human and animal (primate)
Countermeasure Types: assessment, prediction, training.
Current readiness level: 2
Specific Aims:

- Is torsional eye position a context cue for saccade adaptation ?
- Does a rest interval between stimuli promote adaptive consolidation ?
- Can cyclovergence adaptation provide a countermeasure to ocular torsion changes in parabolic flight ?
- How do pursuit and LVOR deficits correlate in cerebellar lesioned monkeys ?
- How do pursuit and LVOR adaptation transfer across frequencies in humans and monkeys
- Can LVOR adaptation be trained with pursuit stimuli, and how do cerebellar lesions influence adaptation.
- Does head tilt adaptation of saccades and VOR transfer to arm movements in monkeys ?
- What is the best way to induce context specific LVOR adaptation in humans ?
- Does the naso-occipial LVOR also show context specific adaptation ?

<u>Neuro-Vestibular Aspects of Artificial Gravity Created by Short-Radius Centrifugation</u>
PI: Laurence R. Young.

CoIs: Hecht, Oman, Mast, DiZio, Lackner, Paloski, B. Cohen, Dai, M. Cohen, Welch, Stone.
Institutions: MIT, Brandeis, NASA-JSC, Mt. Sinai Hospital, NASA-Ames.
Critical Path Risks: 6. Artificial Gravity, 2. Acute space motion sickness, 5. Chronic space motion sickness
Thematic areas: Artificial G, Drug countermeasures
Experimental model: Human
Countermeasure Types: assessment, training, environmental manipulation, drugs.
Current readiness Level: 4
Specific Aims: Using short and medium radius centrifuges and rotating chairs, to determine:

- How context cues influence VOR, perception and motion sickness adaptation.
- What is the role of sensory-motor (non-vestibular) adaptation to AG ?
- What types of sensory conflict drive adaptation ?
- What are the optimal duty cycles and inter-session intervals ?
- Does body orientation re gravity provide a context cue ?
- In what way does adaptation generalize to different rotating environments?
- How does intermittent training influence the accuracy of head movements ?
- How does promethazine affect adaptation and eye movements in humans and monkeys ?

Modification of Eccentric Gaze-Holding.
PI: Millard F. Reschke
CoIs: Paloski, Kornilova, Wood, Leigh
Institutions: NASA-JSC, IBMP/Moscow, BCM, University Hospitals of Cleveland
Critical Path Risk: 1 Vertigo on reentry and landing, 3, postlanding vertigo, 7. peripheral or central vestibular changes.
Thematic areas: Sensory-motor adaptation, Irreversible changes).
Experimental model: Human
Countermeasure types: assessment, prediction, training.
Countermeasure Readiness Level: 2
Specific Aims:

- Effect of tilt and proprioception on centripetal drift time constant
- How rebound nystagmus provides adaptive compensation.
- How centrifugation influences gaze holding.
- Why adaptation fails in cerebellar patients.
- Whether gaze-holding is impaired immediately following spaceflight.

Visual Orientation and Spatial Memory.
PI: Charles M. Oman.
CoIs: Howard, Shebilske, Taube, Hecht, Harris, Jenkin, Liu, Stuerzlinger. Institutions MIT, York University, Dartmouth Medical School, Wright State University.
Critical path risk: 4. Inflight spatial disorientation and frame of reference problems, 2. Acute space motion sickness etiology.
Thematic area: Orientation and Spatial Memory.

Experimental models: Human and animal (rat)
Countermeasure types: assessment, prediction, training, environmental manipulation. .
Countermeasure Readiness Level: **5**
Specific aims:

- Human visual orientation. Effects of visual frame, polarity, brightness, motion, and gravireceptor cues on the subjective vertical, eye movements, and limb movements.
- Three dimensional spatial memory and spatial frameworks. Generic and environment specific preflight and onboard virtual reality training methods, interior architectural standards, and escape path countermeasure design and evaluation.
- Neural coding of spatial orientation. How do visual, vestibular, gravireceptive, proprioceptive, and motor pathways drive limbic head direction cells in the rat, as a model for visual reorientation illusions in astronauts.

<u>Advanced Techniques to Assess and Counter Gait Ataxia</u>
PI: Conrad Wall III
Co-Is:Bloomberg, Oddson, Raphan, Solomon.
Institutions: Mass Eye and Ear Infirmary, NASA-JSC, Boston University, Mt. Sinai Hospital, U. Penn.
Critical Path Risks: 3. Postlanding imbalance, instability, vertigo.
Thematic area: Locomotion and gaze.
Experimental model: Human
Countermeasure types: assessment, prediction, training, prosthesis.
Countermeasure Readiness Level: 5
Specific Aims:

- Quantify body, head, & eye coordination during perturbed straight walking. And also:
- during straight and circular walking on a circular treadmill.
- while ascending/descending stairs.
- while wearing a tactile prosthetic countermeasure.
- assess effect of dynamic balance exercises.

<u>Understanding Full-Body Gaze Control During Locomotion</u>
PI: Jacob J. Bloomberg, Jacob
Co-I:H. Cohen.
Institutions: NASA-JSC, Baylor College of Medicine
Critical Path Risks: 3. Postlanding imbalance, instability, vertigo, and hyptension.
Thematic area: Locomotion.
Experimental model: Human
Countermeasure types: assessment, prediction, training.
Countermeasure Readiness Level: 5
Specific Aims: How are eye, head, trunk, and lower limb movements coordinated. Specifically:

- How do eye, head, trunk, and legs absorb heel strike while treadmill walking? How do subjects adapt to magnifying and minifying lenses ?
- To reduced degrees of freedom, for example wearing a neck brace ?
- To wearing knee braces ?

Pharmacological Countermeasures for Space Motion Sickness.
PI: John L. Dornhoffer
CoIs: Garcia-Rill, Paule, Van De Heyning.
Institutions: U. Arkansas for Medical Sciences, National Center for Toxicological Res., U. Hospital, Antwerp.
Critical Path Risks: 2. Acute space motion sickness, 5 Chronic space motion sickness.
Thematic area: Autonomic/drug
Experimental model: Human
Countermeasure types: assessment, prediction, pharmacological.
Countermeasure Readiness Level: 5
Specific Aims: (2 year project)

- What are the effects of lorazepam, meclizine, promethazine, and scopolamine on coriolis induced motion sickness symptoms ?
- How do these drugs affect reticular sensory gating (P50 double click auditory evoked potential), time perception, short term memory, and learning ?

Each of the current projects resembles a small NIH Program Project Grant in that (Boomberg's project excepted) all involve multiple experiments conducted concurrently at several institutions, and significant collaborations between investigators. In addition, there are significant inter-project collaborations and coordinations. For example, Drs. Wall, Oddson and Bloomberg are coordinating their locomotion research, and developing a portable locomotion testing platform. Dr. Minor (Shelhamer project) assisted Dr. Taube in developing a semicircular canal blocked animal preparation. Drs. Shelhamer, Solomon, and B. Cohen and are working with JSC clinical colleagues on development of a postflight neurological assessment battery.

The NSBRI neurovestibular adaptation research program was reviewed in December, 2000 by the NASA Chief Scientist's site visit team. They judged it a well integrated program with strong leadership and an internal review process, evidence of true collaborative research, and clear added value to NASA.

IV. RESEARCH PROGRAM ACCOMPLISHMENTS

During the past year, our programmatically significant major progress relative to risks and countermeasures has been:

Relative to the postlanding imbalance, instability and vertigo risk:

- Drs. Wall/Oddson delivered a compact, portable balance disturber countermeasure to JSC, where Drs. Bloomberg/Mulavara have established normative data locomotion and dynamic visual acuity for use as a clinical measure of fitness for return-to-duty, and efficacy of rehabiliatative countermeasures.

Relative to artificial gravity related disorientation, nausea, vomiting and loss of coordination:

- Drs. Young/Hecht demonstrated context specific adaptation to Coriolis stimulation, essential if short radius centrifugation is to be used as a countermeasure.

Relative to inflight disorientation and frame of reference problems:

- Drs. Oman/Harris/Taube developed new methods to quantify the "gravitational polarity" of visual scenes useful for design of spacecraft interiors and workspaces, and demonstrated the feasibility of 3D spatial memory training countermeasure. They also demonstrated that animal head direction cells show a distinct "disorientation" response state.

The neurovestibular team has maintained a strong record of scientific productivity. Since the start of phase 2 research in 2000 and the present, 65 papers, abstracts, and abstracts have appeared, which are listed in the appendix. (Between 1997 and 2000, the initial 3 projects published 14 journal articles, along with 3 reports, 6 graduate theses, 23 abstracts, with 15 manuscripts accepted or in review.) Eleven graduate students and 10 postdoctoral trainees participated. We maintain a strong interaction with NASA JSC. Two students have interned at NASA JSC, and several students from our laboratories are now employed there. Dr. Shelhamer serves on the JSC Medical Branch Neurophysiology Integrated Project Team. Dr. B. Cohen serves on the Critical Path Project Review Board. Dr. Oman, Mr. J. Richards, Dr. J. Clark (JSC) and Dr. Marshburn (JSC & Smart Med. Team) prepared a retrospective summary of Mir neurovestibular episodes, which was has been distributed to neurovestibular specialists and crewmembers and is being published as a NASA TR. Several members of our team (Drs. Oman, Bloomberg, Reshke, Paloski, Cohen and Raphan) are concurrently actively involved in the development of NASA sponsored neurovestibular experiments for the ISS.

In June, 2002 team submitted 10 manuscripts for a special issue of the Journal of Vestibular Research. As of September, six had been accepted, with the remainder in the final stages of review. This issue should appear in mid-2003. Dr. Oman took a lead role in organizing the a 6th Symposium on the Role of the Vestibular Organs in Space Exploration in Portland, Oct. 1-3, 2002. This international symposium was a satellite to the concurrent Barany Society meeting, and attracted more than 140 space vestibular researchers and clinicans. Investigators representing all seven NSBRI projects participated, and our annual team meeting was held in conjunction with the Symposium. The meeting gave our team's research increased visibility within the entire space vestibular community, and an opportunity to exchange views with our colleagues from around the world. In the tradition of the first six symposia, held at Pensacola in the 1960s and 70s, NASA is publishing the complete proceedings. Selected papers will appear in a special issue of the Journal of Vestibular Research.

With support from the NSBRI Education and Outreach Team, Drs. Oman, Wall and Young developed a new graduate subject at MIT in vestibular physiology, and collaborated with Harvard Medical School colleagues to develop a vestibular case study for use in high schools ("Cecilia's Story"), and Dr. B. Cohen participated in the summer high school outreach teaching program at Mt. Sinai. The team has held annual panels at the Aerospace Medical Association and Neural Control of Movement meetings. We also informally advise several neurovestibular-related projects underway on other teams: Ray Vestibular Autonomic project /Cardiovascular Team; Morin Vestibular effects on circadian/Chronobiology; Putcha Intranasal motion sickness drug adminstration/Smart Medicine.

The current project portfolio collectively addresses some aspects of six of the seven critical path risks and five of the eight potential thematic areas. One project has delivered a preliminary countermeasure, and most of the others have countermeasures concepts defined and in development, though two currently have not yet reached that stage. Recent retroactive cuts to the NSBRI budget during FY 2002 have impacted progress on several projects. Also, there are significant strategic gaps in the current program, partly due to funding limitations and also to the particular thematic distribution of proposals solicited by the most recent NSBRI research announcement (NSBRI 00-001). The team strategy for closing these gaps is described in our 2002 Team Strategic Plan.

APPENDIX. Publications of the Neurovestibular Adaptation Team (2000-2002)

1. Bassett JP, Taube JS (2001) Neural correlates for angular head velocity in the rat dorsal tegmental nucleus. Journal of Neuroscience 21: 5740-5751
2. Bassett JP, Taube JS (2001) Lesion of the dorsal tegmental nucleus of the rat disrupt head direction cell activity in the anterior thalamus. Soc Neurosci Abstr 27: 852.29.
3. Bloomberg, JJ, Mulavara, A.P., Kozlovskaya, I.B. Adaptive reorganization of locomotor function after long-duration spaceflight. Presented at the XII Conference on Space Biology and Aerospace Medicine, Moscow, June 10-14, 2002.
4. Bloomberg, JJ, Mulavara, A.P., Kozlovskaya, I.B. Reorganization of locomotor strategies after long-duration spaceflight. Presented at the Annual Aerospace Medical Association Meeting, Montreal, May, 2002.
5. Brown, E., Hecht H, and Young L. (submitted) Sensorimotor aspects of high-speed artificial gravity: I. Visual-vestibular conflict in context-specific adaptation. Journal of Vestibular Research, NSBRI Neurovestibular Team special issue.
6. Brown JE, Yates BJ, Taube JS (2002) Does the vestibular system contribute to head direction cell activity in the rat? Physiology and Behavior, in press.
7. Calton JL, Stackman RW, Goodridge JP, Archey WB, Dudchenko PA, Taube JS (2002) Hippocampal place cell instability following lesions of the head direction cell network. Journal of Neuroscience (submitted)
8. Calton JL, Taube JS (2001) Head direction cell activity following bilateral lesions of posterior parietal cortex. Soc Neurosci Abstr 27: 537.30.
9. DiZio P and Lackner J. (Submitted) Sensorimotor aspects of high-speed artificial gravity III: Sensorimotor adaptation. Journal of Vestibular Research, NSBRI Neurovestibular Team special issue.
10. Dornhoffer J, E Garcia-Rill, M Paule, Clinical Investigation of Pharmacological Countermeasures for Space Motion Sickness, Panel Presentation at the Aerospace Medical Association 73rd Annual Scientific Meeting, May 6, 2002, Montreal, Canada.
11. Dornhoffer J, E Garcia-Rill, M Paule, P Van De Heyning, P Bhave, N Mamiya, P Bray, RD Skinner, FL Wuyts, K Williams, DJ Blake, JH Chelonis, M. Hoppenbrouwers, G Pauwels, A Boudewyns, Pharmacological Countermeasures for Space Motion Sickness, poster presentation at the NSBRI Retreat, January 2002, Houston, Texas.
12. Dornhoffer J, RT Boone, EK Gardner, DK Williams, The effect of rotation on the subjective vertical: A new test of otolith function in the normal and diseased ear, presented at the 37th Annual Meeting of the American Neurotology Society, May 10-11, 2002, Boca Raton, Florida.
13. Dornhoffer JL, N Mamiya, P Bray, RD Skinner, E Garcia-Rill. Effects of rotation on the sleep state-dependent midlatency auditory evoked P50 potential in the

human. Submitted to the Journal of Vestibular Research (special NSBRI Neurovestibular Adaptation issue).
14. Dornhoffer JL, RT Boone, EK Gardner, DK Williams. The effect of rotation on the subjective vertical: A new test of otolith function in the normal and diseased ear. Submitted to Otology & Neurotology.
15. Garcia-Rill E, RD Skinner, J Clothier, J Dornhoffer, E Uc, A Fann, N Mamiya. The sleep state-dependent midlatency auditory evoked p50 potential in various disorders. Submitted to Thalamus & Related Systems.
16. Groen, E., I. P. Jenkin, H., and Howard, I.P.(2002) Perception of self-tilt in a true and illusory vertical plane. Perception, (In press). (Abstract)
17. Hecht, H, Brown, EL & Young, L. R.(2002). Adapting to artificial gravity (AG) at high rotational speeds, 23rd ESA ISBP Symposium 'Life in Space for Life on Earth' held in Stockholm, Sweden, June, 2002. Submitted to Journal of Gravitational Physiology.
18. Hirasaki, E., Moore, S.T., Raphan, T., Cohen, B. Head and body movements in the yaw and roll planes during straight walking. Soc. Neuroscience, Nov. 2001.
19. Homma H, Y Homma, L Teneud, RD Skinner J Dornhoffer, E Garcia-Rill. Effects of rotation on the P13 mid-latency auditory evoked potential in rat. Submitted to the Journal of Vestibular Research.
20. Howard, IP and Hu, G. (2001) Visually Induced Reorientation Illusions. Perception 30:583-600.
21. Howard, I.P., Hu, G., and Zacher, J.E. Visual orientation in a 90° mirror world. (Submitted to Perception), October, 2002.
22. Jenkin, HL, Harris,LR, Dyde, RT, Kaiserman, J. and Jenkin MR. (2002) Relative role of visual and non-visual cues in judging the direction of "up": experiments in the York tumbled room facility 6th Symposium on the Role of the Vestibular Organs in Space Exploration, Portland Oregon, September, 2002 (Abstract)
23. Karmali, F. RA Clendaniel, M Shelhamer (2001) Context-Specific Adaptation of Saccade Gain does not Require Opposing Gain Changes in order to be Effective. Soc Neurosci Abstr 27.
24. Mamiya N, J Dornhoffer, P Bray, R Skinner, E Garcia-Rill, (2002) Effects of rotation on the sleep state-dependent midlatency auditory evoked P50 potential in the human, presented at the Association of Professional Sleep Societies 16th Annual Meeting, June 8-13, 2002, Seattle, Washington.
25. Mamiya N, J Dornhoffer, R Skinner, E Garcia-Rill, (2002) Effect of meclizine on the rotation-induced decrease in habituation of the human P50 potential. Neuroscience Abstracts, Volume 28, 2002.
26. Mast F, Newby N and Young L (submitted) Sensorimotor Aspects of High-Speed Artificial Gravity II: Effect of Head Position on Illusory Self Motion. Journal of Vestibular Research, NSBRI Neurovestibular Team special issue.
27. Moore, S.T., Hirasaki, E., Imai, T., Raphan, T., Cohen, B. Rotation axes during active head and trunk movements. In: Duysens, J., Smits-Engelsman, B.C.M., Kingma, H. (Eds), Control of Posture and Gait. Proc. of Symposium of the International Society for Postural and Gait Research, ISPG 2001, pp. 211-214, 2001

28. Moore, S.T., Hirasaki, E., Raphan, T., Cohen, B. The human vestibulo-ocular reflex during linear locomotion. Ann. N.Y. Acad. Sci., (In Press, 2001).
29. Muir GM, Taube JS (2002) Firing properties of head direction cells, place cells, and theta cells in the freely-moving chinchilla. Soc Neurosci Abstr 28: 584.4.
30. Mulavara A.P., Bloomberg, J.J. (submitted). Identifying head-trunk and lower limb contributions to gaze stabilization during locomotion. Submitted to the Journal of Vestibular Research NSBRI Special Issue.
31. Mulavara A.P., Bloomberg, J.J. Identifying head-trunk and lower limb contributions to gaze stabilization during locomotion. To be presented at The Sixth Symposium on the Role of the Vestibular Organs in the Exploration of Space, Portland, October, 2002.
32. Mulavara AP, Miller CA, Houser J, Richard JT, and Bloomberg JJ. Gaze stabilization during locomotion requires full body coordination. Presented at the 25th Annual Meeting of the American Society of Biomechanics, San Diego, CA, August 7-12, 2001.
33. Oman C, Reschke M, Young L, Dornhoffer J and Bloomberg J. (2002) Development of neurovestibular countermeasures for long duration spaceflight. Abstracts of panel session at Aerospace Medical Association Meeting, Montreal Canada.
34. Oman C, Shebilske W, Richards J, Tubre T, Beall A, Natapoff A. (2002) Three dimensional spatial memory and learning in real and virtual environments. J. Spatial Cognition and Computation 2:355-372.
35. Oman, C. Human Visual Orientation. In: Levels of Perception, LR Harris and ML Jenkin, Eds. Elsevier (in press).
36. Oman, CM, Howard, IP, Shebilkske, WL, Taube JS. (2001) Visual Orientation In Unfamiliar Gravito-Inertial Environments. (Long Abstract) Proceedings of the First Biennial Space Biomedical Investigators Workshop, January 11-13, 1999, League City, Texas. USRA Technical Report/CD ROM
37. Peters, B.T., Bloomberg, J.J. Dynamic visual acuity during locomotion using far and near targets. To be presented at The Sixth Symposium on the Role of the Vestibular Organs in the Exploration of Space, Portland, October, 2002.
38. Raphan, T., Imai, T., Moore, S.T., Cohen, B. Vestibular based compensatory and orienting behavior during walking and turning. In: Duysens, J., Smits-Engelsman, B.C.M., Kingma, H. (Eds), Control of Posture and Gait. Proc. of Symposium of the International Society for Postural and Gait Research, ISPG 2001, pp. 234-237.
39. Raphan, T., Imai, T., Moore, S.T., Cohen, B. Vestibular compensation and orientation during locomotion. Ann. N.Y. Acad. Sci., (In Press, 2001).
40. Richards JT, Oman CM, Shebilkse WL, Beall AC, Liu AM, and Natapoff A (accepted) Training, transfer, and retention of three-dimensional spatial memory in virtual environments. Journal of Vestibular Research, NSBRI Neurovestibular Team special issue.
41. Richards, JT, Clark, JB, Oman, CM and Marshburn TH. Neurovestibular Effects of Long-Duration Spaceflight: A Summary of Mir Phase 1 Experiences. NASA Johnson Space Center Technical Report (in press)

42. Shelhamer M, A Tilt-Translation Device for the Study of Vestibular Effects on Orientation, proposal submitted to AFOSR, August 2002.
43. Shelhamer M, R Clendaniel (in press) Sensory, motor, and combined contexts for context-specific adaptation of saccade gain in humans, Neurosci Lett.
44. Shelhamer M, RA Clendaniel (in press) Context-Specific Adaptation of Saccade Gain, Exp Brain Res.
45. Shelhamer M, RA Clendaniel, DC Roberts (submitted) Context-specific adaptation of saccade gain in parabolic flight, J Vestibular Res.
46. Shelhamer M. (2001) Use of a Genetic Algorithm for the Analysis of Eye Movements from the Linear Vestibulo-Ocular Reflex. Ann Biomed Eng 29:510-522.
47. Shelhamer M., GCY Peng, S Ramat, and V Patel (2002) Context-Specific Adaptation of the Oculomotor Response to Lateral Translation using Roll and Pitch Head Tilts as Contexts," Exp Brain Res, in press (online DOI: 10.1007/s00221-002-1235-1).
48. Shelhamer, M, RA Clendaniel, GCY Peng (2001) Relative Effectiveness of Sensory and Motor Cues in Context-Specific Adaptation of Saccade Gain. Soc Neurosci Abstr 27.
49. Stackman RW, Clark AS, Taube JS (2001) Hippocampal spatial representations require vestibular input. Hippocampus, in press.
50. Stackman RW, Golob EJ, Bassett JP, Taube JS (2002) Passive transport disrupts directional path integration by rat head direction cells. Journal of Neuroscience (Submitted).
51. Steven MS, Taube JS (2002) Head direction cell discharge during periods of disorientation. Soc Neurosci Abstr 28: 584.3.
52. Taube JS, Calton JL, Stackman RW, Oman CM, Steven MS (2002) The Neurobiology for a Sense of Direction: An Update from on the ground, upside-down, and space-bound. Journal of Vestibular Research 11: 320-321.
53. Trillenberg, P M Shelhamer, DC Roberts, DS Zee (submitted) Cross-Axis Adaptation of Torsional Components in the Yaw-axis VOR.
54. Trillenberg, P., DS Zee, DC Roberts, M Shelhamer (2000) Adaptation of the Torsional AVOR During Cross-Axis Stimulation. Soc Neurosci Abstr 26.
55. Walker MF, M Shelhamer, DS Zee (submitted) Eye-position dependence of torsional velocity during interaural translation, horizontal pursuit, and yaw-axis rotation in humans.
56. Wall, III C , L.I. Oddsson, N. Patronikband E. Kentala (Submitted) Recovery Trajectories of Vestibulopathic Subjects after Perturbations during Locomotion. Journal of Vestibular Research, NSBRI Neurovestibular Team special issue.
57. Wuyts F, G Pauwels, M. Hoppenbrouwers, J Dornhoffer, A Boudewyns, P Van de Heyning: Pharmaceutical countermeasures for space motion sickness and their effect on the otolith and canal function in men. (Abstract) Barany Society 2002, Seattle, Washington.
58. Wuyts F, M. Hoppenbrouwers, G Pauwels, J Dornhoffer, A Boudewyns, P Van de Heyning, J Furman: Unilateral otolith function testing using eccentric rotation, presented at the Association for Research in Otolaryngology Mid-winter Meeting, January 2002, Florida.

59. Young, L. R., Sienko, K. H., Lyne, L. E., Hecht, H., & Natapoff, A. (2001) Adaptation of the vestibulo-ocular reflex, subjective tilt, and motion sickness to head movements during short-radius centrifugation. Submitted to Experimental Brain Research.
60. Zhou, W. P Weldon, B Tang, WM King (2001) Retinal Slip Not Required for Rapid Adaptation of the Translational Vestibulo-Ocular Reflex. Soc Neurosci Abstr 27.
61. Zhou, W. P Weldon, B Tang, WM King (2002) Rapid adaptation of translational vestibulo-ocular reflex: Independence of retinal slip. Ann NY Acad Sci 956:555-557.
62. Zhou, W. P Weldon, B Tang, WM King (2002) Rapid adaptation of translational vestibulo-ocular reflex: time course and consolidation. Ann NY Acad Sci 956:558-560.
63. Zhou, W. P Weldon, B Tang, WM King (under review after revision) Rapid motor learning in the translational vestibulo-ocular reflex. J Neurosci.
64. Zhou, W. WM King (2002) Attentional sensitivity and asymmetries of vertical saccade generation in monkey. Vision Res 42:771-779.
65. Zhou, W., P Weldon, B Tang, WM King (2001) Initiation of the Linear Vestibulo-Ocular Reflex (LVOR). Neural Control of Movement Meeting, Seville, Spain. II. The Effect of Head Position on Illusory Self Motion, Journal of Vestibular Research (submitted)

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

NUTRITION, PHYSICAL FITNESS & REHABILITATION

Team Leader: Joanne R. Lupton, Ph.D.
Texas A&M University
Faculty of Nutrition
213 Kleberg Center, 2471 TAMU
College Station, Texas 77843-2471
(979) 845-0850; Fax (979) 862-1862
Email: jlupton@tamu.edu

Joanne R. Lupton

Nutritional Countermeasures to Radiation Exposure
Joanne R. Lupton, Ph.D.
Texas A&M University
Faculty of Nutrition
213 Kleberg Center, 2471 TAMU
College Station, Texas 77843-2471
(979) 845-0850; Fax (979) 862-1862
Email: jlupton@tamu.edu

Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress
Robert R. Wolfe, Ph.D.
The University of Texas Medical Branch
815 Market Street
Galveston, Texas 77550
(409) 770-6605; Fax (409) 770-6825
Email: rwolfe@utmb.edu

Nutritional Modulation of Pancreatic Endocrine Function in Microgravity
Brian W. Tobin, Ph.D.
Mercer University School of Medicine
1550 College Street
Macon, Georgia 31207
(912) 301-4026; Fax (912) 201-5478
Email: tobin_bw@mercer.edu

Metabolic Adaptations of Skeletal Muscle to Training/Detraining. A systems Model
Marco E. Cabrera, Ph.D.
Pediatric Cardiology, RBC-389
11100 Euclid Avenue
Cleveland, OH 44106-6011
(216) 844-5085; Fax (216) 844-5478
Email: mec6@po.cwru.edu

TABLE OF CONTENTS

I. ABSTRACT OF REPORT

Optimal human performance during space exploration requires the maintenance of all physiological systems such as cardiovascular capacity, bone mineral density, and skeletal muscle function and in turn is dependent on adequate nutrition and physical fitness. The critical issues for nutrition are: (1) determining nutrient needs to meet modified requirements due to space flight stressors including microgravity; and (2) developing new strategies including use of functional foods, supplements, and timing of food intake relative to specific activities that will optimize human performance. Critical issues for physical fitness include: (1) development of appropriate aerobic and resistive exercises (mode, frequency, duration, intensity) and the appropriate balance for each to maintain aerobic capacity and muscle performance (as measured by strength and endurance) and (2) optimizing the appropriate timing of exercise programs with respect to food intake and other activities (e.g. extra vehicular activity; EVA). Since physical activity will, in part, determine nutrient needs, and the optimization of nutrient delivery will in part depend upon blood flow and muscle mass (which are affected by physical activity) these two disciplines need to be considered together. Examples of relevant risks that may be ameliorated by nutrition and physical activity interventions are: Reduced cardiovascular capacity; Loss of bone mineral density; Diminution of skeletal muscle function; Depressed immune response; Radiation enhanced development of cancer; Decrease in cognitive function; Alterations in sleep patterns; Psychosocial factors.

The nutrition and physical fitness program is new, becoming operational in 2001. It presently consists of three nutrition countermeasure projects (Lupton, Wolfe, and Tobin) and a modeling project (Cabrera). The cornerstone project is the Wolfe bed rest study, which has seven "add on" projects and is fully integrated with the Tobin project. A critical finding from the Wolfe bed rest study was that nutrition may ameliorate muscle wasting but it does not preserve the loss of muscle strength. This reinforces the need for a combined nutrition/physical fitness intervention strategy. Because of Dr. Wolfe's commitment to this integrated approach he has expanded his study at his own expense to now do a physical fitness intervention during the second year. The Lupton project on the development of nutritional countermeasures to radiation enhanced colon cancer resulted in several discoveries: that exposure to 1Gy iron ions does, in fact, enhance preneoplastic markers of colon tumorigenesis, and fish oil feeding can ameliorate this effect. Importantly, if rats are provided diets high in both fish oil and the fermentable fiber pectin, the enhanced tumorigenic effect seen with radiation exposure is no longer observed. The use of microarray technology to monitor changes in gene expression has identified key genes that are turned on (or off) as a result of carcinogen and/or radiation exposure. This technology can later be applied to humans. The Cabrera modeling project is now fully functional and he has established important collaborative efforts with members of other NSBRI teams. A major success of this first year of operation of the team was the publication (October, 2002) of a special issue of the journal Nutrition, on Nutrition in space flight. Every member of the team has an article in the Journal and the team lead and her co-PI were the Journal Editors.

In summary, Nutrition and Physical Fitness is a new, currently small program which is working to fully integrate its existing projects, expand by addition of small projects, and is poised to incorporate newly funded proposals which will fully integrate nutrition with physical fitness. Optimal diet and physical activity protocols for space flight will impact every aspect of astronaut health and performance.

II. INTRODUCTION

The two major problems encountered in space that are currently addressed by the Nutrition and Physical Fitness Research Program are (1) Muscle Alterations and Atrophy and (2) radiation enhanced development of cancer. With respect to Muscle Alterations and Atrophy, the following are the Relevant risks (numbered in parentheses), found on the Critical Path Roadmap, that may be ameliorated by nutrition and physical activity interventions: Loss of Skeletal Muscle Mass, Strength, and/or Endurance (28); Inability to Perform Tasks Due to Motor Performance, Muscle Endurance, and Disruption in Structural and Functional Properties of Soft and Hard Connective Tissues of the Axial Skeleton (29); Inability to Sustain Muscle Performance Levels to Meet Demands of Performing Activities of Varying Intensities (30); Propensity to Develop Muscle Injury, Connective Tissue Dysfunction, and Bone Fracture Due to Deficiencies in Motor Skill, Muscle Strength and Muscular Fatigue (31); and Impact of Deficits in Skeletal Muscle Structure and Function on other Systems (32). Both appropriate nutrition and physical fitness can have a significant impact on muscle mass and strength. Nutrition is required to provide amino acids for muscle protein synthesis and energy for strength and endurance. Muscle protein synthesis is known to be depressed during space flight, due, in large part to muscular inactivity. This depression of protein synthesis is accompanied by an increase in protein degradation due to a moderate level of hypercortisolemia observed during space flight. Both aerobic and resistive exercise are also critical for proper muscle function. Aerobic exercise helps maintain blood flow to muscle so that nutrients can reach myocytes. Resistive exercise is key to maintaining muscle strength. Not only must energy expended on physical activity be balanced by appropriate food intake, the timing of exercise with respect to food ingestion impacts such important physiological effects as uptake of amino acids into muscle. Thus specific nutrients, ingested at the appropriate time, may help to maintain muscle mass.

With respect to radiation enhanced development of cancer: The risks to personnel in space from naturally occurring radiations are generally considered to be the most serious limitation to human space missions and research in this area is now a top priority for NASA. Ionizing radiation results in the production of reactive oxygen species (ROS) including superoxide, hydrogen peroxide, and hydroxyl radical, which are mutagenic and well documented to be carcinogenic in animals and humans. ROS accumulate with time, and it has been shown in a number of different systems that the greater the production of ROS, the higher the level of oxidative DNA damage. ROS can permanently damage nucleic acids inducing some 20 major oxidative DNA adducts some of which can go on to form tumors. Interestingly, diet may play an important role in removal of these DNA-adducted cells and thus protect against radiation-enhanced tumorigenesis. The NSBRI funded project of Lupton et al. uses diet as a countermeasure to selectively remove DNA-damaged cells from the colon by targeted apoptosis. Colon cancer is chosen for the model system as it is the second leading cause of death from cancer in the United States today, it strikes men and women equally, and it is the cancer most responsive to diet. The relevant risk on the critical path that is addressed is: Carcinogenesis Caused by Radiation (38).

III. RESEARCH PROGRAM STRUCTURE & DESIGN

The Nutrition and Physical Fitness Team is new, and became operational in 2001. It presently consists of three nutrition countermeasure projects (Lupton, Wolfe, and Tobin), and a modeling project (Cabrera) which was recently assigned to the team from the former Human Integrated Function Team. Table 1, entitled "Current Project Research Activities," summarizes for each current Nutrition and Physical Fitness Team project what risks are addressed, the experimental system, the countermeasure target and whether a project is part of the strategic plan steps of Phase 1, 2 or 3 Activities (See the strategic plan).

Specifically, ***Nutritional Countermeasures to Radiation Exposure***, JR Lupton, PI, Texas A&M University, is testing the hypothesis that a particular diet intervention (an n-3 lipid and fermentable fiber combination) in rats should protect against radiation-enhanced colon cancer by targeting DNA damaged cells for apoptotic removal. It is directed to Goal 5 of the strategic plan : Reduce Risk of Radiation Enhanced Development of Cancer and will also contribute to Goal 1: Reduce Risk of Suboptimal Nutritional Status. Rats receive one of four diets, are exposed to heavy iron radiation (or not) at Brookhaven National Laboratory and are injected with a colon specific carcinogen. A variety of measurements are taken at three stages of the tumorigenic process (initiation, promotion, and final tumor development). This project also has a noninvasive component of monitoring changes in gene expression over time as a result of radiation and carcinogen exposure using microarray technology. If validated in rats, the diets and techniques can be modified for future studies in humans. This noninvasive technology is also directed at Goal 12: Develop noninvasive techniques for assessing the effectiveness of diet and physical fitness interventions.

Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress, R. R. Wolfe, PI, University of Texas Medical Branch at Galveston, is testing an amino acid supplement designed to ameliorate muscle wasting induced by stress-and microgravity-induced depression of protein synthesis in a bed rest study. The study consists of 12 individuals with or without consumption of the supplement in a 30-day bed rest trial. A unique feature of this study is the use of a cortisol infusion at two times during the intervention period to mimic (in part) the documented elevated cortisol levels during space flight. Although primarily targeted to Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function, we have considered this bed rest study to be our cornerstone project and have added a large number of ancillary grants which use the bed rest model and the nutritional intervention to address issues related to other goals. These "add on" projects will be discussed further in reference to Goal 14: Integrate Research and Analysis. To summarize here, separate projects working off of the Wolfe bed rest study are targeted to: Goal 1: Reduce Risk of Suboptimal Nutritional Status; Goal 2: Reduce Risk of Suboptimal Physical Fitness; Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function; Goal 9: Reduce Risk of Depressed Immune Function; Goal 10: Reduce Risk of Loss of Bone Mineral Density; and Goal 14: Integrate Research and Analysis.

Nutritional Modulation of Pancreatic Endocrine Function in Microgravity, B. W. Tobin, PI, Mercer University School of Medicine, will determine amino acid countermeasure effects on endocrine function of human pancreatic islets of Langerhans with the goal to optimizing insulin synthesis and secretion under microgravity conditions. Dr. Tobin uses human pancreatic islet cells cultured on static plates or in a high aspect ratio vessel (HARV) designed to replicate some of the conditions of microgravity. The goal of this research project is to determine how different physiological conditions, characterized by over or underexpression of certain hormones, affect insulin secretion and to develop an amino acid combination that will optimize this secretion. In becoming part of the Nutrition and Physical Fitness Team, Dr. Tobin has added a myocyte culture model to determine the effect of maximizing insulin secretion on muscle cell response. In addition to targeting Goal 1 (as do all nutrition based projects), this project specifically addresses Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function, since uptake of amino acids into muscle is governed by insulin. Optimal insulin synthesis, should maximize uptake of amino acids into muscle and thus enhance muscle protein synthesis. The other goal targeted by this research project is Goal 14: Integrate Research and Analysis. This goal will be described more fully later under Goal 14, but briefly stated, Tobin's project is using the amino acid levels found in blood of subjects from Wolfe's bed rest study who have received his amino acid supplement. Thus, there is integration between these two projects.

Metabolic Adaptations of Skeletal Muscle to Training/Detraining. A Systems Model, M. E. Cabrera, PI, Case Western Reserve University, uses mathematical modeling to perform quantitative predictions of work capacity after periods of training/detraining. These models and predictive equations are based on data from animal and human studies and will provide a framework for quantitative understanding of the skeletal muscle metabolic adaptations to periods of training and detraining. Part of the database used in these predictive equations is nutritional information or metabolic status. Therefore, this research program serves to integrate both nutrition and physical fitness and targets goals 1, 2, and 3 as well as goal 14, the integration.

We anticipate that the ground based research summarized above, combined with future projects (discussed below) will eventually result in three fundamental countermeasure strategies to provide optimal nutrition and physical fitness, which in turn will ameliorate the risks as elucidated on the Critical Path. These general, broad-based strategies are summarized below.

1) Development of the rationale and mechanistic justification for a combination of traditional and targeted functional foods which are highly palatable and designed to minimize the risks on the Critical Path, without negatively impacting either food intake or other risks for which they may not be specifically targeted. For example, an amino acid supplement designed to enhance protein synthesis should not depress immune response or negatively impact bone health. A coordinated effort at the team level is required to achieve this goal. Some of these foods/supplements will be general to meet the nutrient requirements for all individuals in space. Others may need to be task specific, e.g. time release energy foods for prolonged activity without additional food intake such as may be experienced during Extravehicular Activity (EVA). Although it is not the goal of the nutrition team to develop the foods and supplements, it is a team goal to determine the requirements for what should be in those foods/supplements.

2) Development of an exercise protocol, and the appropriate equipment to maximize both muscle strength, lean body mass, bone strength, and aerobic capacity. Studies will be designed to determine the optimal as well as minimal prescription for frequency, duration, and intensity of the exercise countermeasure to obtain the most time efficient method to maintain muscle and cardiovascular capacity. Traditionally, this prescription is considered to involve two types of exercise protocols (resistance training and aerobic exercise), but where possible, their integration

should be a priority. The overall intention of the physical fitness program is to produce the most physically fit individual (from both a strength and aerobic viewpoint) in the least amount of time. Since exercise takes time from other tasks and also requires energy input, which means greater food intake, accomplishing this task will have many benefits. In addition, the Nutrition and Physical Fitness Team is aware that different forms of preflight and in-flight physical exercise are a major countermeasure thrust for the Muscle Team and will work with the Muscle Team to coordinate and maximize the effectiveness of our collective programs to address shared goals.

3) Development of a strategy of timing of food intake with respect to physical activity. This countermeasure plan will be key to the overall health of individuals in space. Often overlooked, when one eats with respect to when one exercises has important consequences for overall utilization of nutrients and for human performance. The current recommendations for food intake timing with respect to exercise as practiced in flight are not based on strong scientific studies. A scientific basis for the timing of food intake and exercise prescriptions is needed. For example, R. Wolfe has shown in human studies, that providing amino acids prior to rather than after an exercise bout will enhance protein synthesis by up to three fold. The appropriate combination of foods or new functional foods with time release components could provide a certain level of blood glucose over extended periods of time so that exercise or other tasks such as EVA could be performed without stopping to eat.

Keeping these three overarching countermeasure strategies in mind, the following is a discussion of the current status and future plans of the program with respect to the ten risk-based and four non-risk based goals defined in our Strategic Plan. As noted above, goals 1 and 2 are considered central to all of the other goals. They are (1) Reduce Risk of Suboptimal Nutritional Status and (2) Reduce Risk of Suboptimal Physical Fitness. With respect to Goal 1, designing optimal diets for individuals in space is not just taking the recommended dietary reference intake values (DRIs) developed for Americans and Canadians and modifying them for microgravity conditions. Optimal nutritional status for maximal performance both in space and for optimal health after space flight has to be more than meeting minimal RDI requirements. One needs to ask the question: "Optimal for what?" and in this case it is for maintaining muscle strength, bone mass, immune function, etc. This fact means that all of the nutrition projects (Lupton, Wolfe and Tobin) are addressing various aspects of what would represent optimal nutrition – Lupton from a view towards protecting against radiation-enhanced cancer; Wolfe and Tobin from the viewpoint of maintaining muscle mass through amino acid uptake into muscle and appropriate insulin response.

With respect to Goal 2 (Reduce Risk of Suboptimal Physical Fitness), again, development of successful countermeasures to meet this goal underlies all of the other goals. In many ways, there are already potential countermeasures at a high stage of development (exercise equipment and protocols) and with further relatively simple studies, we could have countermeasures in place within a rapid time frame. The Nutrition and Physical Fitness Team sees Goal 2 as being very practically oriented, rather than at the level of basic science. Protocols to be tested need to be ones that can be used in space and should aim towards the maximum benefits in the shortest amount of time. If funding for this team were increased, our next two subgoals within this goal would be to: first have an exercise intervention which involves both aerobic and resistive training and second to initiate a study designed to integrate exercise with diet (such as a study that would use the same protocol as the Wolfe bed rest study). This suggestion was also part of the request for proposals that went out in response to the combined NASA/NSBRI grants program in late 2001.

Goal 3 (Reduce Risk of Diminution of Skeletal Muscle Function), is the primary research focus of the current program and three out of the four projects address this goal (Wolfe, Tobin, Cabrera). The problem addressed is that muscular inactivity leads to decreased protein synthesis. This problem is compounded by the fact that stress (mediated by moderate hypercortisolemia) leads to increased protein breakdown. The combined effect of decreased synthesis and increased breakdown results in loss of skeletal muscle mass, which leads to loss of muscle strength. This compromises crew capabilities, including EVA or potential emergency egress. Countermeasures to these risks include an amino acid supplement designed to enhance protein synthesis (Wolfe bedrest study) which should also enhance insulin secretion and thus amino acid uptake into muscle and muscle synthesis (Tobin, insulin secretion). This dietary countermeasure, combined with an appropriate physical fitness intervention should help maintain muscle strength and aerobic capacity, positively affecting both muscle strength and uptake of amino acids into muscle for protein synthesis. Finally, the newest addition to the team (Cabrera, modeling adaptations of skeletal muscle), will take data from the Wolfe and Tobin and programs and combine it with existing data from previously conducted research, to develop equations that will predict for work capacity after periods of training/detraining. Progress towards achieving this goal is advancing, and the goal is adequately addressed by current research projects. In addition, as we more fully integrate with the Muscle Team (See Goal #14), our combined strengths in this area position us to advance rapidly through phases of countermeasure development.

Goal 5 (Reduce Risk of Radiation Enhanced Development of Cancer) is currently being addressed by the Lupton project. Risks to personnel in space from radiation exposure are considered to be a tier one problem by NASA. A primary risk of radiation exposure is later cancer development. Of all the cancers, colon cancer is the second leading cause of death from cancer in the United States today. It strikes men and women equally. On the positive side, it is the cancer most amenable to diet intervention. Thus, studying mechanisms by which we can protect against the development of this cancer with respect to previous radiation exposure is important. To maximize our effectiveness in addressing this goal, future plans involve adding on projects to work off of the Lupton rat study, since rats irradiated at Brookhaven and kept through until tumor formation are a valuable resource that should be shared wherever possible.

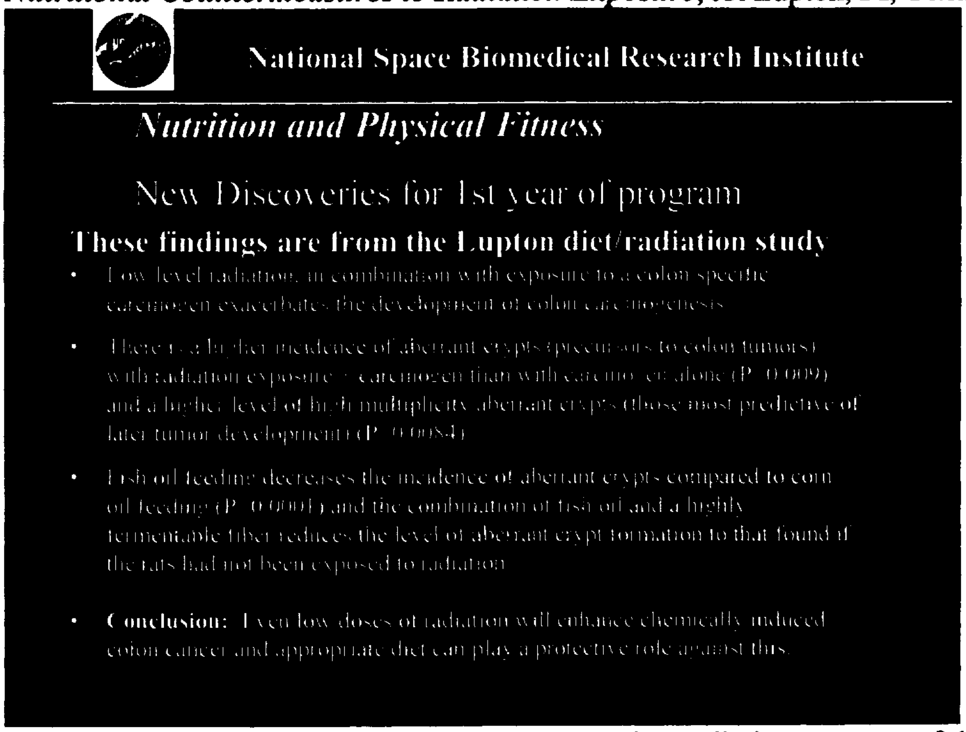
Our team also has non risk-based goals which are at various levels of development at this time. For example, Goal 12: Develop Noninvasive Technologies for Assessing the Effectiveness of Diet and Physical Fitness Interventions is in its infancy. One important aspect of the Lupton project is the use of microarray technology on mRNA from fecal material to see which genes are turned on or off during particular diet interventions, which ones are affected by radiation exposure and how these gene array patterns predict for a variety of endpoints. This patented technique is well developed in the rat, and the plan is to later apply it to humans. As noted previously, diet and physical fitness interventions lend themselves very well to Earth-based applications (Goal 13). In particular, we envision a protein supplement that will enhance amino acid uptake into muscle and muscle protein synthesis as a result of the Wolfe bed rest study. This supplement will also be useful for individuals on earth who have muscle wasting due to a variety of causes. We also envision a supplement of omega 3 fatty acids combined with pectin (a fermentable fiber) which may protect against both oxidative and alkylation damage to colonic DNA. With colon cancer the second leading cause of death from cancer in the US today, such a supplement could prove to be very beneficial.

Goal 14: Integrate Research and Analysis has already been a major part of the Nutrition and Physical Fitness Team. This goal includes efforts to enhance the interaction of individual Nutrition and Physical Fitness Team investigators a) among the current team's infrastructure, b) among investigators within other teams (eg. Muscle, Radiation), and c) with investigators not formally associated with the NSBRI. The activities will allow us to greatly expand the resources of NSBRI and the ability to tackle the risks of space travel. Table 2 summarizes our current efforts at integration. In addition to strong collaborations within our team, a few examples of integration of the Nutrition and Physical Fitness Team with other teams or researchers outside of the NSBRI are as follows: Lupton is collaborating with Judex (bone team) in supplying rat hind limbs from irradiated rats on different diets. The Wolfe bed rest study is a true collaborative effort with the following investigators/projects: P. Uchakin, Mercer University, testing the hypothesis that stress during inactivity alters the balance between cell-mediated and humoral immunity; S. M. Smith, NASA, JSC, The effect of bed rest and amino acid supplementation on bone markers of calcium metabolism; R.R. Fitts, Marquette University, The effect of prolonged bed rest and amino acid supplementation on muscle fiber function; R Stowe, UTMB, Effects of prolonged bedrest on herpesvirus-specific immunity. Similar measurements to the Stowe bedrest study are also being performed on the Shuttle and ISS crewmembers and so the Stowe study would serve to complement in-flight work. Additional collaborative projects with the Wolfe study include: T.P. Stein, UMD-NJ, Does bed rest + hypercortisolemia lead to increased oxidative stress during the recovery phase?; H W Lane, NASA, JSC, The effect of bed rest and amino acid supplementation on muscle energy production during exercise. In addition to collaborative projects, several people who were not directly funded with NSBRI grants have become an active part of our team. They include Helen Lane and Scott Smith from NASA/JSC in the area of nutrition and Don Hagan, also NASA/JSC for physical fitness. These close ties to NASA enable the Nutrition and Physical Fitness Team to be up to date on the most recent countermeasure approaches to addressing nutrition and physical fitness related risks.

IV. RESEARCH PROGRAM ACCOMPLISHMENTS

During the past year excellent progress has been made on each of the 4 funded projects Specifically:

Nutritional Countermeasures to Radiation Exposure, JR Lupton, PI, Texas A&M University.



Risks to personnel in space from naturally occurring radiations are one of the most serious limitations to human space missions (BEIR V, 1990; BEIR VII, 1998; National Research Council, Washington, DC) and thus considered to be a Tier 1 problem for NASA. One of the most important adverse effects of radiation exposure is increased risk for cancer, and colon cancer is the second leading cause of death from cancer in the US today, striking men and women almost equally. Fortunately, of all the cancers, colon cancer has been shown to be the most responsive to diet. Colon cells are arranged in patterns called crypts (Figure 1) in which cells are born towards the bottom of the crypts and daughter cells may migrate up the side of the crypt eventually being exfoliated into the fecal stream. However, radiation may induce oxidative damage to DNA in these cells, whereas a chemical carcinogen may induce methylation damage to DNA. Once damaged, DNA can be repaired by DNA repair enzymes, or the cell can be removed by programmed cell death (apoptosis), if neither of these events occurs, the cell may go on to become a cancer cell (Figure 2).

Figure 1. Diagram of two colon crypts

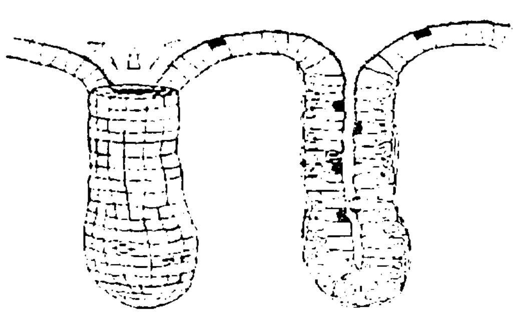
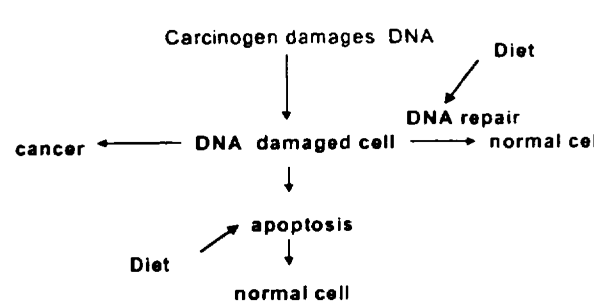


Figure 2. Diet effects on the initiation of cancer



Lupton et al. have shown that a combination of fish oil (high in n-3 fatty acids) and a fermentable fiber (pectin) can upregulate apoptotic removal of DNA damaged cells. The purpose of the NSBRI study is to determine if radiation exposure is promotive of chemically induced colon cancer, thus the experimental design is as shown in Figure 3. The first experiment was initiated in January 2001 in which rats were irradiated with 1 GY heavy iron at Brookhaven National Laboratory and then injected with the colon specific carcinogen azoxymethane (AOM). An equal number of rats were injected with AOM but not exposed to radiation. Results clearly show that there is a promotive effect of the radiation with respect to colon cancer development. Colon cancer proceeds in stages and an intermediate stage is aberrant crypt development. Figure 4 shows a segment of rat colon with several foci of aberrant crypts visible. Figure 5 shows one of the results from this initial study in that the rats that were irradiated and injected with AOM had significantly greater numbers of aberrant crypts than did those that were injected with AOM but not irradiated (P=0.0009). In addition, there were a greater number of aberrant crypts/focus (considered more predictive of colon tumors) in the irradiated group compared to the non-irradiated group (P=0.0084).

Figure3. Experimental Design for NSBRI study

- 560 SpragueDawley rats, 2 x 2 x 2 factorial design
  - Corn oil, fish oil
  - Pectin, cellulose
  - +/- radiation (1 Gy heavy iron)
  - All + AOM (Colon specific carcinogen)
- Specific Aims
  - Effect on initiation, aberrant crypts, tumors
  - mRNA from fecal material predicts the outcomes

Figure 4. Aberrant crypts in rat colon.

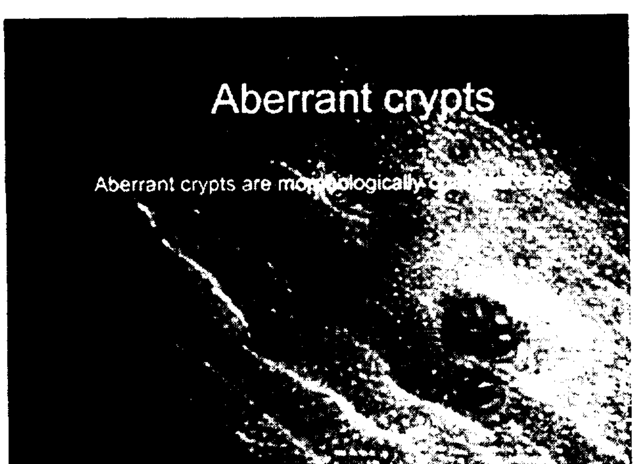
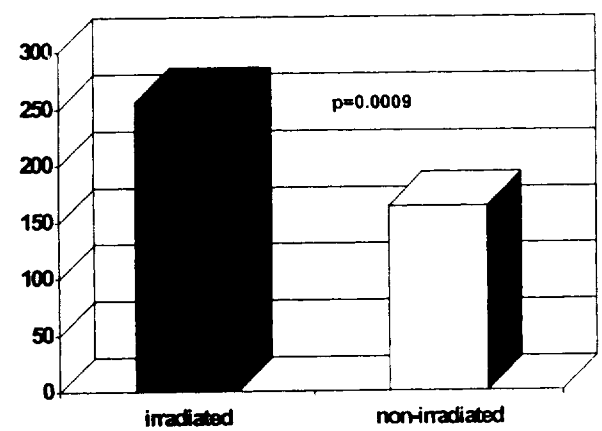


Figure 5. Aberrant crypts in irradiated vs non-irradiated rats



Currently mRNA from the same rats in this experiment is being subjected to both microarray and real time PCR to determine which genes were up or down regulated by the radiation and carcinogen treatments. Also, one half of the control rats for the large NSBRI supported study) are currently in house, receiving experimental diets.

In February 2002, half of the rats that will receive radiation treatment were irradiated at Brookhaven National Laboratory. In November, 2002, the remaining rats will be irradiated. To summarize, this project is proceeding on schedule, and the initial results confirm the hypothesis that radiation exposure on top of chemical exposure, enhances colon tumor development.

Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress, R. R. Wolfe, PI, University of Texas Medical Branch at Galveston.

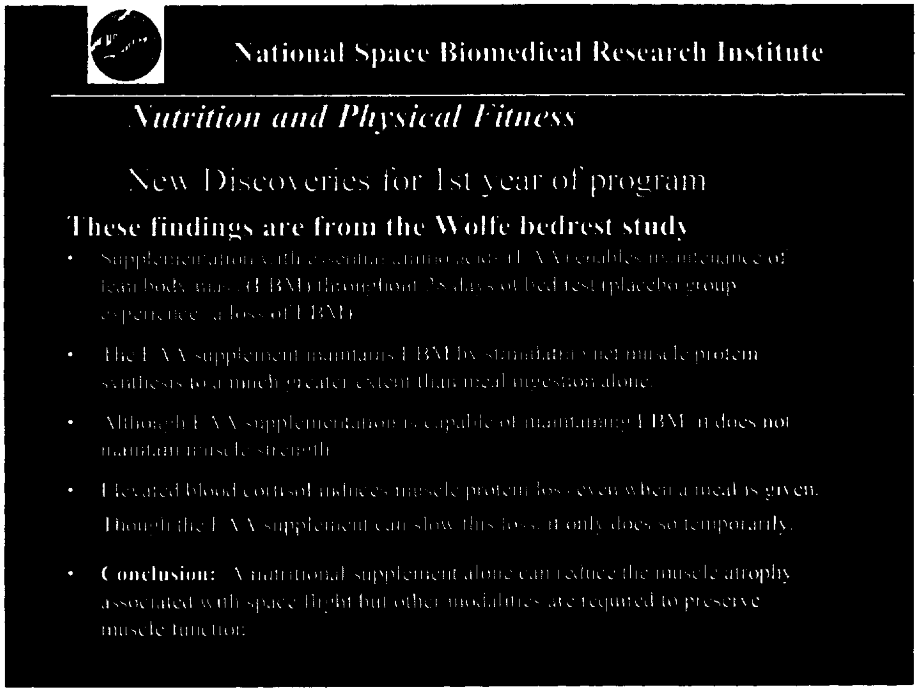


Figure 6 shows the overall protocol for each subject in the Wolfe bed rest study. The purpose of the study is to determine if an amino acid supplement can ameliorate the negative effects of bed rest (a proxy for microgravity) on muscle protein synthesis. The composition of the amino acid supplement is shown in Figure 7.

Figure 6. Time Line for each subject in the

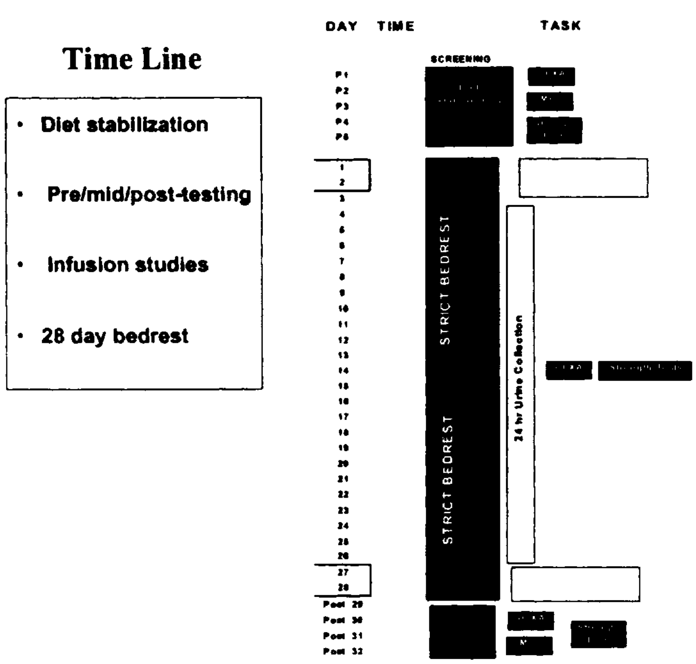
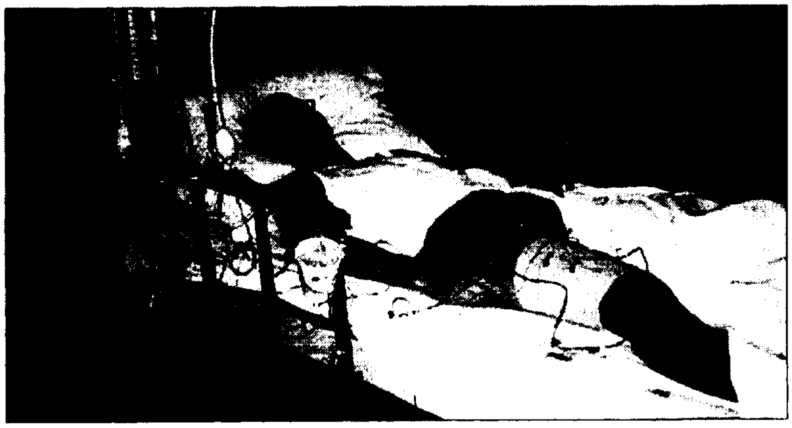


Figure 7. Composition of the supplement

Amino Acid	Amount (g)
L-Histidine	1.70
Isoleucine	1.00
Leucine	3.10
Lysine	2.60
Methionine	0.50
Phenylalanine	2.00
Threonine	2.20
Valine	2.10
Tryptophan	0.60
Glycine	0.70

This research project is proceeding ahead of schedule. To date, all subjects have completed the study. The first subject is shown below in Figure 8.

Figure 8. Subject in Wolfe bed rest study.



Most importantly we have chosen the bed rest study as the cornerstone of our program, and as such have requested and received funding for a number of important additional projects which use samples from this study. The following are descriptions of "add ons" to the Wolfe bed rest study.

1. Helen Lane, Ph.D.
NASA Johnson Space Center
Houston, TX
Title: Response of oxidative capacity in skeletal muscle to prolonged bed rest.
The NSBRI project evaluates a nutritional countermeasure, protein/amino acid supplementation, on leg muscle performance after a month of bed rest. As part of this overall project, Dr. Helen Lane is leading the NMR spectroscopy for determination of oxidative capacity of calf muscle before, during, and after exercise. Phosphorus NMR spectroscopy is a technique to continuously follow high energy metabolism in a localized tissue by determination, using P31, of levels of inorganic phosphate, phosphocreatine, and ATP along with calculation of muscle pH. This technique also allows for determination of creatine kinase reaction at rest and during exercise in skeletal muscles. Creatine kinase catalyses the reversible transfer of high-energy phosphate groups of phosphocreatine to and from adenosine diphosphate. Muscle countermeasures such as training programs changed these parameters both in the level of phosphocreatine as well as the time to recovery of phosphocreatine after fatiguing exercise. The plan is several fold: First, we need to develop the hardware (exercise device, interface for quantification, and other analytical efforts such as precision and reproducibility) and the software interface to determine the oxidative capacity of calf muscle with phosphorus NMR spectroscopy. Next, we will examine the difference in these parameters before and after 28d of bed rest with and without the countermeasure. Our hypothesis is that in subjects without the countermeasure phosphocreatine will be lower at rest and decrease more during exercise than those subjects with a countermeasure. Furthermore, the regeneration of phosphocreatine will be faster in those who have the countermeasure. These measures will be correlated with muscle function (strength measures) and single fiber analyses performed by Bob Fitts (as a separate add-on project). Thus, we will not only determine the effect of bed rest on muscle oxidative capacity, but the relation of

oxidative capacity to muscle function. This project is being conducted at no additional cost to NSBRI.

2. Scott M. Smith, Ph.D. (Also a collaborator on the Tobin project)
Research Nutritionist
NASA Johnson Space Center
Houston, TX
Title: Markers of bone and calcium metabolism
Dr. Scott M. Smith's supplement to the Wolfe project is designed to measure markers of bone and calcium metabolism in the bed rest subjects. These include serum osteocalcin and bone-specific alkaline phosphatase, and urinary collagen crosslinks. Osteocalcin and Bone-Specific Alkaline Phosphatase are both bone formation markers. The collagen crosslinks are bone resorption markers, and represent a family of compounds which include n-telopeptide, pyridinoline, and deoxypyridinoline, among others. Their analyses will tell us if the Wolfe countermeasure, obviously aimed at muscle tissue, has any impact on the bone side of the musculoskeletal system. At present Dr. Smith has approximately 1/3 of the samples, but is awaiting analysis until after all samples are collected, to analyze these in one batch.

3. Raymond P. Stowe
Assistant Professor (Research), Pathology
University of Texas Medical Branch
Galveston, TX
Title: Changes in antiviral immunity during bed rest
Dr. Raymond P. Stowe's project measures changes in antiviral immunity. These measurements are also being performed on the Shuttle and ISS crewmembers through his NASA grant (Epstein-Barr virus flight grant). These include measurement of viral load in blood, urine, and saliva samples using molecular methods. In addition, he will measure virus-specific immunity by measuring anti-viral antibody titers and antigen (virus)-specific T-cells to correlate with viral load.

4. Brian W. Tobin, Ph.D.
Associate Professor
Mercer University School of Medicine
Macon, GA
Title: Blood amino acid levels from Wolfe project for use in Tobin project
In order to test the same protocols in several model systems, the amino acid blood levels produced by the Wolfe supplement have been quantitated and will be used as one of the interventions in the Tobin protocol. This is at no added expense to NSBRI.

5. Peter N. Uchakin, Ph.D. (Also a lead investigator on the Tobin project)
Lead Research Scientist
Division of Basic Medical Sciences
Mercer University School of Medicine
Macon, Georgia
Title: The effect of bed rest and corticosteroid treatment on the secretion of pro- and anti-inflammatory cytokines

Dr. Peter N. Uchakin is investigating the effects of bed-rest and corticosteroid treatment on the secretion of pro- and anti-inflammatory cytokines such as IL-1, IL-6 and IL-10. In addition, Dr. Uchakin will assess immunocyte distribution in whole blood.

6. Robert Fitts, Ph.D.
Marquette University
Milwaukee, WI
Title: Single muscle fiber function in response to bed rest and nutritional intervention.
Investigation of the contractile properties and force of single muscle fibers of the soleus (predominantly Type 1) and vastus lateralis (predominantly mixed) in response to prolonged bed rest with and without the nutritional intervention.

7. T.P. Stein, Ph.D.
Professor of Surgery
UMDNJ-SOM
Stratford, NJ
Title: Markers of oxidative stress
Oxidative damage from free radicals to DNA and lipids has been implicated in the etiology of a wide variety of chronic diseases and acute pathological states. Dr. Stein and his colleagues had the opportunity to obtain data on the question of whether space flight has any effect on the oxidative status of astronauts. They measured the urinary excretion of 8-iso-PGF2a and 8-oxo-7,8 dihydro-2 deoxyguanosine (8-OH dG) on 6 subjects (2 US astronauts and 4 Russian cosmonauts) before, during and after long duration space flight on the Russian space station MIR. The urinary excretion of the isoprostane 8-iso-PGF2a and 8-OH dG are markers for oxidative damage to lipids and DNA respectively.

There was a trend towards an increase in 8-OH dG excretion in flight. Both 8-iso-PGF2a and 8-OH dG excretion were double post flight indicating that oxidative stress was double. The increase persisted for the two-week observation period. The level was akin to smoking a pack of cigarettes a day. The increased oxidative stress damage post flight most likely reflects impaired endogenous anti-oxidant defenses. (Subjects took vitamin capsules throughout the study period). The down regulation of protein metabolism that occurred on MIR could cause some loss of protein-based antioxidant systems. The likely causes of the compromised protein metabolism are: (i) the combination of reductive remodeling in response to the loss of load and the chronic under-nutrition that occurred on MIR and (ii) competition post flight for amino acids between synthesis of defense related proteins and repleting muscle leading to sub-optimal availability of host defense mechanisms.

The problem being addressed is how to study this problem on the ground. The need is for an acceptable ground based model. At present there is no such model. The objectives of this supplementary project are therefore to determine whether cortisol administration to bed rest subjects reproduces the flight situation. Given a model, counter-measures can be explored. Thus the hypothesis being tested is that bed rest plus cortisol reproduces the flight result. Dr. Stein will use the urinary excretion of the isoprostane 8-iso-PGF2a and 8-oxo-7,8 dihydro-2 deoxyguanosine (8-OH dG) to assess oxidative damage to lipids and DNA respectively in the urines from Dr. Wolfe's study.

In summary, the Wolfe/Ferrando bed rest study is proceeding ahead of schedule and all aspects of the study are on target. Important, we have chosen this study as the cornerstone of our program and have acquired additional funding for "add on projects" which will capitalize on this well controlled study. We are very optimistic that definitive data will be obtained from this study which can be used in the very near future to enhance long term travel in space. Examples of answers that will be obtained are: whether or not an amino acid supplement ameliorates the decline in protein synthesis seen in space; if supplements interfere with protein synthesis from meals; if cortisol infusion in addition to bed rest is a better model for what actually occurs in space; if different muscle fiber types are equally affected by bed rest and cortisol; if this nutritional intervention can affect bone loss and muscle strength, among many other questions.

Nutritional Modulation of Pancreatic Endocrine Function in Microgravity, B. W. Tobin, PI, Mercer University School of Medicine, is determining amino acid countermeasure effects on endocrine function of human pancreatic islets of Langerhans with the goal to optimizing insulin synthesis and secretion under microgravity conditions. In addition, he has modified his protocol to include addressing these effects on human myocytes isolated from the same cadavers as the pancreatic islet cells. Figure 9 shows the model used by Tobin et al. Islets or myocytes are cultured in "microgravity" or static plate controls. The HARV rotates at 10 RPM, and islets are eliptical orbit-suspended in media. Measurements are made of medium glucose, lactate, hormones and amino acids. Specific aims of this project are (1) to assess the effect of a microgravity model system on basal amino acid requirements and endocrine secretory function in human islets of Langerhands and (2) to determine human islet endocrine function while testing amino acid countermeasures. Results from the first set of studies illustrate (1) decreased glucose utilization, (2) enhanced insulin secretion, (3) increased utilization of cysteine, and (4) increased production of ornithine, presumably from arginine. Tobin is now beginning the initial testing of countermeasures, to normalize the hormonal secretory profile. This will consist of two amino acid mixtures: (1) the Wolfe mixture and (2) the Tobin formula which is higher in arginine and cysteine as well as other amino acids utilized at high rates. His experimental design for the studies is shown in Figure 10.

Figure 9. HARV Microgravity Model

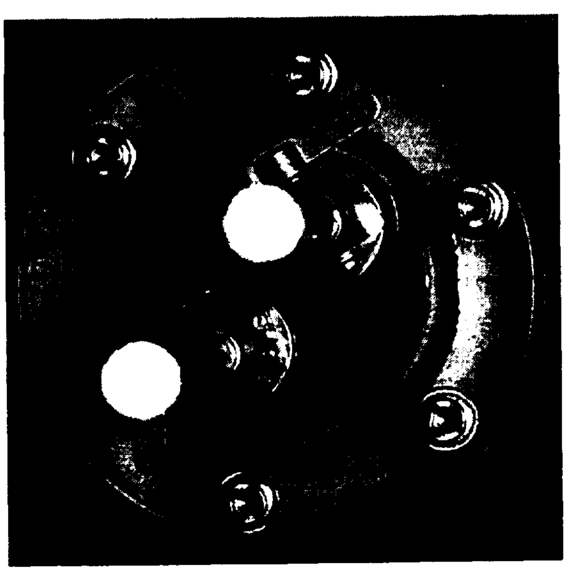
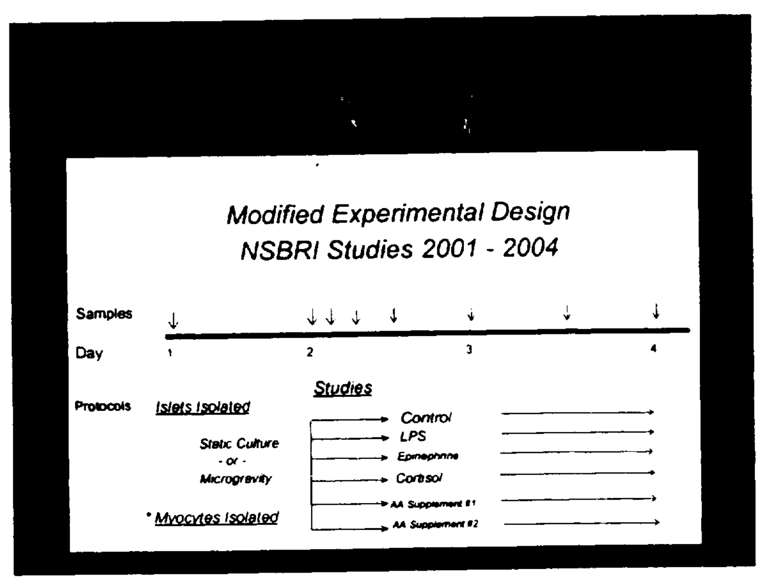
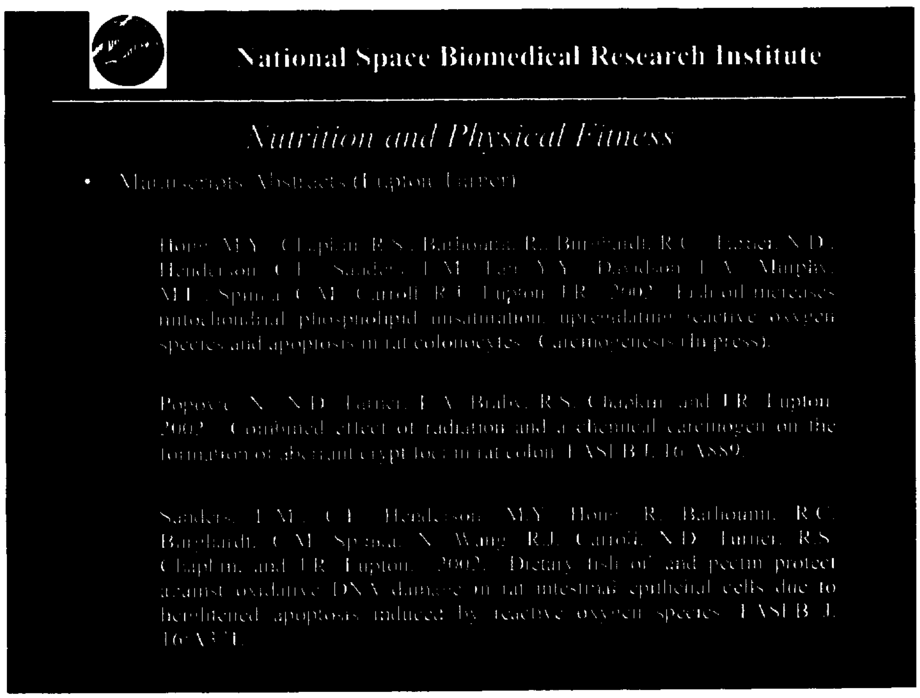
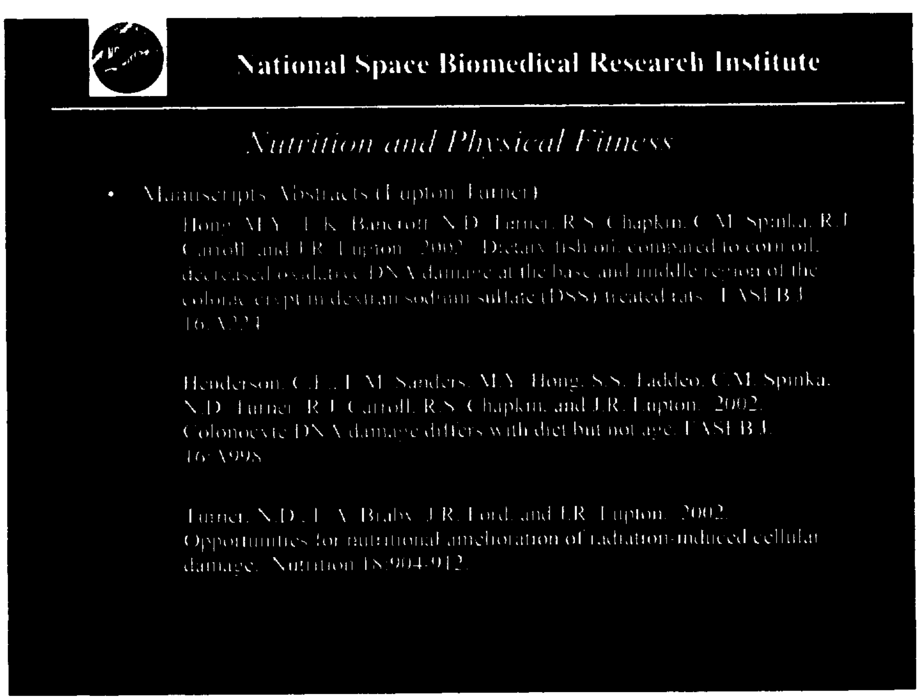


Figure 10. Tobin Experimental Design



In the time that Dr. Tobin has been funded, he has obtained an R15 grant from NIH which allowed him to concentrate more on countermeasures with the NSBRI project. He has published two abstracts and has been interviewed on international television on this NSBRI project and on National Public Radio. He has published one of the articles in the special addition of Nutrition (On nutrition in space). He is actively collaborating with Wolfe/Ferrando and in fact Peter Uchakin (an investigator on the Tobin project) is now working with Wolfe/Ferrando on site (see the Wolfe/Ferrando summary above).





National Space Biomedical Research Institute

Nutrition and Physical Fitness

- Manuscripts Abstracts (Lupton Turner)

  Popovic, N., N.D. Turner, L.A. Braby, J.H. Ford, R.S. Chapkin, and J.R. Lupton. 2002. Nutritional countermeasures to radiation exposure. Paper to be presented to the Annual RHIC AGS User's meeting at Brookhaven National Laboratory, September, 2002.

  Lupton, J.R., N.D. Turner, N. Popovic, R.S. Chapkin, L.A. Braby, J. R. Ford. 2002. Nutritional countermeasures to radiation exposure. Paper to be presented at the Kongress Medizin und Mobilitat in Furstenfeldbruck, Germany, September, 2002.

National Space Biomedical Research Institute

Nutrition and Physical Fitness

Manuscripts Abstracts (Wolfe Ferrando)

Ferrando AA, Paddon-Jones, D, Wolfe, RR. Alterations in protein metabolism during space flight and inactivity. Nutrition 18:837-8341, 2002.

Manuscripts Abstracts (Cabrera)

Soller, **Cabrera ME**, Smith SM, and Sutton JP. Smart medical systems with application to nutrition and fitness in space. *Nutrition* 18(10):139-145, 2002.

Manuscripts Abstracts (Tobin)

Tobin BW, Uchakin PN, Leeper-Woodford SK. Insulin secretion and sensitivity in space flight: diabetogenic effects. Nutrition 18:842-848, 2002.

National Space Biomedical Research Institute
NUTRITION, PHYSICAL FITNESS AND REHABILITATION PROGRAM

Table 1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
CABRERA/Metabolic Adaptations of Skeletal Muscle to Training/Detraining. A Systems Model	Diminished muscle function	Exercise	Computer Simulations and experimental data on rats and humans	Integrate existing knowledge into computational models of muscle metabolism	Predict effects of muscle mass loss and changes in fiber type distribution on muscle metabolism	Predict effects of detraining and/or exercise training on metabolism and work capacity
LUPTON/Nutritional Countermeasures to Radiation Exposure	Radiation-induced carcinogenesis	Diet/Nutrition	Rat	Test diets in rats + or - a colon specific carcinogen with or without radiation exposure to see which diet is protective against radiation and methylation damage, and how it protects	Predict effects of the optimal diet at each stage of the tumorigenic process and optimize noninvasive recovery of mRNA from exfoliated colon cells to predict and monitor the tumorigenic process	Develop and test dietary supplements that will decrease oxidative and methylation damage to colonic DNA and monitor their effectiveness through a noninvasive technique
TOBIN/Nutritional Modulation of Pancreatic Endocrine Function in Microgravity	Diminished muscle function	Diet/Nutrition	Cultured pancreatic islet cells (HARV)	Determine nutrient needs of human pancreatic islet cells under different hormonal conditions designed to mimic microgravity and stress	Develop a nutrition intervention to ameliorate the depressed insulin secretion from human pancreatic islet cells	Test the diet intervention strategy in a bed rest/cortisol stressed research program
WOLFE/Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress	Diminished muscle function	Diet/Nutrition	Human bed rest	Determine if a glucose/ amino acid supplement helps to ameliorate depressed protein synthesis, muscle wasting and loss of muscle strength	Optimize the supplement and the timing of the supplement with respect to exercise	Formulate the supplement for timed release, palatability, etc.

National Space Biomedical Research Institute
NUTRITION, PHYSICAL FITNESS AND REHABILITATION PROGRAM

Table 2. Integration Activities

	CABRERA Metabolic Adaptations of Skeletal Muscle to Training/ Detraining. A Systems Model	**LUPTON** Nutritional Countermeasures to Radiation Exposure	**TOBIN** Nutritional Modulation of Pancreatic Endocrine Function in Microgravity	**WOLFE**/Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress
Internal Communication	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons. P. Uchakin from Tobin project is now situated in Wolfe lab.
Integrated Experiment Development	Integrate existing knowledge into computational models of muscle metabolism using data from nutrition and physical fitness, literature, and the muscle team	Uses the same strain of rat and the same radiation protocol at Brookhaven National Lab as does the Dicello rat long term studies (Radiation Team). Thus results can be compared.	Tobin has redesigned his protocol as a result of talks with team members to include myocyte cultures. He is also using blood from Wolfe study to determine levels of amino acids to use in his cell culture system. P. Uchakin, a co-investigator with Tobin, is now collaborating with Wolfe	This bed rest study is highly integrated with a variety of projects. The same amino acid supplement is tested in the Tobin project and we plan to have it tested in the Baldwin rat model (Muscle Team).
Sample Sharing	Data from Wolfe, Lupton, Schneider, Baldwin (muscle team) and others from muscle team	Tobin will use pancreas from Lupton rats. S. Judex (bone team) will use rat hind limbs, H. Hogan, TAMU, will use other bones.	Will use pancreas from Lupton, will provide pancreatic cells to R Walzem, TAMU, for lipid analysis	There are currently seven "add on" projects to the bed rest study . See discussion of Goal 14 in this report.
Synergistic Studies of Opportunity	Aerobic and resistance exercise training with humans, and applying this to his model	Planned integration with A. Kennedy of radiation team for potential cross-use of each other's diet interventions	Future goal is to fly the HARV with pancreatic cells in space to determine how well the results mimic his system on earth	This study maximally capitalizes on synergistic opportunities which have arisen in the course of meetings and telecons to expand the program with "add on" grants.
Development of Computer Model of Integrated Human Function	This is exactly what the project is and should be an integrating force for the entire team.	Data from this project will be used by Cabrera for his prediction equations.	Currently this research is all ex vivo and not suitable for the integrated function component which we are only doing in animals and humans	Data from this project will be used by Cabrera for his prediction equations

National Space Biomedical Research Institute

National Space Biomedical Research Institute

Radiation Effects Team

Team Leader:
John F. Dicello, Ph.D.
Division of Radiation Oncology
The Sidney Kimmel Comprehensive Cancer Center
At Johns Hopkins
Harry and Jeanette Weinberg Building, Suite 1440/Room 1454
401 North Broadway
Baltimore, MD 1231-2410
(410) 614-4194
(410) 502-1419 fax
diceljo@jhmi.edu

Associate Team Leader:
Ann Kennedy, D.Sc.
Division of Radiation Oncology
University of Pennsylvania Medical Center
195 John Morgan Building
3620 Hamilton Walk
Philadelphia, PA 19104-6072
(215) 898-0079
(215) 898-0090 fax
akennedy@mail.med.upenn.edu

Associate Team Leader:
Marcelo Vazquez, M.D., Ph.D.
Brookhaven National Laboratory
Biology Department, Bldg 463
P.O. Box 5000
Upton, NY 11973-5000
(631) 344-3443

National Space Biomedical Research Institute

Radiation Effects Team

Team Leader:
John F. Dicello, Ph.D.
Division of Radiation Oncology
The Sidney Kimmel Comprehensive Cancer Center
At Johns Hopkins
Harry and Jeanette Weinberg Building, Suite 1440/Room 1454
401 North Broadway
Baltimore, MD 1231-2410
(410) 614-4194
(410) 502-1419 fax
diceljo@jhmi.edu

Associate Team Leader:
Ann Kennedy, D.Sc.
Division of Radiation Oncology
University of Pennsylvania Medical Center
195 John Morgan Building
3620 Hamilton Walk
Philadelphia, PA 19104-6072
(215) 898-0079
(215) 898-0090 fax
akennedy@mail.med.upenn.edu

Associate Team Leader:
Marcelo Vazquez, M.D., Ph.D.
Brookhaven National Laboratory
Biology Department, Bldg 463
P.O. Box 5000
Upton, NY 11973-5000
(631) 344-3443

National Space Biomedical Research Institute

Radiation Effects Team

Team Leader:
John F. Dicello, Ph.D.
Division of Radiation Oncology
The Sidney Kimmel Comprehensive Cancer Center
At Johns Hopkins
Harry and Jeanette Weinberg Building, Suite 1440/Room 1454
401 North Broadway
Baltimore, MD 1231-2410
(410) 614-4194
(410) 502-1419 fax
diceljo@jhmi.edu

Associate Team Leader:
Ann Kennedy, D.Sc.
Division of Radiation Oncology
University of Pennsylvania Medical Center
195 John Morgan Building
3620 Hamilton Walk
Philadelphia, PA 19104-6072
(215) 898-0079
(215) 898-0090 fax
akennedy@mail.med.upenn.edu

Associate Team Leader:
Marcelo Vazquez, M.D., Ph.D.
Brookhaven National Laboratory
Biology Department, Bldg 463
P.O. Box 5000
Upton, NY 11973-5000
(631) 344-3443

(631) 344-5311
vazquez@bnl.gov

Individual Projects and Principal Investigators:

Charged Particle Radiation-Induced Genetic Damage in Transgenic Mice

Principal Investigator:
Polly Chang, Ph.D.
SRI International
PN 175
333 Ravenswood Avenue
Menlo Park, CA 94025
(650) 859-2549
(650) 859-2889 fax
pchang@sri.com

In Vivo Carcinogenesis Studies with the Sprague-Dawley Rat

Principal Investigator:
John F. Dicello, Ph.D.
Division of Radiation Oncology
The Sidney Kimmel Comprehensive Cancer Center
At Johns Hopkins
Harry and Jeanette Weinberg Building, Suite 1440/Room 1454
401 North Broadway
Baltimore, MD 1231-2410
(410) 614-4194
(410) 502-1419 fax
diceljo@jhmi.edu

Chemoprevention and Radiation-Induced Neoplasms

Principal Investigator:
David L.Huso, D.V.M., Ph.D.
Department of Comparative Medicine
The Johns Hopkins University School of Medicine
600 North Wolfe Street
Jefferson Building, Room 1-130
Baltimore, MD 21231
(410) 614-8599
dhuso@jhmi.edu

Countermeasures for Space Radiation Biological Effects

Principal Investigator:
Ann Kennedy, D.Sc.
Division of Radiation Oncology
University of Pennsylvania Medical Center
195 John Morgan Building

3620 Hamilton Walk
Philadelphia, PA 19104-6072
(215) 898-0079
(215) 898-0090 fax
akennedy@mail.med.upenn.edu

Risk Assessment and Chemoprevention of HZE-Induced CNS Damage
Principal Investigator:
Marcelo Vazquez, M.D., Ph.D.
Brookhaven National Laboratory
Biology Department, Bldg 463
P.O. Box 5000
Upton, NY 11973-5000
(631) 344-3443
(631) 344-5311
vazquez@bnl.gov

CNS Damage and Countermeasures
Principal Investigator:
Marcelo Vazquez, M.D., Ph.D.
Brookhaven National Laboratory
Biology Department, Bldg 463
P.O. Box 5000
Upton, NY 11973-5000
(631) 344-3443
(631) 344-5311
vazquez@bnl.gov

TABLE OF CONTENTS

ABSTRACT
For the first time, all four new projects successfully completed experiments in the past year with protons at the Loma Linda University Medical Center and energetic heavy ions at the Brookhaven National Laboratory. The group's activities represent a major fraction of the total research for Radiation Health at the Brookhaven NASA facility. The team will participate in the upcoming accelerator run that is scheduled to start at Brookhaven shortly.

Most recently, Dr. Ann Kennedy's group has compared the efficiency of four types of radiation in inducing oxidative stress in cultured cells and has identified several candidate agents that are highly effective in preventing radiation induced oxidative stress in vitro.

Dr. Chang's analysis of mutation frequency (MF) in the lacZ reporter transgene of mice exposed to acute doses of Gy proton irradiation showed that spontaneous lacZ MF in the control animals is tissue specific (spleen > brain).

Dr. Vazquez has exposed human neural precursor cells (NT2) and rodent glial progenitor cells (CG4) to acute doses of 0.1 to 6 Gy of heavy ions (Fe and Si, BNL-8) and gamma irradiation. Apoptosis induction as a function of time post irradiation was measured, with a dose-dependent peak induction of up to eight-fold above control levels after heavy ion, proton and gamma exposures. Estimated RBE's for apoptosis are the following Fe: 6, Si: 4 and protons: 1. Apoptosis pathways were examined at Doses as low as 0.25 Gy.

In parallel with the in-vitro studies, 498 C57Bl/6 male mice were exposed to 1 Gev/n Fe ions at AGS and gamma rays. Monthly evaluation of the effects of heavy ion and gamma radiation on memory were carried out and monthly monitoring of. cocaine-induced locomotor activity of heavy ion and gamma irradiated mice was done.

Dr. Dicello's group has produced an analysis of the first completed cohort of female Sprague Dawley rats exposed to iron, protons, and gamma rays and has obtained risk estimates for mammary cancer. The relative biological effectiveness of the ion ions was between about 6 and 16 relative to gamma rays with that for protons being about one. These values are generally lower than those obtained for that obtained for tumorigenesis of the Harderian gland of the mouse. Three other cohorts remain under care, including those being treated with Tamoxifen as a countermeasure.

In studies being led by Dr. Huso and not yet completed, he has shown that tamoxifen markedly reduces the incidence (reduces slope) and prolongs the latency (shift to the right) of mammary carcinomas in animals following iron ion radiation exposure. It appears that tamoxifen chemoprevention is similarly effective following exposure to photons or protons. Similar positive trends are emerging concerning tamoxifen's impact on improving survival following irradiation.

The group's activities resulted in several invited presentations at international meetings including the keynote address at the 2nd International Workshop on Space Radiation Research, the key annual meeting in our field, an invited presentation at the 2002 annual meeting of the National Council on Radiation Protection and Measurements (NCRP), and the American Society for Gravitational and Space Biology (ASGSB).

INTRODUCTION

The risks to human health inherent in space exploration are enumerated in the NASA Critical Path Roadmap, which lists radiation as one of the four Severe Type I Risks-the most critical type. It follows that the principal goals of the NSBRI Radiation Program are 1) to improve the predictions of risks to human health from space radiations and 2) to provide effective countermeasures that will significantly reduce these risks. The following risks in the Radiation Effects Discipline Area of NASA Critical Path Roadmap have been identified, and all but the final one are actively being addressed to varying levels by the Team (NASA risk number in parentheses): Carcinogenesis Caused by Radiation (38), Damage to Central Nervous System from Radiation Exposure (39), Synergistic Effects from Exposure to Radiation, Microgravity and Other Spacecraft Environmental Factors (40), Early or Acute Effects from Radiation Exposure (41), and Radiation Effects on Fertility, Sterility, and Heredity (42).

The radiation risk areas in terms of long-term missions, both low-earth orbit or extra planetary, and their relation to the overall space program are shown in the Fig. 1 adapted from NASA's Critical Path Roadmap.

Radiation Effects Risk Area

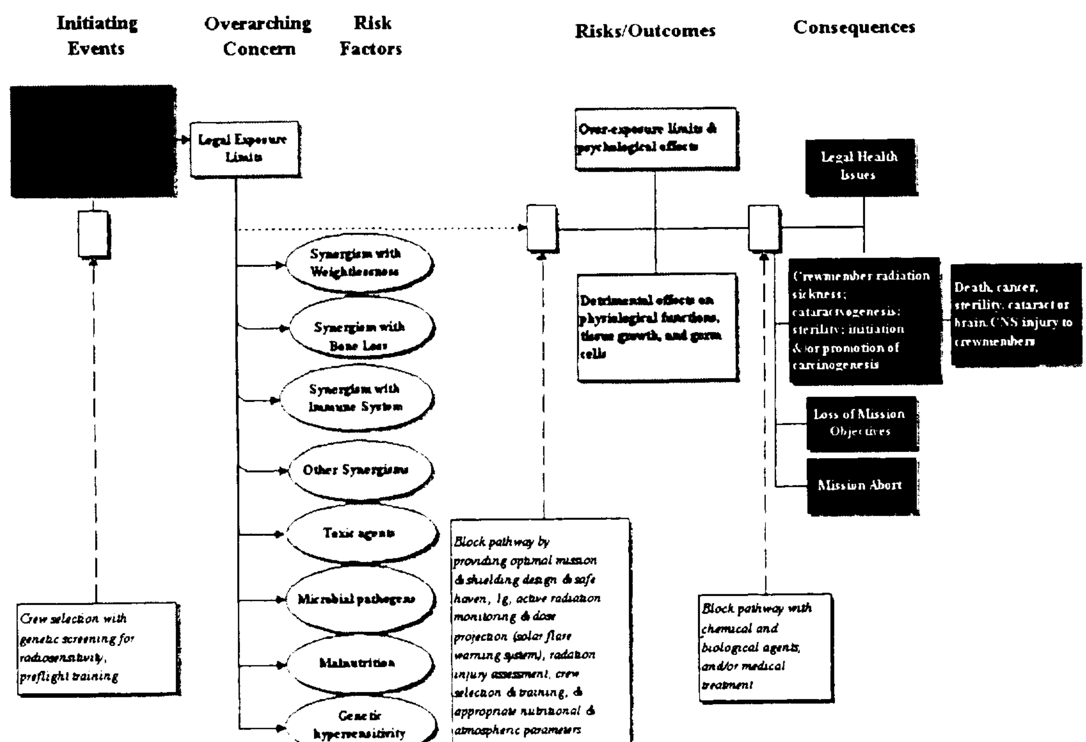


Fig. 1 Roadmap of critical hazards, strategies, and countermeasures

The underlying philosophy of the program's approach is adapted from that proposed in the NASA report on Modeling Human Risk (1997), i.e., that experimentally determined risks for carcinogenesis and CNS damage in appropriate animal models with corresponding in-vitro measurements can be used to validate theoretical mechanistic relations between animal results and human response. These mechanistic theoretical models, then, can be used to extrapolate known responses of humans to acute exposures of low-LET radiations to expected responses to protracted exposures to protons and HZE particles. When such relations have been established, then this same process and these same animal and cell models can be used to determine the potential of pharmaceutical agents, including both chemopreventive drugs and dietary supplements, for reducing risks. This is illustrated schematically in the figure below which is a revision of that proposed in the NASA report on modeling human risk (1997) and Dicello (J. F. Dicello, "How Do We Get from Cell and Animal Data to Risks for Humans from Space Radiations?" Journal of Radiation Research. In press (2002)).

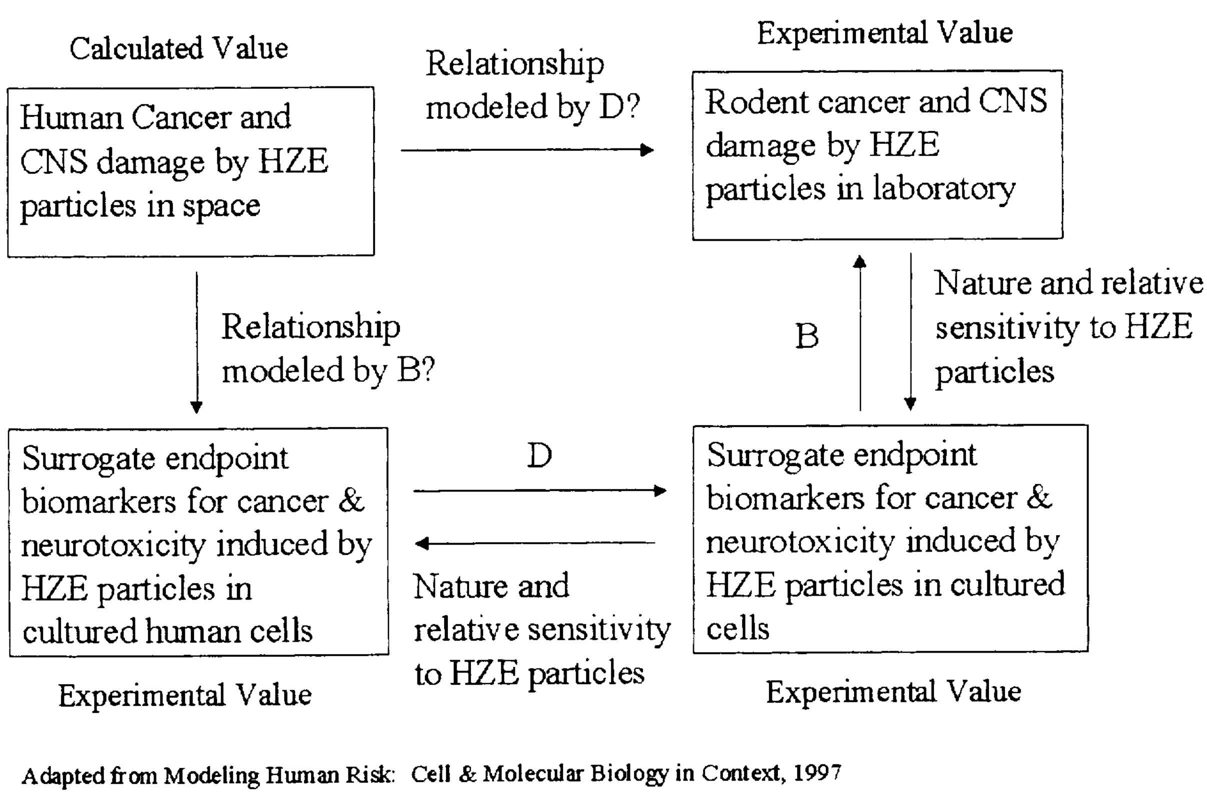


Fig. 2: A schematic description of the procedure for obtaining risk from radiation exposures of humans using mechanistic theoretical models with animal and cell data.

RESEARCH PROGRAM STRUCTURE & DESIGN

DESCRIPTION OF CURRENT (FY 2001-2002) PROGRAM

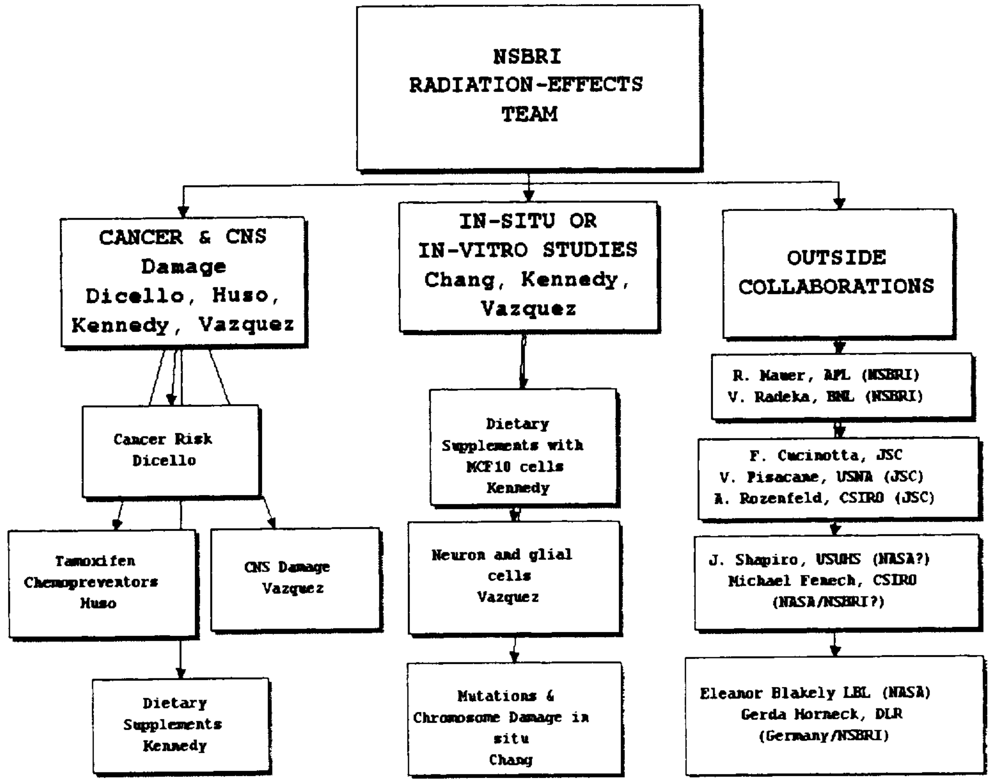


Fig. 3: Present structure of the NSBRI Radiation Team along with active collaborations of members of Radiation with other team members and researchers outside of the NSBRI.

The present Team organization and design, as outlined in Fig. 3, evolved from the original missions of the NSBRI and the Phase-I and Phase-II NSBRI proposals to NASA, as well as the recommendations of the NSBRI External Advisory Council, the NSBRI Board of Scientific Councilors, and peer review of the individual projects. The overall philosophy is that the Core Project provides in-vivo results for risks of cancer and other diseases and the Chemoprevention Project provides proof of principle and feasibility for risk reduction from low-dose exposures from protons and energetic heavy ions (HZEs) using acceptable levels of pharmaceuticals. Tamoxifen was chosen for this benchmark study because it is a drug widely used as a treatment drug for cancer, i.e., therapy rather than prevention, and its effects for x-rays under these circumstances are well known. The Cytogenetics projects, including that of Chang, give us cellular and cytogenetic data for cells irradiated in the animal or in-vitro. The investigation of pharmaceutical countermeasures includes a search for nontoxic dietary supplements, such as the work of Kennedy et al., that will reduce radiation risks. Although the primary risk appears to be cancer, damage to the central nervous system (CNS) may be significant, but the level of risk is poorly known. Dr. Vazquez is examining both the in-vivo effects of proton and HZE exposures and the cellular effects in vitro. Finally, the Core Project assembles all of the data to calculate risks in the animal model. Dr. Dicello has been collaborating extensively with scientists at both JSC and NASA Headquarters, particularly with Dr. Cucinotta's group at JSC, to develop mechanistic theoretical models. This collaboration has resulted in several publications addressing biological risks with impacts in reference to strategies for different flight scenarios, as well as shielding requirements. These collaborations with NASA personnel are not funded through the NSBRI.

BACKGROUND

Background for the Radiation Effects Team is included here in recognition of the changing composition of the External Advisory Committee.

Almost every review of radiation problems in space has recommended the use of animal studies to quantify the risks to these types of radiation and to pursue likely countermeasures. Until the present series of experiments there had been only one comprehensive animal study to investigate the effects of ions of high atomic number and high energy, HZEs. Alpen et al. (1993) conducted that experiment with the Berkeley Bevalac, which has been out of commission for almost a decade. Those experiments have provided invaluable data on carcinogenesis in the Harderian gland of a mouse model as a function of linear energy transfer (LET), and they have provided a cornerstone for risk assessments in space during the last decade. No comparable series of experiments had been conducted to evaluate the use of drugs to reduce the risk of cancer from exposures in space.

As a result of scientific reviews, meetings, and discussions during the developmental period of the NSBRI, the Core-Project proposal chose as its animal model the female Sprague-Dawley rat to be irradiated whole-body with HZE's, protons, or photons, in order to evaluate biological consequences including malignant and benign tumors at all sites, but particularly the breast and the pituitary and other significant diseases. The multiple motives for this choice are presented in detail in the 2000 Final Report for the Core Project; but this choice was ultimately the one recommended by the members of the External Advisory Council. Animal experiments of this type generally were not done previously because of the complicated logistics and the substantial expense. Only three facilities in the world, one at Brookhaven National Laboratory in New York State, one in Germany, and one in Japan, produced the necessary accelerator HZE beams. The costs for HZE beam time is millions of dollars a year, far in excess of any funds available from the NSBRI. Only about 150 hours a year are available for all space-biology irradiations in the U.S.A. Finally, no one had ever carryied out experiments with energetic charged particles at multiple facilities, including Loma Linda University with its energetic proton synchrotron. (The previous study by Alpen et al. was done at a single site by on-site staff.) The logistics of transporting thousands of animals between multiple facilities in controlled, isolated environments and keeping them alive subsequently for three or more years was at best a challenge. To fully exploit the value of the results, the team offered colleagues in the other projects and other institutions the option to join forces to maximize the production of useful scientific data with the irradiated animals and to provide different information correlated to the same animal species and to humans so that the results could be applied most efficiently to humans in the space environment. Two projects other than the Core successfully survived the review process initially with two joining forces to use the Sprague-Dawley, one studying Tamoxifen (Howard/Huso) as a chemopreventing agent and the other to look at cytogenetics to predict cancer risks (Williams) and to correlate the Sprague-Dawley results to human mammary cells, human lymphocytes, and eight different human colorectal cell lines with varying status of p53 expression. The third project (Sinden) proposed originally to use low-energy helium microbeams to study repeated DNA sequences using techniques that were established at that time only for mouse models. During the intervening time, the principal investigator has redirected the project goals to study the more energetic iron beam at BNL and has been developing reporter constructs for the Sprague-Dawley rat. That focused, cooperative effort succeeded in the implementation and execution of one of the most relevant but most difficult series of experiments performed as part of NASA's Life Sciences program in at least a decade.

At the end of the first three years of the team program, the investigators had designed, built, and successfully implemented systems to transport and irradiate both animals and cells. Four series of experiments were performed, each examining the consequences of 1-GeV iron ions, 250-MeV protons, and gamma rays from cesium-137 and cobalt-60, as well as sham irradiations. In each case, the animals were irradiated whole body at doses comparable to those expected in space. The animals are cared for and monitored daily, and all diseases are medically treated.

We now have statistically significant data for the risk for mammary fibroadenomas and adenocarinomas and for pituitary-related diseases as functions of particle type, dose, and time, as discussed at length in the project reports. In parallel with the animal experiments, we have been examining cell systems. The principal objectives of these projects were to examine cell survival, cytogenetic damage, and DNA deletions and recombinations, to understand the initial damage and the mechanisms responsible for the initial damage and the subsequent promotion and progression of the diseases. We are developing theoretical models to simulate the biological alterations and the in-vivo responses. We have used our data and models for preliminary calculations for the risk of carcinogenesis in the animals.

GOALS:

This team has eight scientific goals for its program: 1) the reduction of risk of carcinogenesis caused by radiation; 2) the reduction of risk of damage to the central nervous system from radiation exposure; 3) reduction of the risk of synergistic effects from exposure to radiations, microgravity and other spacecraft environmental factors; 4) reduction of the risk of early or acute effects from radiation exposure; 5) reduction of the risk of radiation effects on fertility, sterility, and heredity; and the non risk-based goals of 6) developing methods for assessing level of health risk, prevention of diseases, and appropriate medical care; 7) developing Earth-based applications; and 8) integration of research and analysis.

RESEARCH PROGRAM ACCOMPLISHMENTS

TEAM ACTIVITIES

The newest principal investigators, Drs. Ann Kennedy and Polly Chang successfully submitted proposals and protocols for beam time at Brookhaven National Laboratory (BNL) and Loma Linda University Medical Center (LLUMC) (protons), and both have only recently had successful runs at both facilities. Kennedy will return to BNL for the next run in November, 2002. Dr. Vazquez also continues CNS studies at BNL and LLUC as well as in Japan. Drs. Dicello and Huso previously completed NSBRI irradiations at BNL and LLUMC, and the animal colonies for studying carcinoma incidence and Tamoxifen intervention are proceeding on schedule. They have not participated in the most recent runs based on an EAC recommendation through Dr. Ron White. One cohort has now produced significant data that have been analyzed and submitted for publication.

A brief description of current research efforts for each investigator is presented, starting with the newer projects, followed by material on collaborations and recent grant and publication activities.

Kennedy: Countermeasures for Space Radiation Biological Effects
Countermeasure: Dietary supplements prior to and after exposure to radiation to reduce the cancer incidence.

The original aim of this study was to select a formula of dietary supplements that protect against space radiation-induced biological effects, with particular emphasis on radiation-induced oxidative stress and cancer. In the initial phase of the study, which was expected to take 18 months, we have performed studies to select dietary supplement agents that are most effective in suppressing radiation-induced oxidative stress in vitro and in animals. It was expected that a radiation carcinogenesis study would take place after the initial phase of the study to determine the effects of the selected dietary supplement agents in preventing radiation-induced cancer development. The effects of the selected dietary supplement agents on radiation-induced oxidative stress and radiation-induced carcinogenesis would then be compared to determine whether the two effects are related. The two specific aims of the first 18 months of the study were to select dietary supplement agents and agent combinations that reduce radiation induced oxidative stress in cultured cells and determine the effect of selected dietary supplement agents on radiation induced oxidative stress in Sprague-Dawley rats.

<u>**New Research Findings**</u>:
1) We have developed and optimized a dichlorofluorescein (DCF) fluorometric assay that can reliably detect oxidative stress induced by radiation at doses as low as 1.4 cGy, and can be used to evaluate the effects of various agents on radiation induced oxidative stress in vitro.

2) We have compared the efficiency of four types of radiation in inducing oxidative stress in cultured cells and observed that γ-rays, X-rays, protons and HZE particles (1-GeV iron ions) are about equally efficient in inducing oxidative stress in cultured cells.

3) We have selected several candidate agents that are highly effective in preventing radiation induced oxidative stress in vitro. The short list of the selected agents includes ascorbic acid, N-acetyl cysteine, co-enzyme Q10, γ-lipoic acid, L-selenomethionine and vitamin E succinate. These agents, when used alone or in combination, are highly effective in preventing radiation induced oxidative stress in cultured cells, and their effects are consistent and reproducible for all of the different types of radiation sources used to induce oxidative stress in these studies.

4) We have verified that an in vitro transformation system based on HTori-3 cells can be used to evaluate the effects of selected agents on malignant transformation induced by the various types of radiation.

5) We have observed that dietary supplementation with agents that prevent radiation induced oxidative stress enhanced the bio-reduction capacity in Sprague-Dawley rats irradiated with γ-

rays or protons and prevented the reduction of bio-reduction capacity in Sprague-Dawley rats exposed to radiation with 1-GeV iron ions.

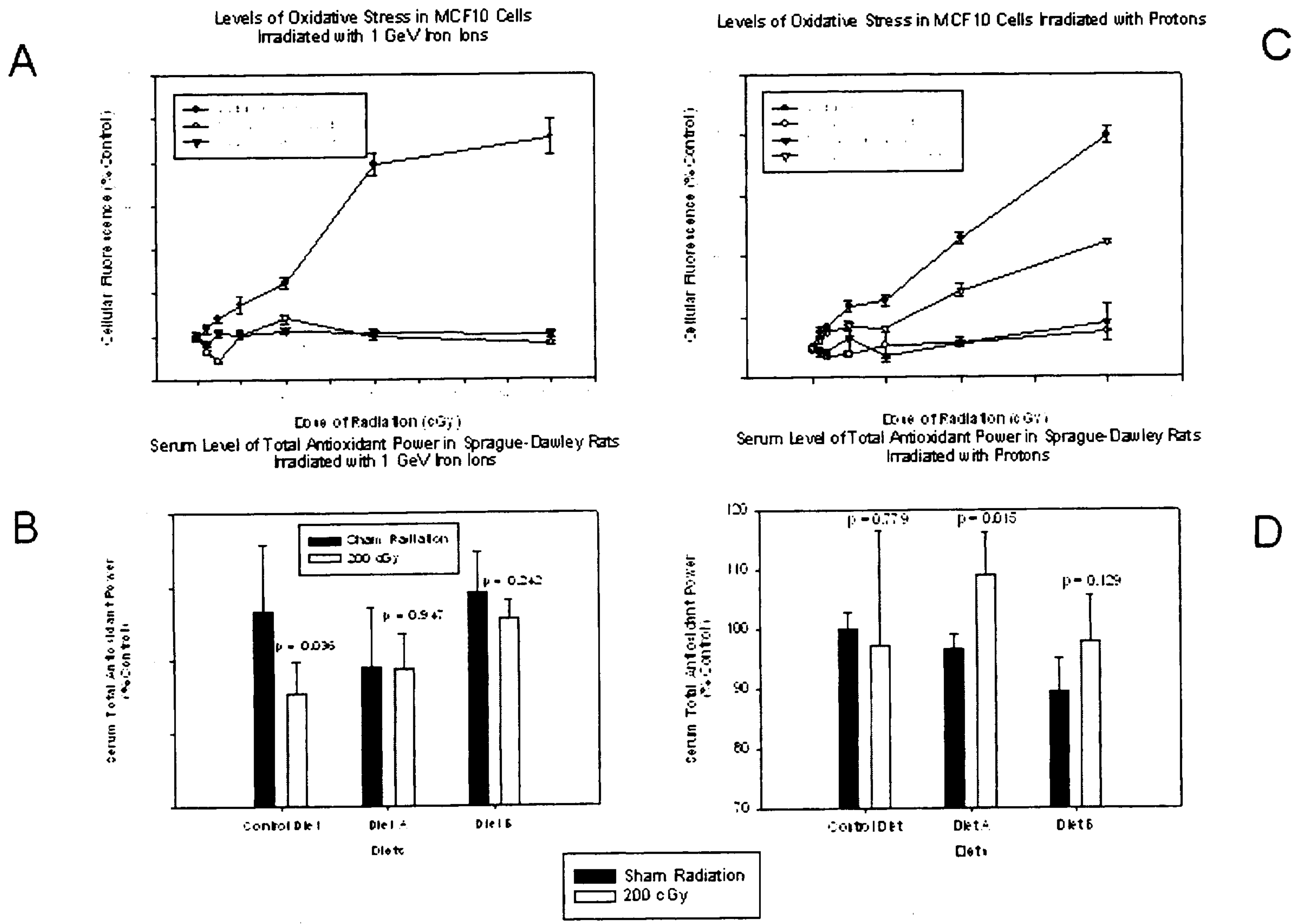


Fig. 4A: A. Radiation with 1 GeV iron ions increased the level of oxidative stress, measured as cellular fluorescence, in MCF10 human breast epithelial cells. The increased level of oxidative stress was observed in cells irradiated with doses as low as 5 cGy. The presence of ascorbic acid or L-selenomethionine during irradiation protected the cells against the radiation induced oxidative stress.

Fig 4B: Radiation with 1 GeV iron ions (200 cGy) caused a reduction in the serum level of total antioxidants in Sprague-Dawley rats. Diet supplementation with L-selenomethionine alone (Diet B) or in combination with ascorbic acid, N-acetyl cysteine, vitamin E succinate and co-enzyme Q10 (Diet A) prevented the decrease in the serum levels of total antioxidants in the irradiated rats.

Fig. 4C: Radiation with protons increased the level of oxidative stress, measured as cellular fluorescence, in MCF10 human breast epithelial cells. The increase in oxidative stress was observed in cells irradiated with doses as low as 5 cGy. The presence of ascorbic acid, N-acetyl cysteine or L-selenomethionine during irradiation protected the cells against the radiation induced oxidative stress.

Fig 4D: Diet supplementation with L-selenomethionine alone (Diet B) or in combination with ascorbic acid, N-acetyl cysteine, vitamin E succinate and co-enzyme Q10 (Diet A) increased the serum levels of total antioxidants in Sprague-Dawley rats irradiated with protons (200 cGy). The increase in the serum levels of total antioxidants was not observed in rats fed with the control AIN-93G diet.

Implications

The results of our experiments performed during the first year of this research project have laid a solid foundation for the research investigations described in our grant. With the development and optimization of the DCF fluorometric assay, we now have a very reliable method to detect oxidative stress induced by radiation at very low radiation doses and to evaluate the effects of candidate agents on radiation induced oxidative stress. The discoveries that the four types of radiation were about equally effective in inducing oxidative stress in cultured cells, and that the effect of the antioxidants and dietary supplement agents on radiation induced oxidative stress did not change substantially in experiments using different types of radiation, suggest that the results obtained with one type of radiation are highly indicative of the results with other types of radiation. Thus, most of the experiments needed for the development of countermeasures for space radiation induced oxidative damage in future studies can be carried out using γ-rays and/or X-rays, which are readily available for routine use in experiments. The scarce resources of protons and HZE particle radiation can be saved for the confirmation of results and validation of important findings observed in studies performed using the readily available types of radiation at the University of Pennsylvania.

We have also confirmed that the HTori-3 cell based in vitro transformation system can be used to evaluate the effects of candidate agents on malignant transformation induced by various types of radiation. This assay system will be used in our studies in the next year to evaluate the effects of the selected candidate agents on malignant transformation induced by HZE particle radiation.

In animal studies, we have demonstrated that the bio-reduction capacity, measured as the serum concentration of total antioxidant power, was affected by radiation exposure and can be modified by treatment with agents that prevent radiation induced oxidative stress in vitro. This system provides us with a means to relate our findings in the in vitro experiments to the results of our animal radiation experiments regarding radiation induced oxidative stress in vivo as well as to the results of other investigators regarding radiation-induced carcinogenesis.

Chang: Charged Particle Radiation-Induced Genetic Damage in Transgenic Mice

Countermeasures: Determine if known radioprotective pharmaceuticals (e.g. tamoxifen, anti-oxidants) or cytokines (e.g., interleukins) reduce tissue-specific mutation frequencies or genetic damage in vivo. Such alterations in the genome may be precursors of cancer.

New Research Findings:

Analysis of mutation frequency (MF) in the lacZ reporter transgene of mice exposed to acute doses of Gy proton irradiation showed that spontaneous lacZ MF in the control animals is tissue specific (spleen > brain). MF in the lacZ transgene is responsive to low doses of protons when compared to the unirradiated controls. Induction of MF in the spleen appears to be dependent on the radiation dose as well as the time post irradiation. Persistent enhanced lacZ MF in the brain and spleen up to 16 weeks post irradiation, suggests proton-induced long-term residual effects in these tissues. Proton-induced genetic effects are tissue-specific, suggesting that tissue physiology may play important roles in determining the long-term mutagenic potential of low LET particle radiation.

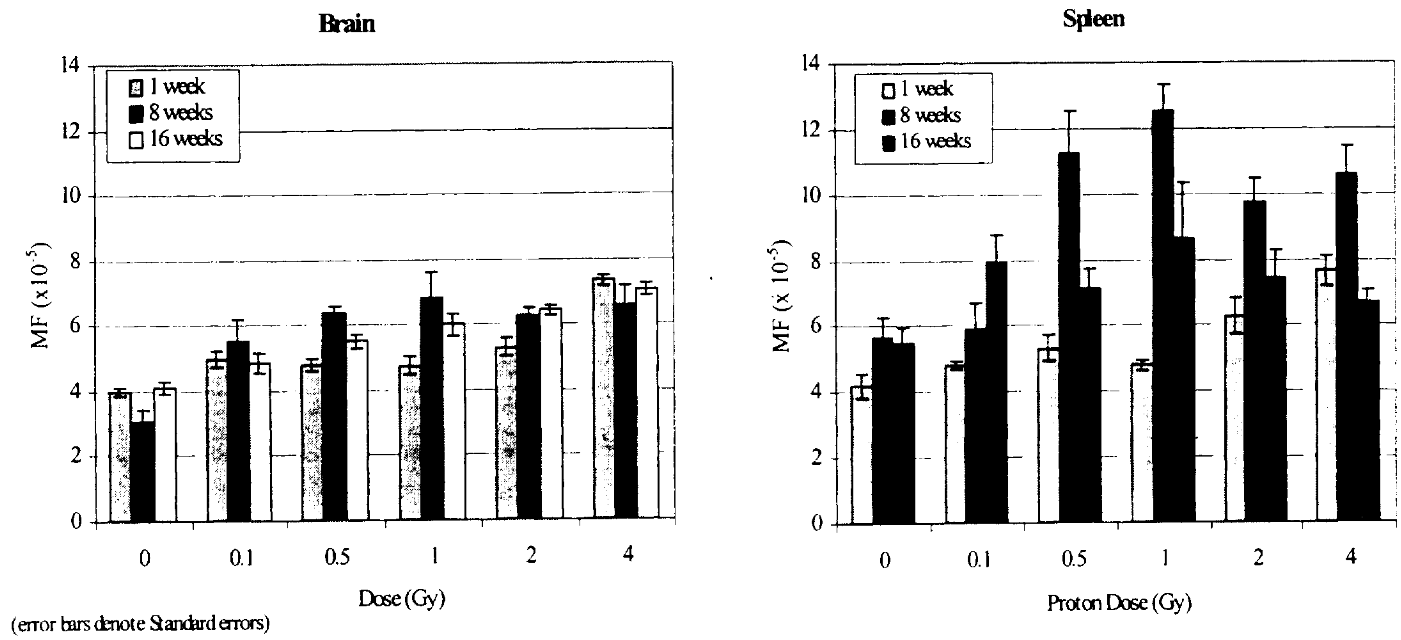


Fig. 5: Kinetics of Proton-induced enhanced transgene Mutation Frequencies

Vazquez: Risk Assessment and Chemoprevention of HZE Induced CNS Damage (In vitro)

Countermeasure: Modulate signaling pathways by pharmacological manipulation (trophic factors, free-radical scavengers, p53 modulators)

New Research Findings:

Human neural precursor cells (NT2) and rodent glial progenitor cells (CG4) were exposed to acute doses of 0.1, to 6 Gy of heavy ions (Fe and Si, BNL-8) and gamma irradiation and the following endpoints were measured:

Apoptosis Induction: The expression of early apoptotic markers (ANNEXIN V) as a function of time post irradiation, with a dose-dependent peak induction of up to 8-fold above control levels at 48 hrs after heavy ion (Fe and Si), proton and gamma exposure. Estimated RBE's for apoptosis are the following Fe: 6, Si: 4 and protons: 1. **Apoptosis pathways:** Doses as low as 0.25 Gy were able to up-regulate p53 and as early as 4 hours post-exposure in CG4 cells and as early as 24 hours in NT2 cells. Caspases were activated in CG4 and NT2 cells exposed to gamma radiation (1 to 2 Gy) 24 hours after exposure. These results confirm previous experiments that p53 and caspases pathways are involved in the stress pathway induced by low- and high-LET radiation exposures.

Vazquez: CNS Damage and Countermeasures (In vivo Studies)

Countermeasure: To protect neural cell populations in vivo using pharmaceuticals, such as neuroprotectants (gangliosides), antioxidants (melatonin) and signal pathways modulators (p53 modulators)

New Research Findings:

498 C57Bl/6 male mice were exposed to 1 Gev/n Fe ions at AGS and gamma rays during the last NASA run (BNL-8, April 2002). Animals were exposed to acute doses of 0.15, 0.3, 0.6, 1.2, 2.4 and 4.8 Gy iron and gamma irradiation and the following endpoints were measured:
Monthly evaluation of the effects of heavy ion and gamma radiation on memory: 19-week-old male irradiated C57 mice were individually placed in a Morris water maze to measure spatial memory (90 Fe ions and 90 gamma, total: 180 animals). Mice exposed to gamma or iron radiation do not show dramatic changes in latency times assessed by the Morris water maze. Animals will be monitored monthly for an additional 6 months to detect memory function alterations and changes in hippocampal biochemistry.
Monthly monitoring of cocaine-induced locomotor activity of heavy ion and gamma irradiated mice: 19-week-old male irradiated C57 mice were individually placed in the locomotor activity detecting boxes and allowed one hour for exploration *(114 Fe ions and 114 gamma, total: 218 animals).* The locomotor activity was further monitored for 150 minutes after cocaine administration. Doses as low as 0.6 Gy of iron ions were able to decrease cocaine-induced locomotor activity as early as 1 month post-exposure. These changes are still present after 4 months after treatment. Similar results were observed for gamma-irradiated animals.

Dicello: In vivo Studies of Mammary Carcinomas
Countermeasure: Spacecraft design and optimized mission scenario to minimize radiation exposure. In part, as a result of the work of our investigators, the paradigm for spacecraft design has changed considerably during the last decade, stressing the need to address the potentially large biological consequences from the abundance of nuclear secondaries being produced primarily from the cosmic protons. Care of animals continues as well as histological and pathological studies of cancers and chemoprevention by use of anti-estrogens administered after low-dose exposures to radiations.
New Research Findings:
This project has now produced the first quantitative risk values of mammary carcinomas in the first colony of rats irradiated with protons and iron ions. These data resulted from animals irradiated originally only to provide baseline data for designing the subsequent experiments, which are still in progress. Drs. Francis Cucinotta and Lief Peterson of the NASA Johnson Space Center have completed their first analysis of our data as well. We already have provided the data to a committee of the National Council on Radiation Protection and Measurements (NCRP) for inclusion in a NCRP report, if the data are accepted for publication.

Six hundred sixty-seven Sprague-Dawley rats were sham irradiated or irradiated whole body at approximately 60 days of age to examine the incidence of mammary carcinomas from beams of iron ions, protons, or gamma rays. Animals were irradiated with 5, 16, or 50 cGy of 1-GeV/nucleon iron ions at the Brookhaven National Laboratory (BNL), with 50, 160, or 500 cGy of 250-MeV protons at the Loma Linda University Medical Center (LLUMC), or with 50, 160, or 500 cGy of gamma rays at BNL, LLUMC, or The Johns Hopkins University. The animals were continuously monitored for all diseases and effects from the radiations until death. There were no significant differences observed in the incidences of mammary cancers between the response to protons and that for gamma rays. Generally, the incidence of mammary carcinomas induced by the iron beam was greater for the same dose in comparison with protons and gamma rays and the rate of increase with increasing dose was also greater.

There is no single calculational or theoretical model, which can be used to unequivocally produce a definitive risk or RBE. We are carrying out extensive analyses of these data to extract relative risks and, if possible, the relative biological effectivenesses using different approaches. If we calculate directly from spline fits to the data, we obtain RBEs for excess incidence of mammary carcinomas of approximately 16 +/- 4 at 5 cGy, and 6 +/- 2 at 16 cGy. Shellabarger et al. (Shellabarger CJ, Chmelevsky D, Kellerer AM. Induction of mammary neoplasms in the Sprague-Dawley rat by 430keV neutrons and X-rays. J.Natl.Cancer Inst. 1980;821-33.), for comparison, obtained an RBE of approximately 12 at a dose of 6.4 cGy of 430 keV neutrons (with the RBE rising to about 200 at a dose of 0.1 cGy). If we use the approach of Alpen et al. (Alpen EL, Powers-Risius P, Curtis SB, DeGuzman R, Fry RJM. Fluence-Based Relative Biological Effectiveness for Charged Particle Carcinogenesis in Mouse Harderian Gland. Adv.Space Res. 1994; 573-81.) by taking the ratio of the initial slopes (although again it should be stressed that a same linear-quadratic relation is not the best fit) we obtain an RBE in the range between 7 and 13. This value for our endpoint, mammary carcinomas in the Sprague-Dawley rat, is lower that the value of (39 +/- 12) obtained by Alpen et al. for tumor prevalence in the Harderian gland obtained for iron ions at the lower energy of 600 MeV/nucleon, but the uncertainties comparable to the observed difference. (Although our energy is somewhat higher [lower linear energy transfer, LET], in a companion study, we degraded the average energy of the iron beam to about 600 MeV/nucleon and saw no significant change in the response). One additional study for comparison is a project still underway, in which Burns et al. (Burns F, Jin Y, Koenig K, Hosselet S. The Low Carcinogenicity of Electron Radiation Relative to Argon Ions in Rat Skin. Radiat.Res. 1993;178-88) irradiated male Sprague-Dawley rats with 640-MeV/nucleon argon ions and compared the resulting yield of skin cancer, primarily firomas, with that from 1.8-MeV electrons. Although they prudently did not provide RBEs in their papers, and the slope for the electrons continues to decrease faster than linearly, a lower value in the neighborhood of 5 would appear to be more reasonable in the region where there are data. In the latest paper, the same group reports that single doses of 1-GeV/nucleon iron ions are two or three fold more effective than argon in producing tumors.

The probability per day of a rat at risk developing mammary cancer is presented as an integral risk as a function of time for each group.

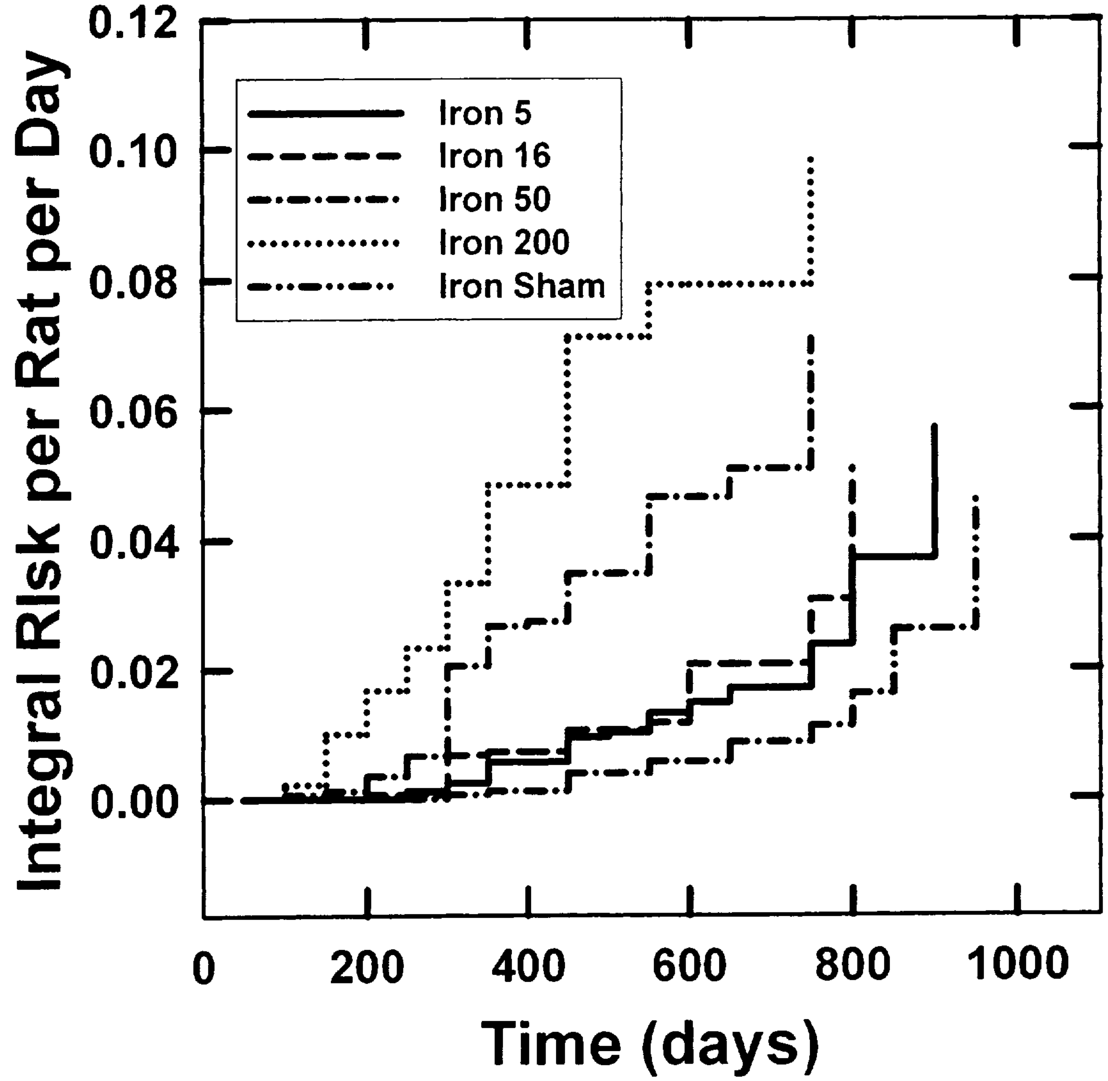


Fig. 7d. The integral risk of mammary carcinomas at a specified time after irradiation for animal sham irradiated or irradiated with 5, 16, 50, and 200 cGy of 1-GeV/nucleon of iron ions.

Huso: Chemoprevention and Radiation-Induced Neoplasms

Countermeasure: The use of Tamoxifen as a model for pharmaceutical intervention in the promotion and progression stages of carcinogenesis to reduce risk after exposure

New Research Findings:

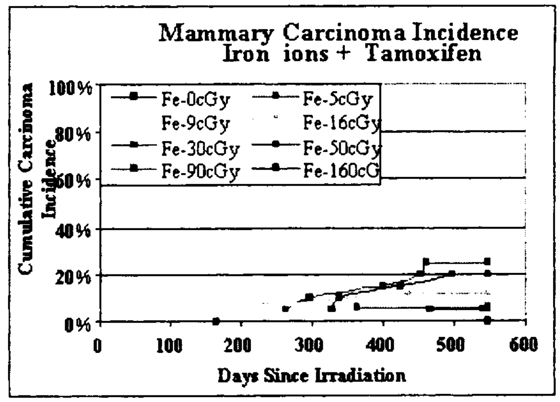
Over the past several years tamoxifen has become the most widely prescribed anticancer drug in the world. Recently it was also demonstrated to be effective in the chemoprevention of human cancer in large scale clinical trials. However, its safety and efficacy as a countermeasure against the potential carcinogenic effects of low dose radiation exposure in space was entirely unknown. Tamoxifen is the prototype for a family of chemopreventives called selective estrogen receptor modulators (SERM) that are currently the focus of intense research and development in the pharmaceutical industry. These efforts promise to provide new and improved alternatives to tamoxifen in the coming years. The rat mammary carcinoma model is a classic animal model that has played an important role in understanding the hormonal interactions, carcinogenesis, and prevention of mammary cancer in mammals. For this reason, we have chosen to focus on this model for our initial "proof of principle" studies on the chemoprevention of radiation-induced cancer.

In studies not yet completed, we have shown that tamoxifen markedly reduces the incidence (reduces slope) and prolongs the latency (shift to the right) of mammary carcinomas in animals following iron ion radiation exposure. It appears that tamoxifen chemoprevention is similarly effective following exposure to photons or protons. Similar positive trends are emerging concerning tamoxifen's impact on improving survival following irradiation. As in humans, tamoxifen resistant tumors do develop. Optimum chemoprevention may benefit from a combinatorial approach using chemopreventives that act on different pathways in radiation-induced carcinogenesis.

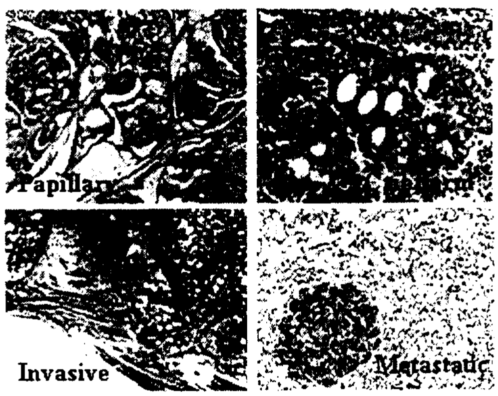
These emerging results suggest that tamoxifen (and newer SERM's such as raloxifene) provides a readily available countermeasure to the carcinogenic effects of radiation. These studies also suggest a "proof of principle" that chemopreventives that have been demonstrated effective in large scale clinical trials against human cancers in the general population may provide fertile ground for discovering and validating chemopreventive approaches that astronauts could potentially use. Furthermore, our studies suggest that chemopreventive administration beginning one month following radiation exposure can prevent a significant proportion of radiation-induced cancers by acting during the promotion and progression stages of carcinogenesis. This is important because it provides the option of doing a risk/benefit analysis for individuals based on actual radiation exposure during space travel before prescribing chemopreventives. This is in contrast to agents that must be present during the time of radiation exposure in order to be effective.

Tamoxifen Chemoprevention:

Potential Countermeasure with Effectiveness Following Radiation Exposure (ongoing studies)



Mammary Carcinoma Examples Following Radiation Exposure



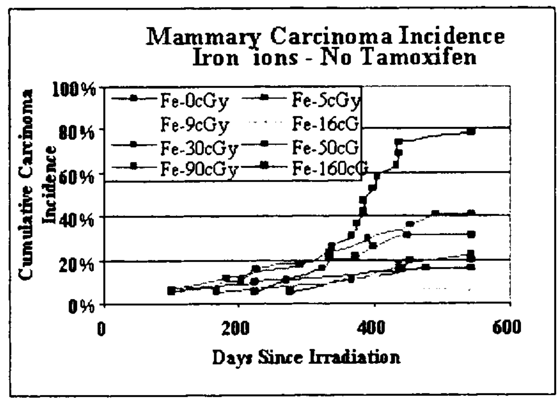


Fig. 6: For the Photos:
Upper left is the most common papillary and cystic mammary carcinoma.
Upper right is the cribiform and solid pattern of mammary carcinoma.
Lower left is a locally invasive mammary carcinoma.
Lower right is a metastatic mammary carcinoma.

COLLABORATIONS:

The Radiation Effects Team currently collaborates with more than nine investigators on research activities or proposals to five agencies: R. Maurer (JHU Applied Physics Laboratory), V. Redeka (BNL), F. Cucinotta (Johnson Space Center), V. Pisacane (U.S. Naval Academy), A. Rozenfeld (CSIRO/JSC), J. Shapiro (Uniformed Services University of the Health Sciences), M. Fenech (CSIRO), Eleanor Blakely (UC LBNL), Gerda Horneck [DLR (Germany/NASA)].

GRANTS AND PROPOSALS				
TITLE	PRINCIPAL INVESTIGATOR	AGENCY	DATE SUBMITTED	OUTCOME
Radiation and Weightlessness Effects on Bone Marrow Cells	Jay R. Shapiro, Ph.D.	USUHS of DoD	1/31/02	Reviewed. Scored below funding cut-off
Automated Non-invasive DNA Damage Measurements in Astronauts	Michael Fenech, Ph.D. and John F. Dicello, Ph.D.	NASA	2/02	Reviewed by astronauts' physician. Undergoing further refinement.
Imaging & Localizing Device Using the Barkhausen Effect	John F. Dicello, Ph.D.	NIH	4/1/02	Reviewed 8/5/02. Score of 314 (below funding cut-off). Discussions in progress with collaborators about resubmission
The Risk of Cancer in a Rat Model: Genetic, Cytogenetic, and Abscopal Factors at Low Doses	John F. Dicello, Ph.D.	DOE Office of Biological and Environmental Research (OBER) and NASA	4/16/02	Reviewed. Scored below funding cut-off.
Radiation-induced Breast Cancer: Detection of Benign and Malignant Lesions in Rat Model	Jerry Williams, Ph.D.	DoD	5/16/02	Awaiting comment.
MIDiN (Microdosimetry investigation) or Microdosimetry of the Earth's Radiation Environment	Vincent L. Pisacane, Ph.D.	U.S. Naval Academy	5/17/02	Awaiting comment.
Nonhazardous Early Detection and In Vivo Functional Imaging of Benign and Malignant Tumors	John C. Murphy, Ph.D.	DoD (BCRP)	6/11/02	Awaiting comment.
Application of Advanced Network Infrastructure Technology in Health and Disaster Management	John F. Dicello, Ph.D.	National Library of Medicine	6/14/02	Results expected in December 2002.
Microdosimeter Engineering Model for Spacecraft Experiment	Vincent L. Pisacane, Ph.D.	NASA-Johnson Space Center	7/24/02	Funded.

PUBLICATIONS AND MANUSCRIPTS

F. A. Cucinotta, J. F. Dicello, H. Nikjoo, and R. Cherubini, "Computational Modes of the Modulation of Gene Expression Following DNA Damage" Radiation Protection Dosimetry 99, 85-90 (2002).

F. A. Cucinotta, W. Schimmerling, J. W. Wilson, L. E. Peterson, G. Badhwar, P. Saganti, and J. F. Dicello, "Space Radiation Cancer Risks and Uncertainties for Mars Missions." Radiat. Res. 156, 682-688 (2001).

L. H. Dang, C. Bettegowda, D. L. Huso, K. W. Kinzler, and B. Vogelstein, "Combination bacteriolytic therapy for the treatment of experimental tumors." Proc Natl Acad Sci U S A. 2001. 98(26):15155-60.

J. F. Dicello, F. A. Cucinotta, "Space Radiation." Encyclopedia of Space Science and Technology, 2Vset (2002, in press).

J. F. Dicello, "How Do We Get from Cell and Animal Data to Risks for Humans from Space Radiations?" Journal of Radiation Research. In press (2002).

P.Y. Chang, D. Torous, L. Lutze-Mann, and R. Winegar, "Impact of p53 status on Heavy-ion radiation induced micronuclei in circulating erythrocytes." Mutat. Res., 466, 87-96 (2000).

P.Y. Chang, N. Kanazawa, L. Lutze-Mann, R.A. Winegar, "P53 deficiencies alters the yield and spectrum of radiation-induced lacZ mutants in transgenic mice." Mutagenesis 16(1), 7-15 (2001).

P.Y. Chang, N. Kanazawa, L. Lutze-Mann, and R.A. Winegar, "HZE particle radiation induced tissue-specific and p53-dependent mutagenesis in transgenic animals." Physica Medica, 17, supplement 1:189-91 (2001).

J. Mann, R. Ricart-Arbona, A. Christian, D. Simonson, J. F. Dicello, and D. Huso, "Epithelial-mesenchymal transition in Tamoxifen resistant tumors." Veterinary Pathology (submitted August, 2002).

Y. Wang, D. L. Huso, H. Cahill, D. Ryugo, and J. Nathans, "Progressive cerebellar, auditory, and esophageal dysfunction caused by targeted disruption of the frizzled-4 gene." J Neurosci. 2001. 21(13):4761-71.

J. Y. Yoo, D. L. Huso, D. Nathans, and S. Desiderio, "Specific ablation of Stat3beta distorts the pattern of Stat3-responsive gene expression and impairs recovery from endotoxic shock.". Cell. 2002. 108(3):331-44.

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

SMART MEDICAL SYSTEMS TEAM

Team Leader (Acting): Lawrence A. Crum, Ph.D.
Applied Physics Laboratory, University of Washington
1013 NE 40th Street, Seattle, Washington 98105-6698
Tel: 206-685-8622 Fax: 206-543-6785
lac@apl.washington.edu

Associate Team Leader: Vacant

Team Projects and Principal Investigators

Guided High Intensity Focused Ultrasound (HIFU) from Mission-Critical Care
PI: Lawrence A. Crum, Ph.D.
Applied Physics Laboratory, University of Washington
1013 NE 40th Street, Seattle, Washington 98105-6698
Tel: 206-685-8622 Fax: 206-543-6785
lac@apl.washington.edu

Vascular Genomics in Gravitational Transitions
PI: Peter F. Davies, Ph.D.
University of Pennsylvania, 1010 Vagelos Research Laboratory
3340 Smith Walk, Philadelphia, PA 19104-6383
Tel: 215-573-6813 Fax: 215-573-6815
pfd@pobox.upenn.edu

Smart Medical System for Detection of Microorganisms
PI: Mark S. Klempner, M.D.
Department of Medicine, Boston University School of Medicine
715 Albany Street, Boston, MA 02118
Tel: 617-638-7654 Fax: 617-638-7513
klempner@bu.edu

Microcapsule Gel Formulation of Promethazine Hydrochloride for Intranasal Administration
PI: Lakshmi Putcha, Ph.D.
NASA Johnson Space Center, Mail Code SD3
2101 NASA Road One, Houston, TX 77058
Tel: 281-483-7760 Fax: 281-244-5734
lputcha@ems.jsc.nasa.gov

Noninvasive Measurement of Blood and Tissue Chemistry
PI: Babs R. Soller, Ph.D.
Department of Surgery, University of Massachusetts Medical School
55 Lake Avenue North, Worcester, MA 01655
Tel: 508-856-5904 Fax: 508-856-7520
babs.soller@umassmed.edu

Near Infrared Brain Imaging for Space Medicine
PI: Gary E. Strangman, Ph.D.
Neural Systems Group, Massachusetts General Hospital
Harvard-MIT Division of Health Sciences and Technology
Building 149, 9th Floor, 13th Street, Charlestown, MA 02129
Tel: 617-726-4350 Fax: 617-726-4078
strang@nmr.mgh.harvard.edu

Diagnostic Three Dimensional Ultrasonography: Development of Novel Compression, Segmentation and Registration Techniques for Manned Space Flight Applications
PI: James D. Thomas, M.D.
Section of Cardiovascular Imaging, Department of Cardiology, Desk F-15
The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195
Tel: 216-445-6312 Fax: 216-445-7306
thomasj@ccf.org

Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity
PI: James D. Thomas, M.D.
Section of Cardiovascular Imaging, Department of Cardiology, Desk F-15
The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195
Tel: 216-445-6312 Fax: 216-445-7306
thomasj@ccf.org

Lawrence A. Crum, Ph. D.
Acting Team Leader

TABLE OF CONTENTS

I. ABSTRACT

The Smart Medical Systems Team (SMST) is one of four new teams of the NSBRI, and is now far enough along in its research to begin making significant advances in research and measurable progress toward countermeasure development. At the present time, there are eight projects headed by seven principal investigators. Five projects (led by Drs. Crum, Davies, Klempner, Soller and Strangman/Sutton) address research and development of novel biometric sensors that are lightweight, portable, low power, non-invasive and unobtrusive. These projects have applications for physiological and medical monitoring of astronauts, as well as for the assessment of countermeasures (CMs) that potentially diminish the deleterious effects of long duration space travel. One project (led by Dr. Putcha) develops a novel pharmacological drug delivery system for near term countermeasure administration, while another project (led by Dr. Crum) develops a revolutionary new form of non-invasive surgery. A NASA echocardiographic resource project (led by Dr. Thomas) is supported by the SMST, and is jointly supervised with the Cardiovascular Alterations Team. Three projects (led by Drs. Klempner, Strangman/Sutton and Thomas) develop "smart" algorithms for minimal user evaluation and interpretation of real time physiological and medical data. All of the projects fit within the strategic plan of the SMST for NSBRI CM development .

Research on the SMST aligns itself most closely, albeit not exclusively, with the clinical capabilities category of the Critical Path Roadmap (CPR; http://criticalpath.jsc.nasa.gov). NASA has identified six of the projects (headed by Drs. Crum, Klempner, Soller, Strangman/Sutton and Thomas (×2)) as relating to Trauma and Acute Medical Problems (risk #43), which is only one of four Type I, or highest level, risk factors for long duration space missions. In the development of CMs to diminish risk #43, and other significant biomedical risks, the SMST has laid out a strategic plan for an advanced, integrated and autonomous system for astronaut health assessment, maintenance and medical care. This plan has initiated, and continues to foster, collaboration with NASA flight surgeons and other medical operations personnel and biomedical researchers affiliated with the NSBRI, Johnson Space Center (JSC), Ames Research Center (ARC), the Jet Propulsion Laboratory (JPL) and NASA Headquarters,. The focus of the plan has been at intermediate Countermeasure Readiness Levels (CRLs = 2 to 7), and linkages to NASA programs in medical systems at lower and higher CRLs. Each project within the SMST has been mapped onto the strategic plan to identify strengths and weaknesses of individual projects and the team as a whole.

Within the first year of the SMST, significant advances have been made to coordinate research projects and efforts to provide added value. New intra-team (e.g., Drs. Davies and Thomas) and inter-team (e.g., Drs. Soller and Cabrera (Integrated Human Function Team)) NSBRI collaborations have formed. New collaborations between the SMST and JSC flight surgeons (e.g., Drs. Strangman, Sutton and Marshburn (JSC)) and researchers (e.g., Drs. Klempner and Pierson (JSC)) have developed. A new biotechnology company, SRU BioSystems, has become involved with the SMST through Dr. Klempner's project. As the SMST evolves, the integration of projects and the team's approach to CM development continues to be refined. Regular Team telecons have taken place and specific discussions of intra-team integration, as well as collaborative interactions with JSC will be discussed in some detail at the SMST retreat, scheduled to be held in one day in advance of the Bioastronautics Investigators' Workshop, on January 12, 2003.

II. INTRODUCTION

A. Team Objective

An important goal of the SMST is to take a leadership role in the research and development of an advanced, integrated and autonomous system for astronaut health assessment, maintenance and medical care. This includes the delivery and evaluation of medical interventions and other CMs that reduce the deleterious effects of space travel and enhance the overall well being of astronauts. In achieving this goal, it is anticipated that there will be significant impact and applications for earth-based health and medical care.

B. Health Concerns and Hazards

Health problems associated with space travel may be related to the effects of microgravity, radiation and other risks to the body that are particular to space flight, but they may also be independent of these effects. Medical problems may arise in association with a given demographic population or as a result of a toxic environmental exposure. Moreover, complex interactions may result in alterations and disorders presenting and/or responding differently in a microgravity environment relative to earth. The unique medical circumstances, requirements and limited health care resources in space pose challenges and opportunities for new strategies of physiological monitoring, medical diagnosis and treatment.

In-flight medical events are not uncommon. On STS-1 through STS-89, 98% of crew members reported medical events, excluding space motion sickness (R. Williams, NASA HQ, personal communication). In total, 1867 separate events were logged (1613 men, 254 women), with 141 (7.6%) being due to injury. It is estimated that the risk on the ISS of a significant event, equivalent to one requiring an emergency room visit or hospitalization, is between 1-3 events per annum. The risks increase for long duration space flight and for older crew members. In the Russian space program, two evacuations have been precipitated by medical conditions; in both cases, the entire crews returned.

Given the importance of maintaining crew health, and since medical events can seriously impact astronauts and missions, the CPR ranks Trauma and Acute Medical Problems (risk #43) as one of the four Type I (most severe) risks. Toxic Exposure (risk #44), and Altered Pharmacodynamics and Adverse Drug Reactions (risk #45), are Type II risks. Illness and Ambulatory Health Problems (risk #46), Decompression Sickness Complicated by Microgravity (risk #47), and Post-landing Rehabilitation (risk #48) are Type III risks.

C. Topics to Address

The SMST recognizes that to achieve its objectives (section IIA), it must (a) utilize a team approach within the context of the NSBRI CM driven mission, (b) coordinate and collaborate with other NASA efforts in space and critical care medicine, (c) emphasize research that leads to testing and monitoring of physiological functions and CM effectiveness in healthy astronauts (i.e., link the SMST to other NSBRI teams and promote CM research with broad utilization), as opposed to emphasizing trauma and acute problems only, and (d) develop alternative approaches to medical care, given that resources are limited, there may be no M.D. in flight and communications to earth are limited and delayed.

The NSBRI assigned the SMST a mandate to develop innovative, possibly revolutionary, techniques for medical monitoring, diagnosis and treatment. To achieve these goals, several infrastructural needs have been identified. These include:

- New types of biometric sensors
- Novel medical and surgical techniques
- Robotic medical assistance systems
- Advanced drug synthesis and delivery systems
- Smart algorithms for medical data systems
- Automated decision support for training and care
- Systems engineered platforms for sensor, algorithm and effector integration

III. RESEARCH PROGRAM STRUCTURE & DESIGN

A. Program Structure and Interactions

As stated in section IIA, the SMST objectives are broad and ambitious. However, the research program needs to be focused in order to ensure clear scientific progress towards CM development. To this end, specific synergistic relationships either exist or are being developed among team projects, as well as between SMST projects and other NSBRI and NASA projects. These relationships are summarized in Fig. 1.

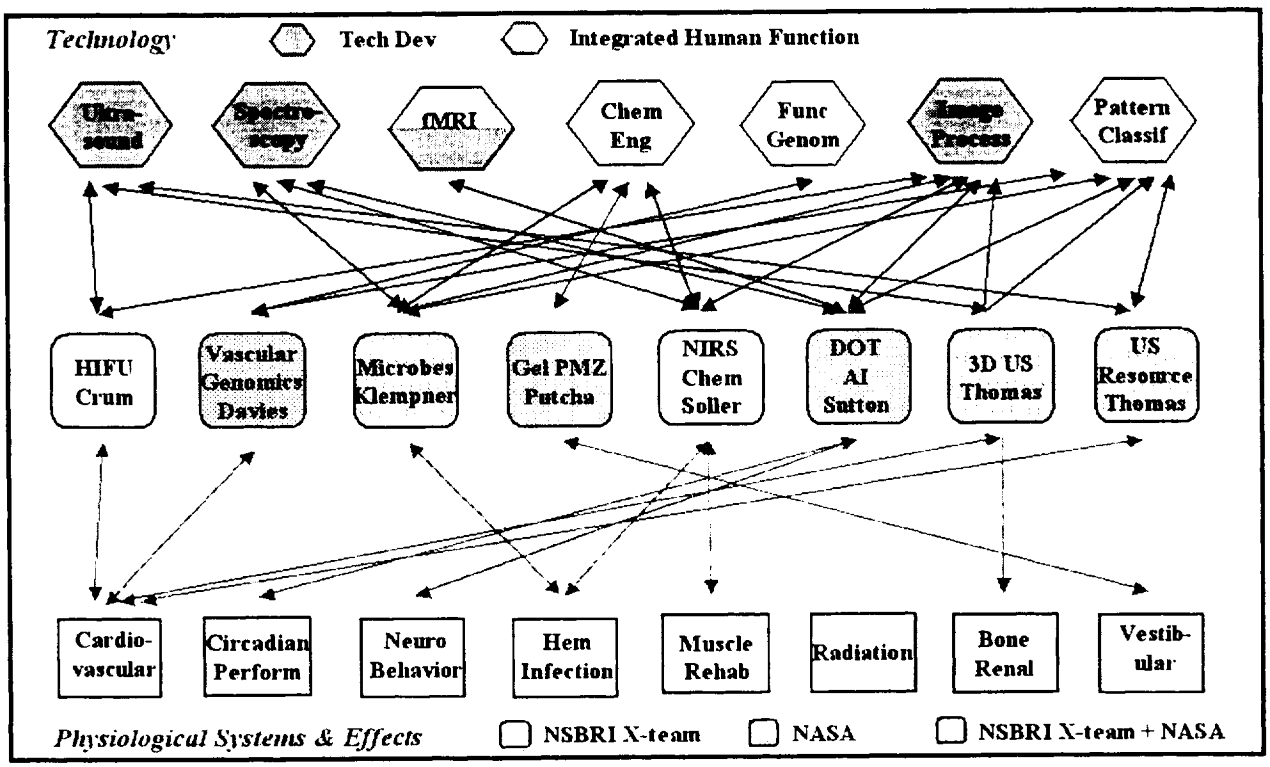


Figure 1. SMST project interactions showing relationships within and between NSBRI teams

In Fig. 1, each of the eight SMST projects is represented along the middle row. The projects are coded to depict (a) NSBRI cross-team interactions (Soller with Cabrera (Integrated Human Function Team)), (b) NASA interactions (Davies with Luzod (ARC); Putcha (JSC); Strangman/Sutton with Marshburn (JSC)), (c) NSBRI cross-team and NASA interactions (Klempner with Fox (Immunology, Infection and Hematology Team) and Pierson (JSC); Thomas with Cohen (Cardiovascular Alterations Team) and JSC)), and (d) none of the above (although Crum has strong ties to DoD medical technology programs).

The bidirectional arrows in Fig. 1 represent relationships (a) among projects within the SMST and (b) between SMST projects and the other NSBRI teams. These relationships are broken down into two main categories: Technology; and Physiological Systems and Effects. Across the top row, interactions between SMST projects and the Technology Development and Integrated Human Function Teams are shown. These interactions correspond roughly to experimentation (Technology Development Team) and theoretical or modeling (Integrated Human Function Team) interactions. Arrows pointing to particular boxes *from* SMST projects *to* boxes in the upper row show how SMST projects contribute to NSBRI developments in specific domains on *other* teams. For example, the Klempner, Soller and Strangman/Sutton projects all develop novel spectrographic devices that complement one or more projects being developed in the Technology Development Team (specifically, projects headed by Potember and by Maurer).

Arrows that originate *from* boxes in the upper row of fig. 1 and project *to* SMST projects represent links among projects *within* the SMST. The relationships are incomplete and are evolving, sometimes with added benefit to the overall NSBRI scientific program. For example, ultrasound technologies link projects by Crum and Thomas, although Thomas' projects do not develop hardware. The functional magnetic resonance imaging (fMRI) aspects of Strangman/Sutton's project adds to the (non-functional) MRI developments in the Technology Development Team; hence the half shaded box in Fig. 1. The chemical engineering and functional genomic and proteomic approaches on the SMST complement other core technology developments within the NSBRI program.

Bidirectional arrows between the boxes representing the SMST projects and the system teams along the bottom row of fig. 1 work similarly to those just described. There is synergy with every system team, especially the Cardiovascular Alterations Team. There is also an emerging emphasis on brain and neurobehavioral alterations within the SMST (Strangman/Sutton project). At present, there is no synergy with the Radiation Effects Team, although there is scientific overlap with that team.

B. Program Strategy

While the previous section outlines the relationships among projects, it does not describe the design of the SMST to address research problems and develop countermeasures. To understand how team R&D might lead to deliverables for eventual implementation for flight, a strategic plan is required. To achieve this goal, a high level description of the system for health and medical monitoring, as well as interventions, that are currently in place was constructed. In this system, the astronaut and environment are handled in similar ways, since space medicine is effectively a branch of aerospace or environmental medicine. Sensors monitor the environment and astronaut, and after calibration, signal conditioning and processing, data are either stored and/or relayed to earth. Ground based personnel oversee, in coordination with the astronaut, flight surgeon and possibly the PI if appropriate, any treatment or countermeasure that is administered. There is limited autonomy and ability to assess deconditioning effects in space. Countermeasure modification and medical care delivery is severely limited.

In collaboration with NSBRI, NASA JSC, ARC, JPL and other personnel, a strategic plan for the SMST was developed during the winter and spring months of 2001. The objectives were to develop a schematic that (a) characterized a "smart medical system", (b) linked NSBRI SMST research and countermeasure development to basic research, industry, space hardware and medical operations, (c) provided a format to map current projects within the SMST onto a system prototype, both at the component level and at the level of the system itself, and (d) allowed for the identification of gaps in the SMST program.

In this plan, information from the environment and astronauts is sensed by a suite of small, lightweight, low power, portable, non-invasive, unobtrusive, intelligent sensors with pattern recognition capabilities. These sensors feed automatically analyzed, rather than raw, data into decision making algorithms, that also have cognitive input from the astronauts themselves. There is a model of the system, which is where the Integrated Human Function Team collaborations fit in the scheme. The model not only (a) assesses input from multiple sources, but it (b) pre-plans notification for onboard alarms and information transfer to the ground, (c) looks at contingencies and outcomes for effectors and treatments prior to the administration of CMs, (d) assesses the effectiveness of treatments and CMs, (e) monitors consequences of actions and CMs, and (f) interfaces with models for pattern recognition and analog hardware learning. Since feedback loops exist which are independent of external and M.D. control, the system is, in principle, autonomous. Moreover, the design is achievable, to varying degrees, and proposes a revolutionary new health care system for space, which is central to the initial research charge assigned to the SMST. In summary, the main points are as follows:

- Enhanced small sensor platforms with pattern recognition and wireless capabilities
- Adaptable system of systems for sensor integration
- Algorithms and models for human assisted monitoring, CM assessment and decision making
- Common platforms for sensing and CM delivery

C. Countermeasure Development

To see that the program strategy of the SMST is aligned with the mission of the NSBRI, each SMST project, along with its relationships to other projects, was mapped onto the SMST strategic plan. The CM development plan for the SMST was then identified. It includes several types of measures, as outlined below.

Specific countermeasure developments include:

1. Exercise
   Soller: non-invasive tissue and blood chemistry measures for physiological monitoring and assessment of exercise effectiveness; applicable across ethnic races

2. Pharmacology
   Putcha: novel drug delivery system, with first application to intranasal promethazine HCl to reduce space motion sickness

3. Training
   Thomas: ultrasound resource to train naïve users in medical image acquisition, with multi-systems applications (e.g., cardiovascular, bone, renal)

4. Performance Adjustments
   Strangman: non-invasive assessment of brain function under cognitive load and sleep disturbance to adjust performance expectations

5. Environmental Manipulation
   Klempner: real-time assessment of distributed microbial environment for early detection and manipulation of significant alterations; sensors applicable for a broad range of environmental monitoring and manipulation

6. Surgery
   Crum: non-invasive use of ultrasound for diagnosis and treatment of injury

7. Gene Therapy
   Davies: functional genomic and proteomic approaches to address vascular changes in microgravity

8. Adjunctive Developments to Other CMs
   Klempner, Soller, Strangman/Sutton, Thomas:
   suite of passive continuous physiological monitors and algorithms to identify the need for, and efficacy of, specific CMs, including those related to medical care

IV. RESEARCH PROGRAM ACCOMPLISHMENTS

A. Accomplishments

Although SMST is still a relatively new start, considerable progress has been made. From a general perspective, the SMST has developed a strategic plan and coordinated research team efforts that (a) successfully interfaces with other programs within the NSBRI and NASA medical operations, and (b) has high potential impact for NASA through CM development to reduce the risks associated with long duration space travel. While the start dates for projects have ranged from October 1 2000 to the relatively recent September 1 2001, and funding interruptions have delayed and disrupted steady progress, effective synergies have been formed and progress has been made on each of the projects. There was a PI meeting in April 2001, and a second one is scheduled for January 2003; regular telecons, multiple site visits among investigators, and education and evaluation of previous and current medical CMs have occurred. The team strategy was expanded from its initial focus on medical care to research on physiological monitoring, algorithms and CM effectors and assessment. More specifically, the main findings and accomplishments during the past year for each project are summarized below.

PRINCIPAL INVESTIGATOR: Lawrence Crum, Ph.D.
PROJECT TITLE: Guided High Intensity Focused Ultrasound (HIFU) for Mission-Critical Care

PURPOSE

The principal objective of this project is to develop an image-guided ultrasound therapy system for mission critical care. In long-term space flight missions, a number of medical situations could develop that if not adequately addressed would result in mission failure. For example, although gravity is significantly reduced in space, inertia is not, and the collision of an astronaut with a heavy object could result in blunt internal trauma and its often associated internal bleeding. In addition, as recent experiences in Antarctica demonstrate, medical conditions that require some form of surgery may well appear without warning, even when extensive pre-screening is undertaken.

BACKGROUND

Currently, medical devices are being developed that utilize high-intensity focused ultrasound as a noninvasive method to treat tumors and to stop bleeding (hemostasis). The primary advantage of ultrasound is that it delivers intense heating to a millimeter to centimeter size region deep in the body without damaging intervening tissue such as the skin. The second advantage is that ultrasound can simultaneously be used to monitor the treatment [1].

RESULTS

We show in Fig. 1 some initial progress. This figure shows the apparatus being developed, and some initial results.

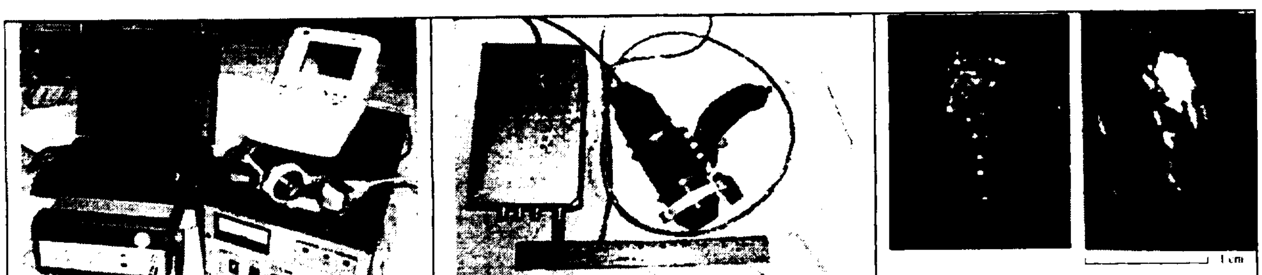


Fig. 1 (left) Initial image-guided HIFU system; (middle) dynamic focusing transducer; (right) lesion in tissue (left) and corresponding ultrasound image (right).

We are developing a smart medical device that will provide a versatile capability to treat a variety of these mission-critical medical conditions. On the left in Fig. 1, we show the complete system, in which a laptop synchronizes the imaging unit (white color) and the therapy transducer, shown in the middle frame. This (middle) frame shows the new motor-controlled transducer and combined function generator and amplifier unit. The box in the middle figure replaces the function generator (under the laptop) and the blue amplifier (under the imager and transducers) and enables the entire unit able to be battery powered. The right frame shows a lesion in tissue created by the new system shown in the middle figure as well as the corresponding image in B-mode ultrasound.

CONCLUSIONS

We have demonstrated that a device that produces High Intensity Focused Ultrasound (HIFU) can be combined with a device that provides ultrasound imaging to produce a duplex system that can both image a particular condition of interest and provide therapy to that region. "Image-Guided Therapy" provides enormous potential for the treatment of a variety of medical conditions, particularly those associated with blunt trauma and internal bleeding. In addition, we have demonstrated significant progress toward making the system both lightweight and portable.

REFERENCES

1. S. Vaezy, M. Andrew, P. Kaczkowski, and L. Crum, "Image-guided acoustic therapy," Annu. Rev. Biomed. Eng. 3, 375-90 2001.

PRINCIPAL INVESTIGATOR:	**Peter Davies, Ph.D.**
PROJECT TITLE:	**Vascular Genomics in Gravitational Transitions**

AIMS

When changes in the biomechanical environment of the circulation occur, blood vessels undergo well-orchestrated structural and metabolic remodeling to restore optimal function. We propose that this remarkable adaptive ability lies at the center of orthostatic intolerance exhibited by most astronauts on return to earth's gravitational field after modest-to-long periods in microgravity. We are therefore mapping gene expression (transcription profiling) of the different vascular steady states exhibited *in vivo (mouse)* in simulated hypergravity and microgravity, and the transitions between them, in order to design better countermeasures for undesired vascular consequences in long-term space flight.

KEY FINDINGS

(i) During the first 9 months we have refined the antisense RNA techniques necessary to amplify RNA from small numbers of cells with high fidelity. This became necessary when it was apparent that no literature exists for a rigorous test of the new RNA amplification protocols required in the mouse experiments. In a model experiment, vascular cells were stimulated with the cytokine TNF for which a small number of genes are known (through conventional Northern analyses) to change. RNA from the same pool was analyzed by microarray with and without amplification. Sophisticated bioinformatics analysis of 13,800 genes was performed. The data from unamplified and amplified RNA were analyzed for fidelity, sensitivity and utility. The expected prominent changes in known genes were detected in both groups with high retention of accuracy, an essential requirement for the proposed *in vivo* gravity experiments. An interesting additional and unexpected finding is that RNA amplification increased the detection rate of genes whose differential expression was just below a significance threshold in the unamplified assay i.e. greater sensitivity of detection of differential gene expression conferred by the linear amplification techniques employed. Most important, these differences were confirmed by real-time quantitative PCR of unamplified RNA. A manuscript is near completion (ref 2 below). This work was necessary for the gravitational studies because no such analysis existed that rigorously evaluates the accuracy of the transcription profiles arising from amplification of small amounts of blood vessel.

(ii) Techniques for the dissection of mouse blood vessels, RNA isolation and amplification has been verified under normal gravitational conditions. The microarray experiments are pending. These are evaluative experiments to ensure that we can successfully perform the entire sets of protocols from animal to bioinformatics and annotation prior to imposing simulated gravitational shifts.

IMPACT

The improved sensitivity of the amplification technique enhances the database of changes in gene expression expected by simulated gravitational shift. Validation of this by real-time PCR (the 'gold-standard' in the field) strengthens the data that will be generated using our approach.

COMING YEAR PLANS

The murine suspension model of simulated *micro*gravity is a well-characterized approach suitable for inducing orthostatic changes that mimic microgravity. For studies of *hyper*gravitational changes, the facilities of the Chronic Hypergravity Exposure Centrifuge at

NASA/Ames are suitable for long-term exposure of mice at 3G to simulate return to earth (or landing on Mars surface) after long term space travel.

Mice will be exposed to micro or hyper gravity for up to 28 days and the effects upon gene expression in the major arterial system will be measured by the techniques outlined above. Reversal of the conditions in both sets of experiments will also be evaluated on a temporal basis.

PUBLICATIONS:

Davies, P.F. 2002. Multiple Signaling Pathways in Flow Mediated Endothelial Mechanotransduction: PYK-ing the right location *Arter. Thromb. Vasc. Biol.* In press

Polacek, D.C., Passerini, A., Manduchi, E., Grant, G., Shi, C., Stoeckert, C., Davies, P.F. Fidelity and enhanced sensitivity of differential transcription profiles following linear amplification of nanogram amounts of endothelial mRNA. *Physiological Genomics* Submitted

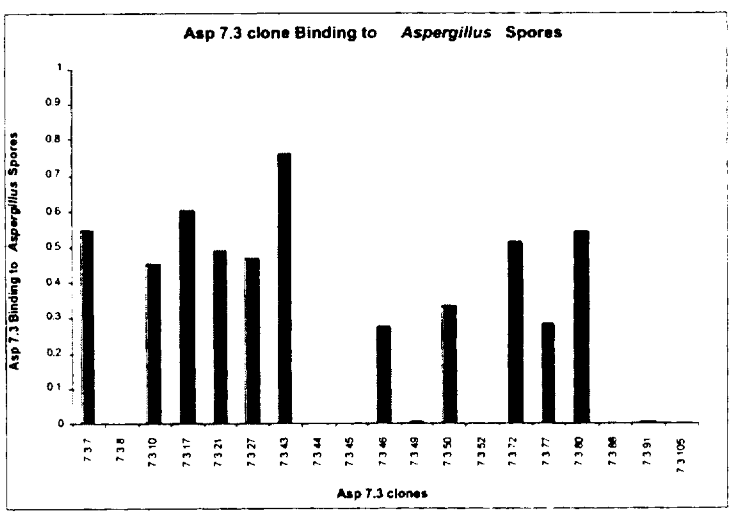
[redacted]
PROJECT TITLE: Smart Medical System for Detection of Microorganisms

ACCOMPLISHMENTS

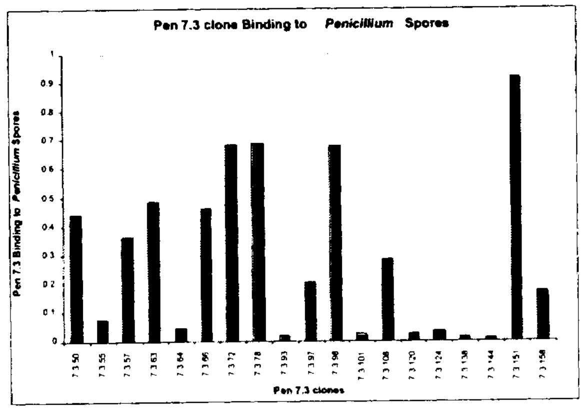
The overall objective of our project entitled, "Smart Medical System for Detection of Microorganisms", is to develop a rapid, non-culture based method to detect, identify, and quantify microorganisms from environmental and clinical samples. The method relies on using highly diverse phage displayed peptide libraries from which phage clones that bind to the surface of various organisms are selected. It is possible to discriminate one organism from another using phage clones expressing different peptides that bind to various organisms with different affinities.

As shown in the figures below, we have successfully isolated and sequenced different phage clones that bind with high, intermediate and low affinities to Aspergillus and Penicillin spores. These fungal species were isolated from environmental samples taken from the MIR space station.

Asp 7.3 Phage Binding to Aspergillus Spores

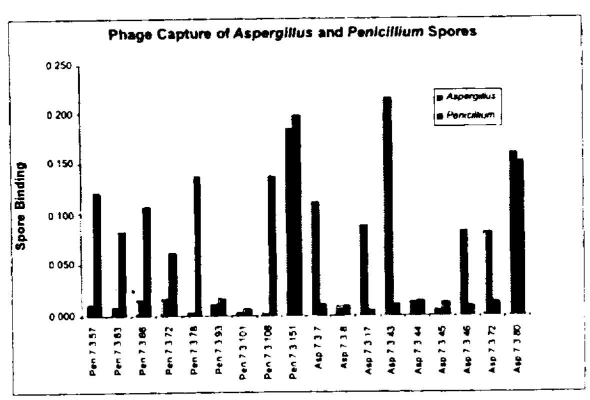


Pen 7.3 Phage Binding to Penicillium Spores



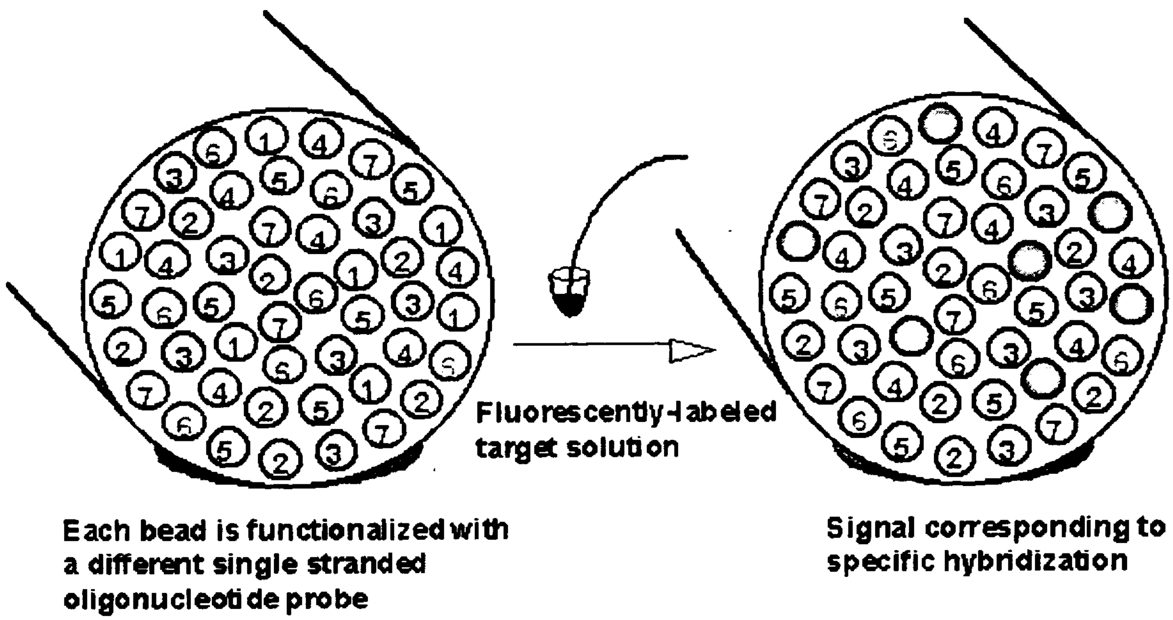
As shown in the figure below, we have used these phage clones to differentiate between fungal spore species. For example, phage clone Pen 7.3.57 binds with high affinity to Penicillin spores but binds minimally to Aspergillus spores. In contrast, phage clone Asp 7.3.43 binds with very high affinity to Aspergillus spores but minimally to Penicillin spores. Thus, in a microtiter plate format, we have demonstrated proof of principle that we can use this method to identify and distinguish between microbial species.

Phage Capture of *Aspergillus* and *Penicillium* Spores



Current efforts are directed at developing an expanded collection of phage displayed peptides which bind to other organisms and on developing a more robust sensor platform onto which these reagents can be applied. To the latter end, we have begun a collaboration with Dr. David R. Walt, Tufts University Professor of Chemistry, who has developed a self-assembled bead array sensor. The bead arrays, which Dr. Walt has used for oligonucleotide arrays, are assembled on an optical fiber substrate. We are in the process of adapting this platform, which is not mass based, for use with the phage displayed peptide libraries that will be designed to detect intact microorganisms. A brief schematic follows and a detailed description of this method is contained in the appended material.

A schematic of a fiber optic microsphere-based microarray for the detection of microorganisms using phage displayed peptides is shown in the figure below. Each circled number represents a phage displayed peptide-functionalized microsphere, or bead, in an etched well. The fiber on the left has multiple replicates of different bead types (numbered 1-7).



Adapted from Anal. Chem. (2000) 72, 5618-5624.

The fiber on the right represents an array after exposure to fluorescently-labeled fungal spore targets. Only the probe containing the peptides which bind to that specific spore provides a positive signal response.

In the past 12 months, we have also extended the concept of using phage displayed peptide libraries to the detection of bioterrorism agents and we were recently awarded an NIH grant (R21 AI53376) entitled, "New Method for Detecting *Bacillus anthracis* Spores." The two projects are synergistic and both related to national priority issues.

PRINCIPAL INVESTIGATOR:	**Lakshmi Putcha, Ph.D.**
PROJECT TITLE:	**Microcapsule Gel Formulation of Promethazine Hydrochloride for Intranasal Administration**

EXECUTIVE SUMMARY

The goal of this project is to develop an intranasal, sustained delivery dosage form of promethazine hydrochloride to be used for the treatment of space motion sickness. This controlled release dosage needs to overcome the irritation and necrosis observed in previous attempts[1,2].

Significant progress was made against each aim of the effort. A microencapsulated formulation of PMZ.HCl was developed which produces zero order release *in vitro* with minimal burst (rapid initial release). Significant screening of ointment and cream formulations to uniformly deliver the microcapsules was accomplished. Mucosal irritability and toxicity derived from PMZ.HCl under a variety of delivery formulations was assessed. Data gathered has served to further focus ongoing efforts for development of a nasally delivered dosage form of PMZ.HCl

The specific aims for this years award were the following:

1. Develop a microencapsulated, pH balanced gel dosage form of PMZ.HCl and a combination dosage form with a corticosteroid.
2. Establish *in vitro* release kinetics and shelf live for these dosage forms
3. Assess preliminary absorption characteristics, nasal mucosal irritability and toxicity of the dosage forms in rats.

RESULTS

Towards the first and second aim, an Ethocel® coated stearine-27 microcapsule was developed that eliminates burst and controls release of the PMZ.HCl, achieving nominally zero order release within 2 hours of dosing. (See Fig. 1)

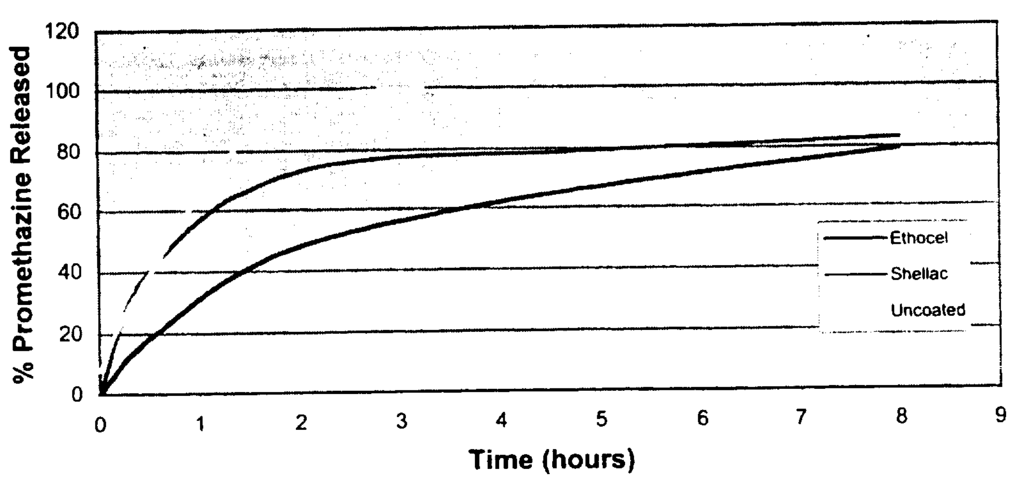


Fig. 1. Release of PMZ. HCl from Ethocel Coated Microcapsules

A nasal mucosal irritation and toxicity study was conducted with 60 rats to assess nasal toxicity of the formulations and carrier vehicls. In addition, blood levels of the drug at 30 min post-dosing were determined to examine absorption of PMZ from test dosage forms. The formulations administered included PMZ freebase in 70/30 PEG/Glycofurolam, PMZ.HCl in phosphate buffered saline, PMZ HCl in saline, saline alone, PMZ.HCl Ethocel coated microcapsules in PEG/Glycofurolam, and 70/30 PEG/Glycofurolam alone.

Results from this study indicated that the encapsulated PMZ and the PEG-Glycoferan PMZ free base formulations did not produce nasal irritability and toxicity. Plasma concentrations after 30 minutes after intranasal administration of PMZ (Table 1) indicated PMZ buffered dosage form had highest level in blood followed by the saline, PMZ freebase in PEG carrier and the microencapsulated PMZ formulations, respectively.

Treatment	**PMZ**
PMZ in Saline	**212.2**
STDEV	86.8
%STDEV	40.9
PMZ in Buffer	**265.7**
STDEV	157.6
%STDEV	59.3
PMZ Freebase in PEG	**192.9**
STDEV	118.6
%STDEV	61.5
Encapsulated PMZ in PEG	**173.4**
STDEV	95.1
%STDEV	54.8

Finally, Dr. Ed Boland, expert in cellular biology and physiology from University of Texas Health Science Center has been added as an animal scientist on the team.

REFERENCES

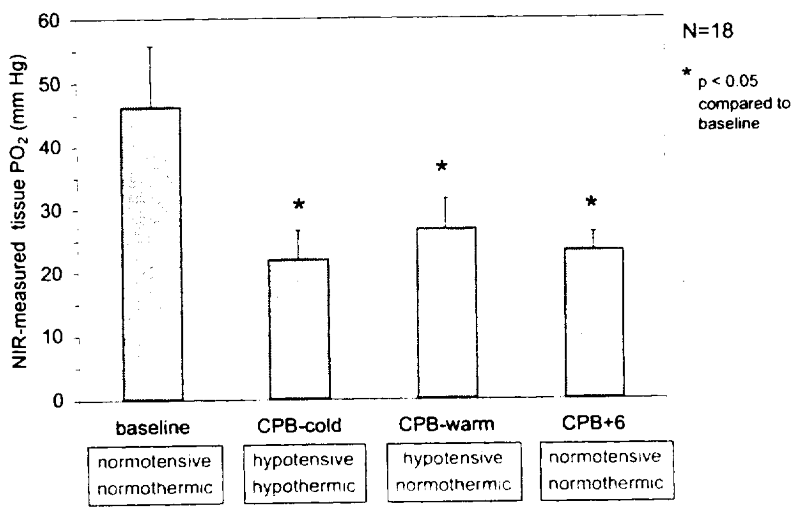
[1] Davis, J.R., Jennings, R.T., Beck, B.G., Bagian, J. P., Aviat. Space Environ. Med., 1993, 64: 230-233.

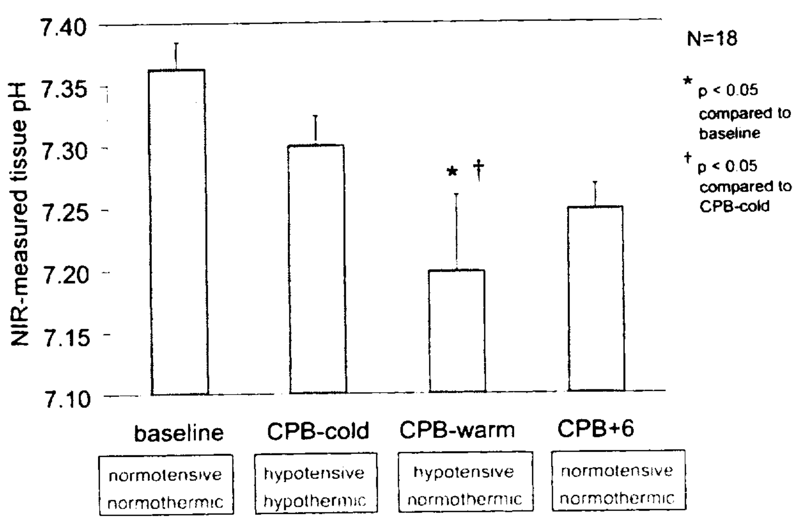
[2] Ramanathan, R., Geary, R.S., Putcha, L., Pharmacol. Res. 38(1), 1998, pg. 36 – 39.

PRINCIPAL INVESTIGATOR:	**Babs R. Soller, Ph.D.**
PROJECT TITLE:	**Noninvasive Measurement of Blood and Tissue Chemistry**

ACCOMPLISHMENTS

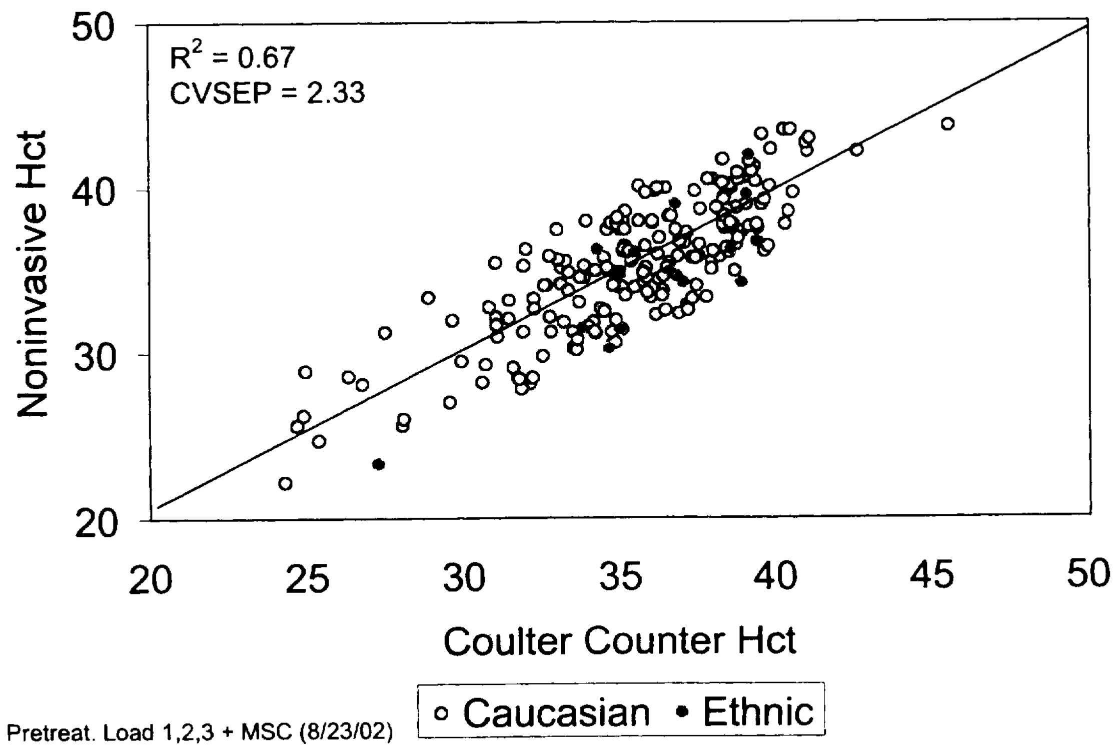
We have completed analysis of near infrared (NIR) pH and PO_2 spectral data from cardiac surgery patients. We demonstrated a good correlation between invasive and noninvasive measurements with accuracy adequate to detect small changes in perfusion which result from fairly minor variations in blood pressure and metabolic demand. Figures below shows that the near infrared technique was able to distinguish a 50% decrease in PO_2 that resulted from a 20 mm Hg change in blood pressure and that a significant drop in pH could be detected as a result of increased metabolic demand on rewarming the patients to normal body temperature. A paper on this study has been submitted to the journal Critical Care Medicine.





We have begun enrollment of subjects who experience trauma and sepsis to help optimize the NIR technique for this type of patient and also to collect data to determine critical values for therapeutic action. A comparison of invasive and NIR pH measurement on a trauma victim for 4 days after admission resulting from a motor vehicle accident indicate excellent agreement between the 2 measurements and the ability to detect small changes in pH as a result of changing medical conditions.

We have also been working on improvements to our hematocrit calibration equation. Currently we have been able to achieve calibration accuracy of 2.3 Hct% with comparable measurement accuracy for Caucasian and non-Caucasian subjects. This is illustrated in the figure below. Here the NIR hematocrit measurement is plotted against the invasive (from a blood draw) measurement. The blue circles are Caucasian subjects, while the red circles are non-Caucasian subjects. We would like to have accuracy below 1.5% and are currently developing methods to ensure and correct for variation in sensor placement.



OTHER FUNDING

I have just been awarded the grant entitled "Noninvasive Sensor System to Determine Tissue Perfusion and Guide Resuscitation" from the US Army Medical Research Command. In this project I will work with a local company, Luxtec Corporation, to develop a miniaturized, portable version of our NIR system for trauma applications. This grant meets my Aim 4 objectives of identifying a partner to help investigate hardware design factors required for the development of a miniature system that will be suitable for space flight.

PUBLICATIONS AND PRESENTATIONS

Soller BR, Cabrera M, Smith SM, Sutton JP. Smart Medical Systems with Application to Nutrition and Fitness in Space. Nutrition, 18, 139 – 145 (2002). *Note: Part of a special issue on Nutrition in Space, edited by Joanne Lupton, Team Lead of the NSBRI Nutrition and Fitness Team. Co-authors include Marco Cabrera, now part of Joanne's team, Scott Smith from NASA-JSC and Jeff Sutton*

Soller BR, Idwasi P, Collette H, Vander Salm TJ, Heard SO. Noninvasively measured muscle pH indicates tissue perfusion for cardiac surgical patients. Crit Care Med, 29:A114, 2001.

Soller BR, Idwasi PO, Balaguer J, Levin S, Simsir SA, Vander Salm TJ, Collette H, Heard SO. Noninvasive, NIRS-Measured Muscle pH and PO2 Indicate Tissue Perfusion for Cardiac Surgical Patients on Cardiopulmonary Bypass. Critical Care Medicine. *Submitted.*

Naghavi M, John R, Naguib S, Siadaty MS, Grasu R, Kurian KC, van Winkle WB, Soller B, Litovsky S, Madjid M, Willerson JT, Casscells W. pH Heterogeneity of human and rabbit atherosclerotic plaques; a new insight into detection of vulnerable plaque. Atherosclerosis, 164, 27-35 (2002).

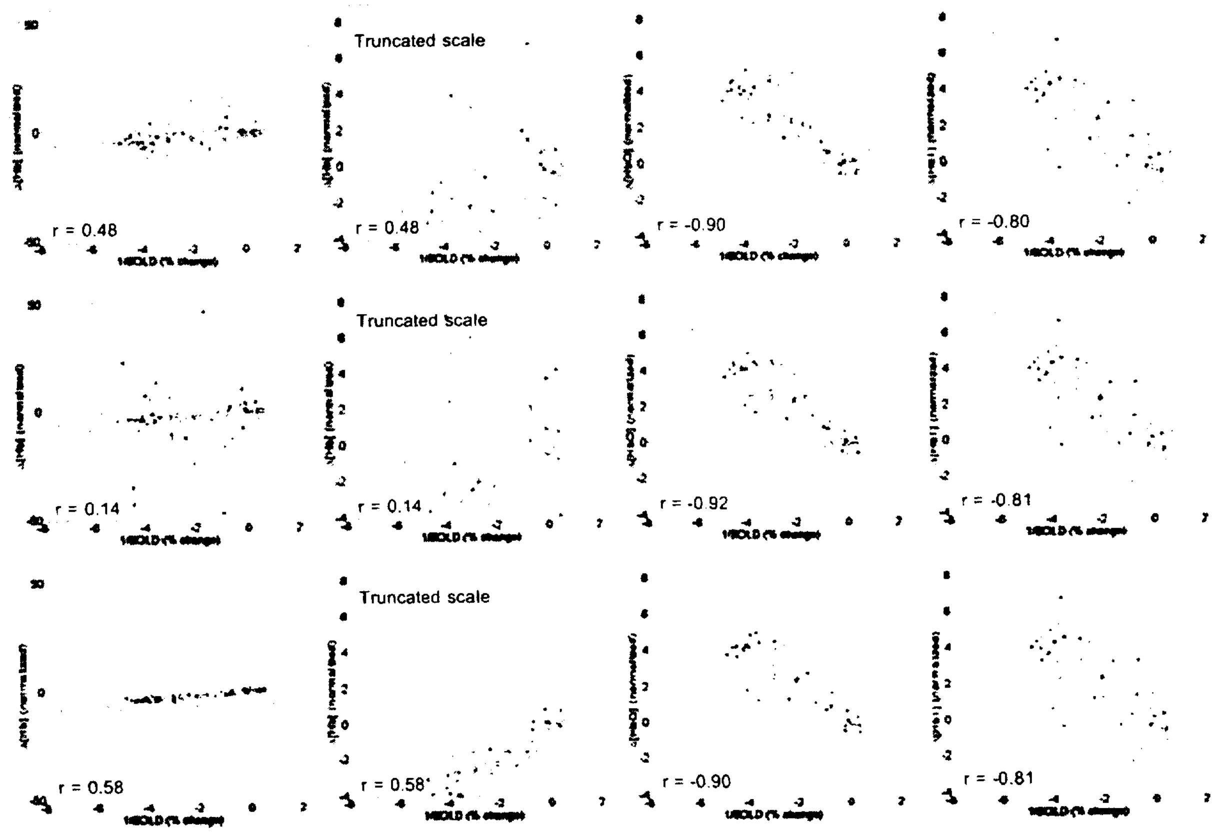
Soller BR, Khan T, Cingo N. Fiber optic sensing of tissue pH to assess low blood flow states. Proceedings, First IEEE International Conference on Sensors. 32-1.

Soller BR, Favreau J, Idwasi P. Investigation of Electrolyte Concentration in Diluted Whole Blood Using Spectroscopic and Chemometric Methods. Applied Spectroscopy. *In Press.*

PRINCIPAL INVESTIGATOR:	**Gary Strangman, Ph. D./Jeffrey Sutton, M.D. Ph.D.**
PROJECT TITLE:	**Near Infrared Brain Imaging for Space Medicine**

Progress on our project over the past year has been along two separate fronts: (1) the validation and use of diffuse optical technologies for brain imaging, and (2) the development of a demonstration system for automated, intelligent medical decision making based on continuous, multi-sensor input.

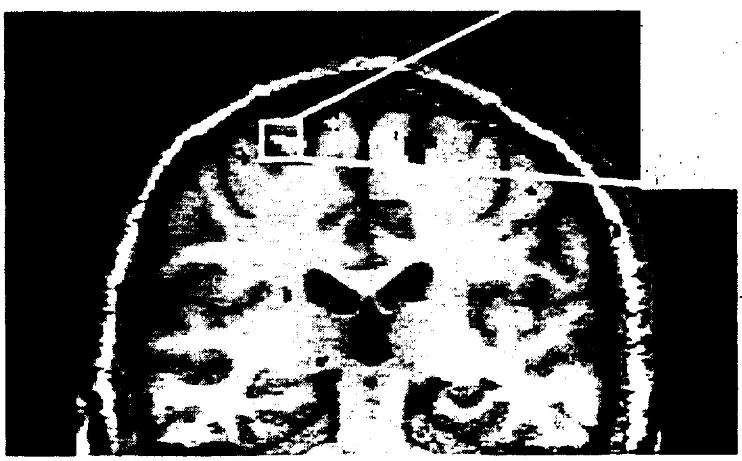
On the validation topic, Figure 1 (below) shows the correlation between three optically-derived signals—deoxyhemoglobin (columns 1 and 2), oxyhemoglobin (column 3) and total hemoglobin



(column 4) recorded from the brain and the co-localized blood oxygenation signal acquired simultaneously via functional magnetic resonance imaging (fMRI). The rows reflect different optical data analysis parameters. Strong correlations exist between all pairs of measures, indicating that the optical measurement compares well with the temporal changes in brain oxygenation resulting from simple motor tasks performed by the subjects, largely regardless of optical analysis method. We are currently investigating the detailed spatial correspondences between optical and fMRI techniques. Success in the validation of near infrared imaging is expected to provide the as-yet only option for functional brain imaging in space, which will also clearly be amenable to use in other environments that are remote from standard health care facilities.

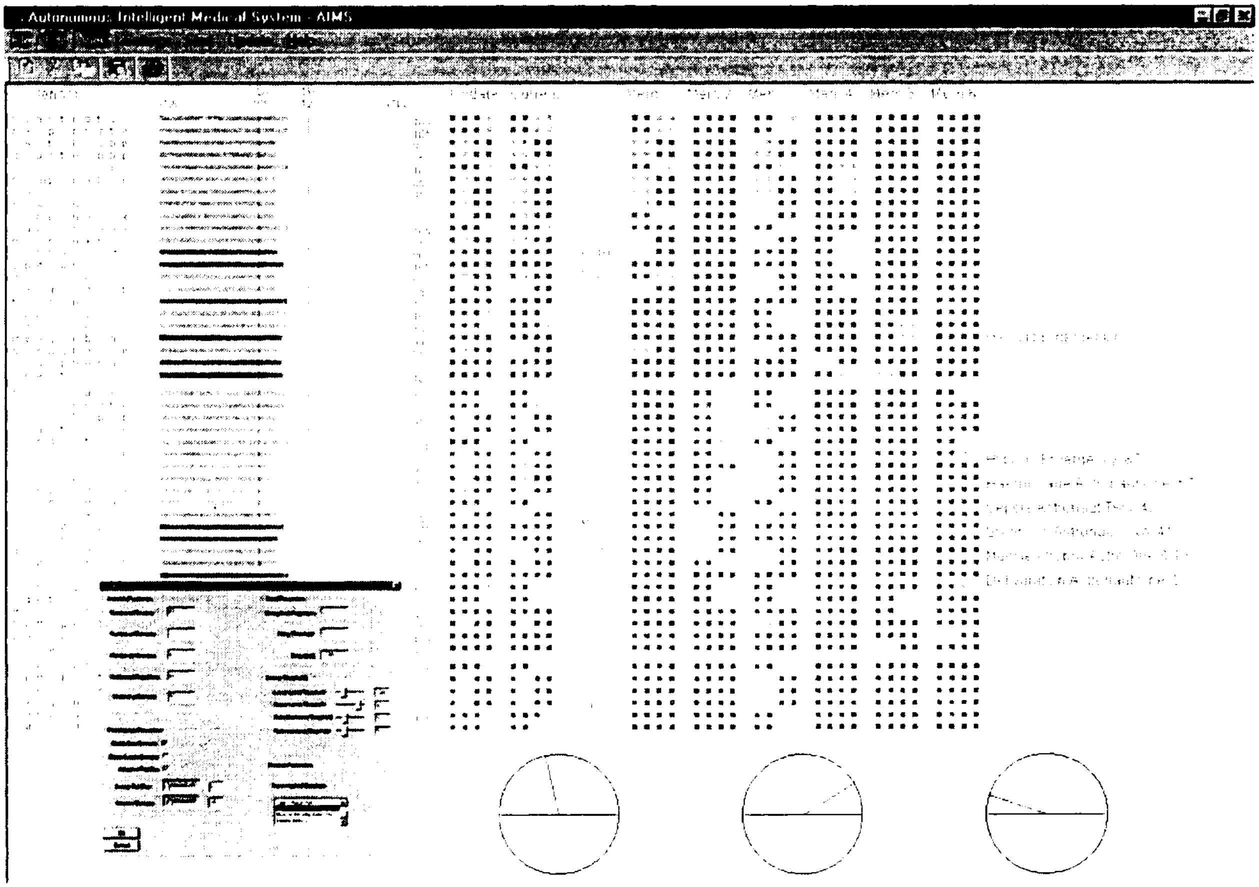
We have also applied our simultaneous optical and fMRI recording technique to subjects that are performing a simulated docking task (spacecraft to satellite) under both rested and sleep-deprived conditions. Preliminary functional MRI scanning during the performance of our space-relevant docking task (SpaceDOCK) indicates a broad network of focal brain regions involved in task performance, including primary visual and motor cortex, as well as prefrontal and lateral superior temporal areas.

Figure 2 (below) represents preliminary data on this aspect of the project, indicating the clear modulation of the fMRI signal (black trace, right) with task performance (red trace, right). The colorized map indicates regions of increased brain activity in (box=primary motor cortex) during task performance relative to rest. The effects of sleep deprivation are still being analyzed. However, such changes will be examined for their ability to predict performance impairments on the task, potentially providing an independent measure of fitness/readiness to perform a docking maneuver.



Finally, we have developed an Autonomous Intelligent Medical System—including user-friendly interface—that demonstrates the feasibility of using many sensors (from astronauts and their environment) to perform real-time evaluation and prediction of medical conditions and environmental changes. Figure 3 (next page) shows this system and part of the user interface (inset), as designed around a "world" consisting of two astronauts and their environment (e.g., space capsule). The columns in this figure are, in order from left to right:

1) sensor name (heart rate, respiration, etc.),
2) sensor value bar (blue=value, red/yellow vertical lines=thresholds for system action, and numerical value),
3) system status lights (red/blue boxes indicate threshold exceeded/not) for the new (update) sensor state, the current sensor state,
4) system memory lights; for comparison to the current status lights, activation patterns for each sensor in each of 6 embedded memory states are shown,
5) general system status, system evaluation of the current state, and system confidence in the in that evaluation/prediction.



This particular example indicates that the system has identified a current or impending hypoxic emergency in the cabin (with a likelihood of 83%). The system accomplishes this by looking at the patterns of activation across all sensors (on both astronauts as well as within the cabin) and comparing these patterns probabilistically to previously stored patterns indicating (e.g.) hypoxic emergency, cardiac arrest in one astronaut, an astronaut undergoing an exercise regimen, etc. The inset image shows how the system can be modified via multiple user-input parameters. We envision this system eventually being capable of taking brain imaging (or other multi-sensor data) and evaluating, in real time, the probable condition/state of the subject. Ultimately, this information would be fed into a simulation module, that could be used to evaluate the effects of various possible countermeasures prior to the actual introduction of such countermeasures.

PUBLICATIONS/COPYRIGHTS:

Strangman G, Boas DA, Sutton JP (2002): Noninvasive brain imaging using near infrared light. *Biological Psychiatry* 52: 679-693.

Strangman G, Culver JC, Thompson JH, Boas DB (2002): A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *NeuroImage* 17: 719-731

Strangman GE, Sutton JP. SpaceDOCK. Unpublished copyright Massachusetts General Hospital. April 2002

Sutton JP, Jamieson I. Reconfigurable networking for coordinated multi-agent sensing and communications. *Information Sciences*. In press.

Soller BR, Cabrera M, Smith SM, Sutton JP. Smart medical systems with applications to nutrition and fitness in space. *Nutrition*. In press.

PRINCIPAL INVESTIGATOR:	**James Thomas, M.D.**
PROJECT TITLE:	**Diagnostic Three Dimensional Ultrasonography: Development of Novel Compression, Segmentation and Registration Techniques for Manned Space Flight Applications**

INTRODUCTION

Significant progress has been made in pursuit of all specific aims, plus additional work recently undertaken.

AIM 1) OPTIMIZE ACQUISITION FOR 3D ULTRASOUND

To date we have performed over 2000 patient examinations with real-time 3D echocardiography, including exercise and intraoperative (epicardial) examinations, with quantitative validation in aneurysmal ventricles [1], aortic regurgitation [2], hypertrophic cardiomyopathy [3], mitral regurgitation [4], and dilated cardiomyopathy [5]. We have validated 3D color Doppler stroke volume [6] and will soon have a much higher acquisition device to test. We have also validated 3D reconstruction using a device identical to the ultrasound system on the ISS.

AIM 2) DEVELOP NEW COMPRESSION, VISUALIZATION, SEGMENTATION, AND REGISTRATION TECHNIQUES FOR 3D ULTRASOUND

We have validated 3D wavelet transform for 100:1 compression of 3D echo [7], developed highly compact software for visualization [8], segmentation [9, 10], and registration [11, 12]. These now can register pre- and post-exercise images and cross-modality data, (echo-SPECT and echo-MRI). For expedition-class spaced missions, comprehensive 3D datasets could be obtained on the ground, then 3D ultrasound exams obtained in flight for comparison, either for physiological monitoring or medical emergencies.

AIM 3) TEACH NOVICE EXAMINERS TO OBTAIN 2D AND 3D DATA WITH MINIMAL TRAINING

After only 4 hours of training, 5 novices were able to perform technically adequate 2D echocardiograms with remote coaching from an experienced sonographer. Quantitative parameters (e.g., LV mass, ejection fraction, mitral inflow) agreed with ($<\pm10\%$) and correlated well with ($r>0.85$) measurements by an expert [13]. 3D studies are ongoing.

AIM 4) FACILITATE ISS ULTRASOUND USE AND DEVELOP WIRELESS TECHNOLOGY

A Philips HDI-5000 ultrasound system was launched to the International Space Station in March, 2001, [14] with engineering tests of digital file transfer and live video feed for acquisition guidance ongoing. Digital echocardiography is now fully feasible on the ground [15] with over 250 studies being stored daily at the Cleveland Clinic (~3 terabytes annually).

AIM 5) DEVELOP WIRELESS TRANMISSION OF ULTRASOUND DATA

We have recently begun a collaboration with John Hines (ARC), Kevin Montgomery (Stanford) and the Department of Defense to develop methodology for wireless transmission of ultrasound. We can now send data from a hand-held ultrasound system wirelessly via 802.11b to an iPAQ palm computer with a resolution of 320x240 pixels and 15 frames/sec. This could be implemented aboard the ISS to acquire ultrasound anywhere in the space station, such as the air lock. Further improvements in speed and resolution are expected.

REFERENCES

[1] Qin et al (2000) *J Am Coll Cardiol* 35:900-907.
[2] Shiota et al *J Am Soc Echocardiogr* 15:966-71.
[3] Qin et al (2002) *J Am Coll Cardiol* 39:308-314.
[4] Gillinov et al (2000) *Ann Thorac Surg* 69:717-21.
[5] McCarthy PM (2001) J Thorac Cardiovasc Surg 122:482-90.
[6] Tsujino H (2000) *Ultrasound in Med & Biol* 26 (7):69-74.
[7] Hang et al (2000) *Comp in Card* 27:123-126.
[8] Saracino et al (2002) *Comp in Card* (in press).
[9] Corsi et al (2001) Eur J Ultrasound 13:41-51.
[10] Corsi et al (2001) *Comp in Cardi* 28:109-112.
[11] Shekhar et al (2002) *IEEE Trans. Med. Imag* 21:9-22.
[12] Shekhar et al (2002) *Proc CARS* 873-878.
[13] Troughton et al (2002) *J Am Soc Echocardiogr* 15:548.
[14] Thomas JD (2002) *Medica Mundi* (in press).
[15] Thomas et al (2002) *J Am Soc Echocardiogr* 15:831-8.

PRINCIPAL INVESTIGATOR: James Thomas, M.D.
PROJECT TITLE: Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity

INTRODUCTION

Significant progress has been made in pursuit of all specific aims.

AIM 1) IMPACT OF VOLUME/PRESSURE UNLOADING ON LV PROPERTIES

16 patients with aortic stenosis and 8 with aortic insufficiency have been recruited for 3D echo, demonstrating a fall in LV mass from 181 ± 42g at baseline to 149 ± 34g at 6-weeks post valve replacement ($p=0.03$) with further fall at 6 months (limited followup to date). In 16 patients with hypertrophic cardiomyopathy, LV mass fell from 250 ± 80g at baseline to 210 ± 62g at 6-months post septal myectomy or ablation ($p<0.001$).

AIM 2) NON-INVASIVE ECHO ASSESSMENT OF LV FUNCTION

We have validated echocardiographic myocardial systolic strain as a noninvasive surrogate for end-systolic elastance with diastolic strain correlating with end-diastolic pressure [1] and demonstrated regional variance in strain to be a powerful measure of success in biventricular pacing [2]. Age-stratified reference values have been obtained in 102 normals for tissue velocity, displacement, strain rate and strain for 4 LV walls at 3 levels (base, ,mid, apex) [3], critical for assessing changes in microgravity. We have assessed the preload and inotropic dependency of tissue velocity in dogs [4] and normal humans undergoing microgravity-mimicking bedrest [5]. We have validated measurement of intraventricular pressure gradients (IVPG) via application of the Euler equation to color M-mode (CMM) Doppler transmitral flow data [6] and used it to quantify changes in diastolic suction following septal ablation in hypertrophic cardiomyopathy, a presentation that won the young investigator competition for the American College of Cardiology [7]. We have shown CMM data to be largely independent of preload [5, 8], making it an attractive index to assess cardiovascular countermeasures in space.

AIM 3) EXERCISE ASSESSMENT FOR EARLY DETECTION OF MYOCARDIAL DYSFUNCTION DURING PROLONGED SPACE FLIGHT

31 patients with heart failure and 15 normals underwent metabolic stress testing. Although resting IVPG by CMM was only weakly associated with VO_2max, the *increment* in IVPG (2.6 ± 0.8 in normals versus 1.1 ± 0.8 mmHg in patients, $P<0.05$) was most predictive of exercise capacity ($r=0.8$, $P<0.001$) [9]. We have also demonstrated a simplified index of cardiac power as a way to monitor cardiac reserve in space flight [10].

AIM 4) DEVELOPMENT OF SOFTWARE FOR QUANTITATIVE ASSESSMENT OF LV FUNCTION

We have developed stand-along software for quantification of IVPG from CMM data and strain data from 2D tissue Doppler data. These can be applied to DICOM-formatted data from any echo machine, such as the HDI-5000 aboard the ISS.

AIM 5) ESTABLISH AN ECHOCARDIOGRAPHIC CORE FACILITY FOR NSBRI AND NASA

We have performed core lab analyses for NSBRI-funded bedrest studies in Boston (Richard Cohen, P.I.) and NASA funded work in Dallas (Ben Levine, P.I.). The latter work has demonstrated that tissue velocity shows significant preload dependency, while CMM flow propagation is virtually independent of loading conditions. By using these indices together, we may be able to tease out changes in cardiac performance in microgravity due to altered preload (TDI) and primary myocardial changes (CMM).

REFERENCES

[1] Greenberg et al. (2002) *Circulation* 105:99-105.
[2] Popovic Z et al (2002) *J Clin Electrophysiol* (in press).
[3] Sun et al (2002) *J Am Coll Cardiol* 39:380A.
[4] Firstenberg et al (2001) *J Appl Physiol* 90:299-307.
[5] Firstenberg et al (2000) *J Am Coll Cardiol* 36: 1664-9.
[6] Greenberg et al (2001) *Am J Physiol* 280: H2507-H2515.
[7] Rovner et al (2002) *J Am Coll Cardiol* 39:451A.
[8] Garcia et al (2000) *J Am Coll Cardiol* 35:201-8.
[9] Rovner et al (2002) *J Am Coll Cardiol* 39(5):451A.
[10] Armstrong et al (1999) *Heart* 82:357-64..

B. Implications

- Dr. Crum's team have made significant progress toward the development of a lightweight and portable device for using ultrasound to identify internal bleeding, to also use low-intensity imaging ultrasound to target the vascular breaches that lead to this bleeding, and to apply high intensity focused ultrasound to retard and even terminate this bleeding. Furthermore, this form of image-guided therapy could be used to necrose tumors and other pathological tissues. Although this research is still in animal trials, it has demonstrated both efficacy and safety, and thus can be moved to human trials in the near future. The ability of a device to address a mission critical event such as blunt trauma and internal bleeding would be a major success for the NSBRI.

- Dr. Davies' group has demonstrated that the amplification of RNA for the expression profiling of very small amounts of tissues/cells. This technique is a developing technology in which his team is contributing fundamental evaluative data (the past several months' work reported above). His findings support the 'high risk' conviction that the techniques, essential for the gravity experiments, will provide a comprehensive profile of vascular gene expression.

- The principal objectives of Dr. Klempner's team is to develop a rapid, non-culture based method to detect, identify, and quantify microorganisms from environmental and clinical samples. The method relies on using highly diverse phage displayed peptide libraries from which phage clones that bind to the surface of various organisms are selected. It is possible to discriminate one organism from another using phage clones expressing different peptides that bind to various organisms with different affinities. A device that could rapidly detect and assess the presence of specific pathogens within the space environment is a prototypical example of a smart medical device. His team has also made significant progress up the CM ladder with their association with private industry.

- Significant progress has been made by Dr. Putcha's team in developing a microencapsulated formulation of PMZ.HCl. This drug is used to treat motion sickness and is currently administered by injection. Because there is a significant reaction associated with the injection—the muscle can be sore for days--astronauts are reluctant to administer it. Dr. Putcha's approach is to encapsulate the drug in microcapsules that can be applied via a nasal spray. Significant screening of ointment and cream formulations to uniformly deliver the microcapsules has also been accomplished. She has assessed the Mucosal irritability and toxicity derived from PMZ.HCl under a variety of delivery formulations and found them more acceptable to human volunteers than needle injection. This project is already at a high CRL.

- The development by Dr. Soller and her colleagues of a method to accurately and non-invasively measure muscle pH and oxygenation using multi-spectral near infrared (NIR) light in normal subjects and in critically ill surgical patients is a major accomplishment. Indeed, this technology recently been applied to the assessment of individual exercise protocols as a CM. Since this assessment can be perfomed in real-time, one could envision also real-time modification of these prototols—"You can't stop now, you have to exercise longer!"

- The observations by investigators on Dr. Strangman and Dr. Sutton's project of an excellent correlation between diffuse optical tomography (DOT), using NIR spectroscopy (NIRS), and functional magnetic resonance imaging (fMRI) to non-invasively assess human brain activity in subjects performing simple motor tasks. DOT sensor validation is important if the technology is to be used as an objective means of assessing brain function under various cognitive loads and sleep alterations, with the aim of adjusting performance expectations as a viable CM. Drs. Strangman and Sutton and colleagues have demonstrated the successful use of anatomical and functional MRI data as a constraint on the calculation of deoxyhemoglobin and oxyhemoglobin changes in brain tissue. This finding speaks to the issue of individualized, digitized human, anatomical brain models upon which time-derivative functional data is co-registered and overlaid for automated interpretation in real time. The determination by this group of learning curves during off-line testing of SpaceDOCK, a visuomotor task developed for the optical / MRI environment. The task emulates a space relevant task for performance assessment using behavioral and brain imaging methods. Dr. Sutton and Dr. Strangman have also developed an Autonomous Intelligent Medical System—including user-friendly interface—that demonstrates the feasibility of using many sensors (from astronauts and their environment) to perform real-time evaluation and prediction of medical conditions and environmental changes.

- To date, Dr. Thomas and his colleagues have performed over 2000 patient examinations with real-time 3D echocardiography, including exercise and intraoperative (epicardial) examinations, with quantitative validation in aneurysmal ventricles, aortic regurgitation, hypertrophic cardiomyopathy, mitral regurgitation, and dilated cardiomyopathy. They have validated 3D color Doppler stroke volume and will soon have a much higher acquisition device to test. A Philips HDI-5000 ultrasound system was launched to the International Space Station in March, 2001, with engineering tests of digital file transfer and live video feed for acquisition guidance ongoing. Dr. Thomas and his group have validated 3D reconstruction using a device identical to the ultrasound system on the ISS. In addition, they have recently begun a collaboration with John Hines (ARC), Kevin Montgomery (Stanford) and the Department of Defense to develop methodology for wireless transmission of ultrasound. They can now send data from a hand-held ultrasound system wirelessly via 802.11b to an iPAQ palm computer with a resolution of 320x240 pixels and 15 frames/sec. This could be implemented aboard the ISS to acquire ultrasound anywhere in the space station, such as the air lock, and represents again that the SMS Team is rapidly scaling the CRL ladder.

- In addition to findings stemming from individual projects on the SMST, effective synergisms have been established within and between the SMST, the Technology Development Team and the Integrated Human Function Team, as well as the specific system teams within the NSBRI. It is clear that there is a need to enhance the system or platform component of the SMST in order for the team to achieve its goals, as well as to interact better with the other NSBRI teams, and other programs within NASA (e.g., the Biosensor Group at ARC). To this end, gaps have been identified, especially with respect to the "smart" and "systems" components of the SMST. Specific needs include (a) supplemental research in decision support systems for monitoring and (b) decision support systems and knowledge bases for diagnosis and treatment. Research gaps in the treatment, or effector, modalities have also been characterized, and are deemed necessary in order to solidify, and eventually move beyond, proof-of-principle demonstrations to the actual construction and implementation of a smart medical system.

RECEIVED

NOV 1 2 2002

National Space Biomedical Research Institute
ANNUAL PROGRAM REPORT

Team Name: Technology Development Team

Team Leader: Harry K. Charles, Jr. Ph.D.
Principal Professional Staff
Assistant Department Head for Engineering
The Johns Hopkins University Applied Physics Laboratory
11100 Johns Hopkins Road, Laurel, Maryland 20723-6099
Telephone: 240-228-8050; Fax: 240-228-8050
E-mail: harry.charles@jhuapl.edu

Associate Team Leader: Jay C. Buckey, Jr., M.D.
Research Associate Professor of Medicine
Dartmouth Medical School, Department of Medicine
1 Medical Center Drive, Lebanon, NH
Telephone: 603-650-6012; Fax: 603-650-6571
E-mail: jay.buckey@dartmouth.edu

Projects and Project Principal Investigators:

1. Advanced, Multiple Projection, Dual Energy X-ray Absorptiometry (AMPDXA) Scanning System
   H. K. Charles, Jr. Ph.D.
   Principal Professional Staff
   Assistant Department Head for Engineering
   The Johns Hopkins University Applied Physics Laboratory
   11100 Johns Hopkins Road, Laurel, Maryland 20723-6099
   Telephone: 240-228-8050; Fax: 240-228-8050
   E-mail: harry.charles@jhuapl.edu

2. Portable Neutron Spectrometer
   R. H. Maurer, Ph. D.,
   Principal Professional Staff
   Johns Hopkins University Applied Physics Laboratory
   11100 Johns Hopkins Road, Laurel, Maryland 20723-6099
   Telephone: 240-228-6482; Fax: 240-228-6696
   E-Mail: maurerh1@spacemsg.jhuapl.edu

3. Miniature Time-of Flight Mass Spectrometer
   R. S. Potember, Ph.D.
   Principal Professional Staff
   Johns Hopkins University Applied Physics Laboratory
   11100 Johns Hopkins Road, Laurel, Maryland 20723-6099
   Telephone: 240-228-6482; Fax: 240-228-6696
   E-Mail: redwing@aplcomm.jhuapl.edu

4. Improved Bubble Detection for EVA
   J. C. Buckey, Jr., M.D.
   Research Associate Professor of Medicine
   Dartmouth Medical School, Department of Medicine
   1 Medical Center Drive, Lebanon, NH
   Telephone: 603-650-6012; Fax: 603-650-6571
   E-mail: jay.buckey@dartmouth.edu

5. Scanning Confocal Acoustic Diagnostic (SCAD) System for Bone Quality Assessment
   Y-X. Qin, Ph.D.
   Assistant Professor of Biomedical Engineering
   State University of New York – Stony Brook
   350 Psychology A Building, 3rd Floor, Stony Brook, New York 11794
   Telephone: 631-632-1481; Fax: 631-632-8577
   E-mail: yi-xian.qin@sunysb.edu

6. Heavy Ion Microbeam and Micron Resolution Detector
   V. Radeka, Ph.D.
   Senior Scientist, Division Head
   Brookhaven National Laboratory
   Instrumentation Division, Building 535B, Upton, New York 11973
   Telephone: 631-344-4266; Fax: 631-344-7586
   E-mail: radeka@bnl.gov

7. Design of a Dynamic Exercise Countermeasure Device
   B. L. Davis, Ph.D.
   Staff Scientist
   The Cleveland Clinic Foundation
   Lerner Research Institute, 9500 Euclid Avenue, Cleveland, Ohio 44195
   Telephone: 216-444-1055; Fax: 216-444-9190
   E-mail: davis@bme.ri.ccf.org

8. Space Qualifiable MRI System
   I. N. Bankman, Ph.D.
   Senior Professional Staff
   The Johns Hopkins University Applied Physics Laboratory
   11100 Johns Hopkins Road, Laurel, Maryland 20723-6099
   Telephone: 240-228-6097
   E-mail: issac.bankman@jhuapl.edu

Harry K. Charles, Jr.

Harry K. Charles, Jr., Ph.D.
Team Leader

National Space Biomedical Research Institute
ANNUAL PROGRAM REPORT

Technology Development Team

TABLE OF CONTENTS

I. ABSTRACT

The objective of the Technology Development Program of the National Space Biomedical Research Institute is to develop devices, instrument systems, and associated algorithms and software that lead to a better understanding of the barriers to long-duration space exploration and assist in the development of countermeasures to assure safe and productive space missions. The primary focus of the Technology Development Program is directed towards those technologies that support the ground-based and space-based activities of the other NSBRI Research Teams. The unique feature of this program is the opportunity to bring an integrated system engineering perspective to bear on the technological developments necessary to support basic research. Multidisciplinary development teams have been established to work on strategically focused projects that integrate individuals and institutions with vastly different capabilities into a cohesive team.

Eight development projects were selected, by independent review, for pursuit under the Technology Development Program. Three of the projects were continuing from the previous proposal cycle and these projects continue to demonstrate excellent progress in achieving their individual goals and objectives. Four of the projects were started in February 2001 and all have made substantial progress consistent with their start dates and their stated objectives and goals. Due to budget cuts and change in the Principal Investigator, the eighth project start was delayed until July 1, 2002. To preclude unexpected technology issues and assure that the projects address needs established by the other Research Teams, rigorous reviews of both the continuing and new projects were conducted during the year. Each project team was encouraged to work closely with one or more of the other Research Teams that would benefit from their project's development. The eight Technology Development Team development projects directly support the technology needs of nine of the ten remaining NSBRI research teams. In several of the projects, prototype instruments and systems are already operating and have moved along the path to the establishment of definitive scientific results. For projects with more recent starts, instrument designs have been completed and some prototype equipment development has begun, which, when completed, will have significant relevance to the research of several NSBRI teams.

The eight Technology Development Team projects are:

1. Advanced, Multiple Projection, Dual Energy X-ray Absorptiometry (AMPDXA) Scanning System. A highly accurate precision measurement instrument for bone mineral density, bone structure, muscle loss, and determination of bone fracture risk.
2. Neutron Energy Spectrometer. A lightweight, portable instrument capable of accurately measuring the neutron energy spectrum of the energy range from 20 keV to 500 Mev.
3. Miniature Time-of-Flight Mass Spectrometer. A portable, highly accurate mass spectrometer system capable of identifying biomarkers in urine, blood, saliva, and breath samples.
4. Improved Bubble Detection System. A new system (based on ultrasound) to locate and monitor nitrogen bubbles in human tissue and blood as well as extra-vehicular activity.
5. Scanning Confocal Acoustic Diagnostic (SCAD) System. An ultrasound system designed to measure bone loss in space due to microgravity effects.
6. Heavy Ion Microbeam/Detector System. A system aimed at studying radiation effects at the cellular level in order to better understand human health in high radiation environments.
7. Dynamic Exercise Countermeasures Device (DECD). Uses jumping as a mode of exercise for astronauts as a direct countermeasure to microgravity-induced muscle and bone loss.
8. Space Qualifiable Magnetic Resonance Imaging (MRI) System. The MRI project goal is to develop an MRI system capable of flying in space to perform small animal studies.

II. INTRODUCTION

The Technology Development Program (Team) of the National Space Biomedical Research Institute (NSBRI) is chartered with developing technologies that will lead to a better understanding of the barriers to long-duration space exploration and assist in the development of countermeasures to assure safe and productive missions. The primary focus of the Technology Development Program is directed toward those technologies that support the ground-based and space-based research of the other NSBRI research teams and space life science research community at large. Accordingly, it creates systems and tools such as sensors, instruments, devices, and intelligent software. Requirements for these tools and technologies are predicated on the carefully developed needs of the other research teams. In particular, the Technology Development Team selects projects that: (1) support the investigation of the effects of spaceflight on human physiology and behavior; (2) apply this information toward the development of techniques, technologies, instruments, and countermeasures that will sustain humans during future long-duration space missions; and (3) benefit the quality of life and medical care on Earth.

Synergism is a key element of the program and the Technology Development Team strives to bring the engineering and biological science disciplines together in the identification and development of devices, instrumentation, and systems that address the fundamental research issues critical to the human exploration of space. A unique feature of the Technology Development Team's projects are their ability to bring an integrated systems engineering perspective (cross discipline) to bear on technology development as it supports the basic research. An important by-product of this integrated approach is the cross-education of the basic and applied science researchers in engineering and technology disciplines and the applied research and development engineers in biological and medical science.

Since such a myriad of potentially useful technologies, devices, and instruments could have significant impact on an astronaut's health and his ability to perform his mission, it is important for the Technology Development Team to identify the most important of NASA's risk factors for humans in space and then from these risk factors identify technology applications and devices that might produce significant risk countermeasures or aid human adaptation or health care in prolong flight environments.

The Critical Path Roadmap (CPR) provides the foundation needed by NASA to ensure that human spaceflight now and in the future is as safe, productive, and healthy as possible (within the mission constraints) regardless of the mission duration or destination. The CPR provides a framework for risk identification, risk prevention, and the need for viable countermeasures associated with humans in long-duration spaceflight. The Technology Development Team uses this roadmap as one means of prioritizing project selection. For example, bone loss in microgravity is considered one of the most serious risk factors (Type 1). Bone loss and the causal or associated muscle alteration in space are being addressed by two NSBRI research teams. The Technology Development Team has ongoing projects that directly support the efforts of both the bone and muscle teams.

Using the roadmap alone is not sufficient to identify all technology needs of the NSBRI research teams as well as the needs for human spaceflight. The Technology Development Team actively engages members from the other research teams, the medical science community, and NASA to assess additional technical requirements. Through various individual team leader and working group interactions, the needs are identified, distilled, and then focused into a technology development program.

The Technology Development Team has the following goals for its program:

Goal 1: Identifying new technological advancements and developments that can have a major impact on space biomedical research and astronaut health.

Goal 2: Contribute to risk reduction in each CPR priority area by developing new medical instruments and devices for both ground- and space-based research and countermeasure development.

Goal 3: Exploit the developments and advances made by Technology Development Team projects to improve the quality of life and health care delivery on Earth.

Goal 4: Promote the transfer of NSBRI-developed technological advances to industry for the benefit of Earth-based medical care.

Goal 5: Integrate technology development needs across other NSBRI teams, medical science community, and NASA through service and communication to become recognized as an important service arm that helps these researchers develop needed tools and instrumentation.

III. RESEARCH PROGRAM STRUCTURE & DESIGN

The risks associated with long-term exposure to microgravity and a high radiation environment are numerous; they represent the basis for the research program pursued by the NSBRI. Most of the ongoing NSBRI research is vertically integrated within a specific thrust area. For instance, the research teams typically have a core research topic that is combined with several special topic areas to form a disciplined approach to addressing a number of related issues.

The Technology Development Program is implemented in a different manner. The funded projects are selected, among other reasons, for their ability to provide necessary and enabling technologies for the basic research areas. Thus, the thrust area is laterally integrated with the other research areas. Figure 1 is a diagram showing the interaction between the eight current Technology Development Team projects and the other ten NSBRI research teams. As can be seen in Figure 1, the current Technology Development Team projects support nine of these remaining ten research areas.

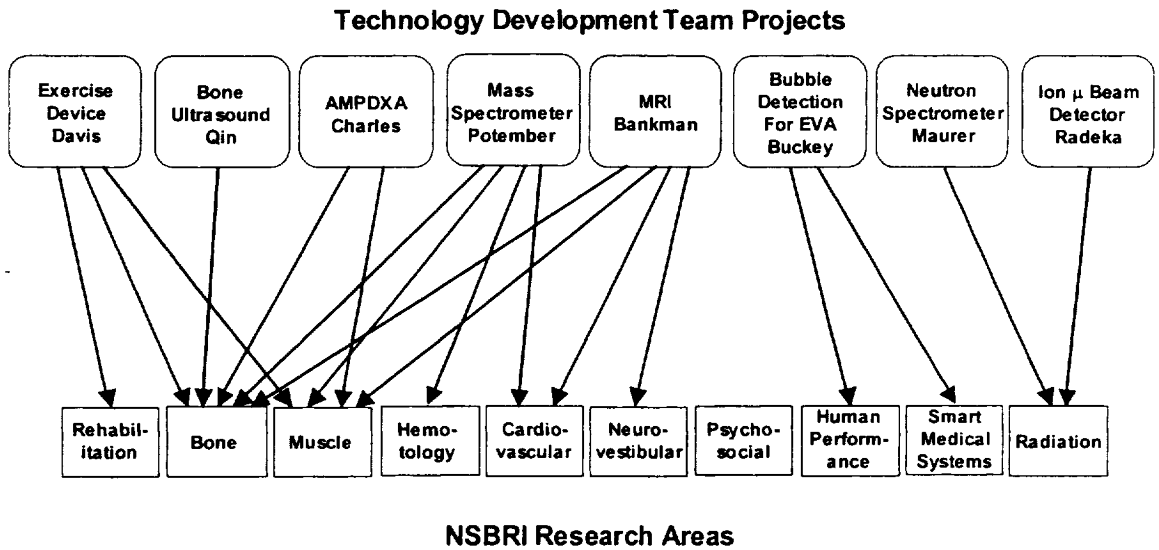


Figure 1. Mapping of current NSBRI Technology Development Team projects into the remaining ten NSBRI research areas.

The Technology Development Team generally focuses on projects that will deliver a specific product (e.g., sensor, instrument, etc.) in a specified period of time, typically one to three years. Of particular interest are projects that have strong technology transfer potential to industry so that the products of the development can be made available to support the research activities of other teams and achieve maximum societal benefit. Projects under the Technology Development Team umbrella are encouraged to interact with industry early in the development cycle. The NSBRI's Industrial Forum helps foster such interactions.

Proposals to the NSBRI Technology Development Program are expected to be of sufficient maturity (i.e., NASA Phase A (Conceptual Design)) so that: (1) the critical research issues can be readily identified, (2) the relevance of the technology development to the key research needs of the other NSBRI research teams and human spaceflight is evident, and (3) the technical approach and development plan directly lead to a deliverable (instrument, sensor, countermeasure device, etc.) within a reasonable timeframe.

Currently, there are eight projects under the umbrella of the NSBRI Technology Development Team: three projects continuing from the first research cycle (1998-2000) and five new projects that were nominally started in February 2001. Some projects had slightly later starts due to funding transfer issues. Due to budget cuts and change in Principal Investigator, one project, the Space Qualifiable MRI, delayed its start to July 1, 2002. As shown in Figure 1, the Technology Development Team projects address research needs and risk reductions in nine of the ten NSBRI basic research areas.

Project 1

PI/Project Title: Harry K. Charles, Jr., Ph.D.
Advanced Multiple Projection Dual Energy X-ray Absorptiometry (AMPDXA) System

Need(s) Addressed: Provide accurate measurement of bone and muscle loss both in space and on Earth. Measure the location of the bone loss and assess the integrity of the bone structure.

Countermeasures Target: Provide highly accurate bone mass loss and structural information so that appropriate countermeasures can be developed, applied, and monitored.

Project Description: The purpose of the Advanced Multiple Projection Dual Energy X-ray Absorptiometry (AMPDXA) Scanning System project is to design, build, and test a precision scanning system for monitoring the deleterious effects of weightlessness on the human musculoskeletal system during prolonged spaceflight. The instrument uses dual energy X-ray absorptiometry (DXA) principles and is designed to measure bone mineral density (BMD), decompose soft tissue into fat and muscle, and derive structural properties (cross-sections, moments of inertia). Such data permits assessment of microgravity effects on bone and muscle and the associated fracture risk upon returning to planetary gravity levels. Multiple projections, coupled with axial translation, provide three-dimensional geometric properties suitable for accurate structural analysis. This structural analysis, coupled with bone models and estimated loads, defines the fracture risk. The scanner will be designed to minimize volume and mass (46 kg goal), while maintaining the required mechanical stability for high-precision measurement. The AMPDXA will be able to detect 1% changes in bone mass and geometry and 5% changes in muscle mass.

Two instruments (the Laboratory Test Bed (LTB) and a Clinical Test System (CTS)) have been constructed to date. The LTB has been used to develop source and detector parameters and to test human bone segments. The LTB has been fully operational for the last four years. It has allowed the AMPDXA project to develop sources, detectors, and software algorithms necessary for the high-precision detection of BMD and bone structure. In this current period, the LTB has allowed the refinement of our BMD and structure extraction algorithms as well as making continued progress on the high-resolution separation of soft tissue from bone. The CTS has been designed to conduct human patient testing. The CTS is operation and clinical trials are about to begin.

Project 2

PI/Project Title: Richard H. Maurer, Ph.D.
Neutron Energy Spectrometer

Need(s) Addressed: Monitor the neutron radiation environment inside spacecraft, large space habitats, and on planetary surfaces.

Countermeasure Target: Provide highly accurate neutron radiation monitoring so that appropriate countermeasures can be developed, applied, and monitored.

Project Description: A Neutron Energy Spectrometer (NES) is being developed to monitor the flight radiation environment on the International Space Station (ISS), an interplanetary transport vehicle, or on a planetary surface. Detector types were selected for the complete neutron energy range and experimentally validated the concept for the low- and high-energy intervals. The effectiveness of our charged particle discrimination system was demonstrated. Data analysis and modeling efforts have verified the experimental results to date and the procedure for deconvolving deposited energy spectra into incident neutron energy spectra. The engineering prototype instrument has been successfully flown on a NASA aircraft and a high altitude balloon, demonstrating the robustness and operational capability of our design.

Project 3

PI/Project Title: Richard S. Potember, Ph.D.
Miniature Time-of-Flight Mass Spectrometer

Need(s) Addressed: Develop a miniaturized instrument that can quantitatively measure critical biomarkers from breath, body fluids, products of infection, etc.

Countermeasure Target: Provide a highly accurate measure of human biomarkers associated with many of the deleterious effects and conditions caused by microgravity and prolonged spaceflight so that appropriate countermeasures can be developed, applied, and monitored.

Project Description: The long-term objective of the Miniature Time-of-Flight Mass Spectrometer (TOFMS) project is to design, build, and launch a flight-qualified TOFMS for use on space platforms such as the Shuttle, ISS, or a planetary mission. The TOFMS can identify and quantitatively measure critical biomarkers associated with the deleterious effects of microgravity and long-duration spaceflight. The biomarkers can be determined from the analysis of breath, body fluids, products of infection, and, perhaps, DNA repair products and DNA mutations. As currently configured, the system appears to be of particular value to both the Bone and Muscle Teams, but biomarkers important to several other research teams can also be obtained. The TOFMS system being developed is small (less than 1 cubic foot), lightweight (less than 5 kg), low power (less than 50 W), and rugged. This NSBRI-sponsored TOFMS is building upon technology developed for DARPA to analyze chemical and biological weapons, while being optimized for astronaut use and the identification and quantification of biomarkers.

Many of the biomarker identification procedures are complex, requiring special protocols and associated laboratory equipment. To carry the equipment and chemical supplies required to monitor the health of an astronaut would be weight prohibitive, would necessitate specialized training, and would require a significant fraction of the astronaut's time. The TOFMS provides a small, efficient, broadband diagnostic instrument that can rapidly identify biomarkers important for successful human space exploration.

Project 4

PI/Project Title: Jay C. Buckey, Jr., M.D.
Improved Bubble Detection for Extra-Vehicular Activity

Need(s) Addressed: Careful monitoring and understanding of the bubble nucleation process associated with decompression sickness is required to reduce astronaut risks associated with extra-vehicular activity.

Countermeasure Target: Provide an understanding of blood bubble nucleation and growth so that effective countermeasures can be developed, applied, and monitored.

Project Description: The Improved Bubble Detection for Extra-Vehicular Activity (EVA) project goal is to improve current bubble detection methods. The assembly of the ISS requires extensive and unprecedented extra-vehicular activity. Because spacesuits operate at low internal pressures, the astronauts are highly susceptible to decompression sickness (DCS) (gas bubbles in the blood). A range of pre-breathe strategies, as well as suit gas mixtures and pressures, are employed to mitigate the risk. During EVA activities aboard the Shuttle and the International Space Station, in-suit Doppler bubble monitoring will be provided to detect conditions that increase DCS risk. Doppler bubble detection, while effective, has three primary limitations: (1) it is motion sensitive; (2) it detects only moving bubbles; and (3) it does not detect bubbles with diameters less than 80 μm.

The Improved Bubble Detection for EVA project will exploit two transcutaneous ultrasonic bubble detection and sizing instruments under development by NASA. These instruments utilize bubble resonance (not Doppler) techniques, thus allowing the instruments to measure stationary bubbles as well as bubbles of smaller size. One instrument is optimized for intravascular bubble detection in the size range of 30 to 200 μm. The other monitors extravascular bubbles in the 1- to 10-µm-size range.

Project 5

PI/Project Title: Yi-Xian Qin, Ph.D.
Scanning Confocal Acoustic Diagnostic (SCAD) System

Need(s) Addressed: Measurement of bone loss in space so that appropriate countermeasures can be developed, applied, and monitored.

Countermeasure Target: Provide measurement of bone material properties and relate to countermeasure development and processing.

Program Description: The Scanning Confocal Acoustic Diagnostic (SCAD) System project is focused on the measurement of bone loss is space. On Earth, early diagnosis and proper treatment of progressive bone loss (and/or poor bone quality) can dramatically reduce the risk of bone fracture. Ultrasound systems have the potential for determining the material properties of bone in a safe, repeatable, and highly accurate manner. Limitations in the performance of current ultrasound systems restrict their application to first-order screening, rather than the clinical standard upon which osteoporotic diagnosis and treatment regimens are based.

The SCAD is usable not only for ground-based determination of bone's physical properties; but, because of its low weight and size, it is also suitable for monitoring subtle changes in bone density and strength during extended spaceflight. The SCAD project is divided into four basic parts: (1) development of the SCAD system hardware, (2) correlation of SCAD-determined sound velocity and attenuation measurement with micro-CT bone BMD and structure, (3) prediction of the risk of trabecular bone failure associated with osteoporosis in the animal model, and (4) correlation of SCAD-derived BMD and structural modules with DXA measurements.

Project 6

PI/Project Title: Veljko Radeka, Ph.D.
Heavy Ion Microbeam and Micron Resolution Detector

Need(s) Addressed: The micron resolution detector, together with the microbeam, will allow the localized position of an ion impact within a cell to be determined. This is an enabling technique for radiobiology studies.

Countermeasure Targets: Understanding of the effects of radiation damage within the cell so effective countermeasures can be developed.

Program Description: The Heavy Ion Microbeam and Micron Resolution Detector System is aimed at studying radiation effects at the cellular level. Using microbeam irradiation facilities, it is now possible to place discrete numbers of particles in defined cellular and extracellular locations. Such facilities permit heavy-ion radiobiologists to explore the impact of signal transduction between cellular compartments as well as issues related to intercellular communication at low limiting fluences where not all cells in a population have been traversed. A high-energy, heavy-ion microbeam will allow an important unanswered question to be addressed, i.e., whether neurons that survive transversal by high-energy heavy ion (HZE) particles develop changes as a late consequence of the damage they incurred. These low-fluence studies will increase the understanding of the consequences of exposure to high, linear energy transfer (LET) radiation, such as encountered in the space radiation environment. (See the NES project above.)

The purpose of the Heavy Ion Microbeam and Micron Resolution Detector project is to allow such radiation studies as described above to take place by developing the following tools: (1) a microbeam (diameter 10 μm) of heavy ions (e.g., iron) at energies higher than existing ion microprobes (3 GeV/nucleon), and (2) an electronic position-sensitive detector for heavy ions with a position resolution better than 1 μm. Interactions between the Heavy Ion Microbeam and Micron Resolution Detector project and the Radiation Team have taken place.

Project 7

PI/Project Title: Brian L. Davis, Ph.D.
Dynamic Exercise Countermeasure Device (DECD)

Need(s) Addressed: Demonstrate that proper in-flight exercise can counter the microgravity-induced bone and muscle loss.

Countermeasure Target: Develop a direct countermeasure to bone and muscle loss in space.

Program Description: The Dynamic Exercise Countermeasures Device (DECD) is aimed at developing a countermeasure to bone and muscle loss in space. Bone demineralization (bone mass loss) is a well-documented physiologic effect of long-duration spaceflight and microgravity. Animal experiments on Earth have clearly indicated that: (1) certain bone strains and strain rates stimulate bone deposition, and (2) repetitive loading of the lower extremity can increase osteonal bone formation even as proximally as the vertebral column. Such studies have also indicated that a relatively small number of appropriate weight-loading cycles may be sufficient to stimulate bone deposition. Based on prior research with weight-loading experiments upon the foot, a dynamic exercise countermeasure device that utilizes jumping as the mode of exercise for the astronauts is under development. The DECD project is divided into three phases: (1) develop a lightweight, vibration-isolated exercise device, suitable for use on the ISS, that will permit dynamic jumping exercise within microgravity; (2) perform system testing using zero-gravity simulation; and (3) verify DECD efficacy in true microgravity through KC-135 experiments.

Project 8

PI/Project Title: Isaac Bankman, Ph.D.
Space Qualifiable Magnetic Resonance Imaging (MRI) System

Need(s) Addressed: MRI needed in space for animal studies and peripheral (limb) measurements on humans.

Countermeasure Target: Provide highly accurate bone and soft tissue measurements to verify countermeasures in space-based animal studies.

Program Description: The goal of the Space Qualifiable Magnetic Resonance Imaging (MRI) System is to develop a proof-of-concept engineering model of a space-qualified MRI system for small animals studies with a mass of less than 150 kg and low average power (<1 kW quiescent and <1.2 kW when scanning). An on-board processor or personal computer can be adapted to display the collected information. MRIs provide high-resolution, high-quality anatomical information without ionizing radiation, so they can be safely and repeatably used to track changes without deleterious effects.

As a result, the study of physiological alterations in space and the development, verification, and maintenance of countermeasures will be significantly enhanced. Mice and small rat models are useful surrogates to carry out in-orbit physiological studies. In-flight MR imaging of these animals will be of particular benefit to countermeasure development by several of the NSBRI research teams.

IV. RESEARCH PROGAM ACCOMPLISHMENTS

Project Accomplishments

The Technology Development Team supports the needs of the other NSBRI teams and NASA. Through close communications with these groups, this team develops devices, instruments, and systems to improve research techniques and medical care on the ground and in space. Projects of the Technology Development Team focus on designing lightweight, compact research tools and on developing simple, minimally invasive and non-invasive sampling and measurement methods. Currently, there are eight active projects being pursued by the NSBRI Technology Development Team: three projects continuing from the first research cycle (1998-2000) and four new projects that were nominally started in February 2001. Some projects had slightly later starts due to funding transfer issues. The eighth project (Space Qualifiable MRI) began in July 2002. Several projects have also operated with reduced funding due to NASA funding shortfalls for the NSBRI. Research program accomplishments during the last 12 months are reported below.

Project 1: Advanced, Multiple Projection, Dual Energy X-ray Absorptiometry (AMPDX) Scanner System
PI: H. K. Charles, Jr.

This project used advanced sensor and detector design and fabrication techniques to develop a compact, storable, low mass, and low powered dual energy X-ray absorptiometry (AMPDXA) Scanning System that is capable of determining bone mineral density, bone cross sectional area, and bone moments of inertia at any body site.

This project supports the explicit needs of both the Bone Demineralization/Calcium Metabolism Research Team and the Muscle Alterations and Atrophy Team. The prototype system is capable of real-time monitoring of bone and potentially muscle loss at extremely high precision. Since the resultant measurements are patient specific, the system is useful for monitoring the effectiveness of countermeasures as well as determining the risk of fracture of individual astronauts under deployment scenarios. On Earth, the system is a natural adjunct to research on the effects of aging and disuse on bone integrity along with routine screening for osteoporosis and monitoring for efficacy of osteoporosis therapy.

The AMPDXA project has had several notable accomplishments during the last 12 months. These accomplishments were focused in the following areas: (1) Laboratory Test Bed (LTB), (2) Clinical Test System (CTS) for ground-based human testing, (3) Commercialization of the AMPDXA, and (4) prototype design for space applications.

Accomplishments:

- Laboratory Test Bed

The LTB has been fully operational for the last four years. It has allowed the AMPDXA project to develop sources, detectors, and software algorithms necessary for the high-precision detection of BMD and bone structure. In this current period, the Laboratory Test Bed has allowed the refinement of our BMD and structure extraction algorithms as well as making continued progress on the high-resolution separation of soft tissue from bone. Multiple-projection analysis enables the user to evaluate bone structural properties (e.g., bending strength) independent of subject position and orientation. Analysis of LTB images and ancillary data has demonstrated an average coefficient of variation in the maximum and minimum moments of inertial (I_{max} and I_{min}) on the order of 1% for a three-projection estimate. Preliminary experiments with more than three projections have indicated even further reductions are possible.

Multiple-projection imaging has led to the ability to generate three-dimensional reconstructions of the imaged bones. Future progress has been made on relating the structural information extracted from the weight-bearing bones by the AMPDXA to the mechanical properties and ultimately the risk of fracture. Since the AMPDXA stores and analyses patient-specific mechanical as well as BMD information on each patient, the risk assessment for each individual will be unique and not based on population means as is done today with conventional DXA systems. Preliminary progress has also been made on the extraction of standard radiographic images using the AMPDXA.

- Clinical Test Unit

The CTU is capable of translation and rotation of the image plane, unlike commercial DXA systems. The objective of this system, built on the chassis of a used CT scanner to save time and cost, is to provide three-dimensional bone structural information as well as directly determine magnification. During the current period, the machine control software has been refined along with the development of a complete patient imaging protocol. Initial human images have been taken. Last year, the AMPDXA was moved to a refurbished patient test area within APL's secure compound. Given the events surrounding September 11, 2001, the ability to access the APL site by outside visitors has been significantly reduced. Such restrictions would significantly hamper the clinical testing proposed for the AMPDXA and approved by the Johns Hopkins Medical Institution's Institutional Review Board (IRB). Thus, a decision was made to move the AMPDXA outside APL's secure compound and into an adjacent industrial park along with other APL activities. This moves was completed by late summer and the CTS is now operational in its new home.

- Commercialization of the AMPDXA

Significant activities have taken place over the last year in the process to commercialize the AMPDXA. First, a new low-cost commercial unit design was completed. Next, a review of the potential market and the need for the AMPDXA was assessed. With positive results from the market study, The Johns Hopkins University Applied Physics Laboratory (JHU/APL) made the decision to go ahead with commercialization by forming a spin-off company. A business plan has been written and JHU/APL is in the process of searching for venture capital.

- Space Prototype System

Launch weight and spacecraft payload size limitations are serious factors associated with the viability of a piece of flight hardware. Without these constraints, commercial DXA systems are primarily designed for subject comfort and convenience. The project team has pressed hard to achieve exceptional system performance while also accommodating ease of use, minimum size, and a significant reduction in weight. The CTS was fabricated with existing components to meet the budgetary constraints, but a design exists of a system with a mass estimate of 86 kg, which is notably lower than the originally projected weight of 100 kg. In the 1-3 year timeframe, it is expected that advancements in x-ray tube technology will further reduce the weight to approximately 60 kg. In about 3-5 years, all of the component technologies (i.e., x-ray tube, detector, power supply, electronics) will have matured to the point where a target weight of approximately 46 kg will be achievable.

As mentioned above under commercialization, a configuration for the AMPDXA has been conceived that offers design simplicity resulting in lower development and manufacturing costs. This unit would also be suitable as a starting point configuration for a space mission.

<u>*Project 2*</u>: Portable Neutron Energy Spectrometer
PI: R. H. Maurer, Ph.D.

Galactic and solar cosmic rays are inordinately effective at producing secondary neutrons when they encounter spacecraft or habitat material. These neutrons can cause cellular and DNA damage to those exposed. The neutron component of radiation in a space structure is estimated to be between 30 to 60 percent of the total radiation environment when outside the Earth's magnetic field. To be able to measure the neutron spectrum, a portable brief case size, real-time neutron spectrometer prototype with a mass of less than 10 kg has been developed to support the research of the Radiation/DNA Effects Research Team. It can be used to characterize the environment for the development of a countermeasure and also can be used as a real-time monitor to control the application of countermeasures. The instrument measures neutrons in the range from 10 KeV to 500MeV with at least 10 percent energy resolution and count the number of neutrons below 10 KeV. This portable instrument incorporates the latest advances in energetic particle detection technology, including energy loss and total energy measurement, while building on the successful charged particle instruments built by JHU/APL for NASA/GSFC and NASA/JPL for many previous near-Earth and planetary missions. As the neutron energy spectrum is measured, an incorporated alarm will warn astronauts when a safe threshold is exceeded. The device, because of its small size, can be ported within a space vehicle or on a planetary surface to map the local neutron environment. This project addresses an explicit need of the Radiation Effects/DNA Damage and Repair Team.

Accomplishments:

- Detector Hardware

The neutron spectrum of interest spans several orders of magnitude from the thermal (keV) to the highly energetic (MeV). There does not exist a single detector technology that will provide adequate sensitivity over this large range. The project team re-examined a number of detector schemes that might be combined to provide adequate coverage and sufficient overlap between each detector's neuron energy range. The original prototype detector used a He^3 tube coupled with a thick, solid-state, lithium-drifted silicon detector. The flight equipment (aircraft and balloon) was a cesium iodide (C_sI) crystal surrounding the thick silicon detector to veto charged particles passing through the silicon detectors. In this period, a stack detector system consisting of a silicon transmission detector and a 5-mm thick lithium-drifted silicon detector. This system has the same charged particle anti-coincidence efficiency under accelerator testing as our flight detector. This has been verified in experiments with the 14 MeV neutrons. The NES project also added a Bicron 454 plastic scintillator detector with an attached photomultiplier tube to cover the mid-range neutron energies.

- Modeling and Analysis

Modeling of the response of the high-energy channel from detailed cross-sections of the basic neutron-silicon interactions was undertaken using state-of-the-art computer codes. The purposes for developing the models were: to assess the accuracy of these codes for neutron-silicon interactions; to use these codes to understand the results of the energy deposition measurements; to determine whether these codes can be used to calculate the effects of packaging and instrument surroundings on the incident neutron spectrum; and, to assess the ability of the codes to supplement the experimental determination of the instrument response function. The current model using GEANT4 (a code library widely used in high energy detector design and simulations produced at CERN) reproduces the energy deposition spectra measured at RARAF reasonably well, although discrepancies for the highest energy depositions remain to be resolved. One interesting result of this model is a discrepancy at low energies indicating that gamma production during exposure may not have adequately been accounted for by measuring the background spectrum when the beam is off. In further work, a deconvolution technique that calculates a most probably incident neutron energy spectrum from the deposited energy spectra measures by the 5-mm thick silicon detector has been verified. A publication on this result is currently in a journal review cycle.

- High-Altitude Testing

The prototype neutron energy spectrometer made several flights aboard F15 and F18 aircraft during the latter part of FY01. The prototype functioned properly to altitudes in excess of 40,000 feet. Most of FY02 was spent getting the instrument ready for a balloon flight in October 2002. This flight has occurred and the experimental results are under analysis. The balloon flight was made at altitudes in the 85,000 to 90,000 foot range. At 85,000-90,000 feet, the remaining atmosphere of nominally 25 g/cm^2 creates a high-energy neutron environment similar to that on the surface of Mars (the target Earth nuclei are nitrogen and oxygen, instead of the carbon and oxygen nuclei on Mars). It should be noted that a prior year proposal for an instrument to fly on the Mars 2003 Lander was made by the team and was accepted. With the cancellation of the Mars 2003 mission, the NES project lost that opportunity. The team is preparing additional information to support a proposal to the Mars 2007 Lander project. In the meantime, a publication on the NES design concept for the Mars 2003 Lander has been accepted for publication in *Acta Astronautica*.

- Materials Analysis and Testing

The proposed research, "Development of a Neutron Spectrometer to Assess Biological Radiation Damage Behind Spacecraft Materials," was selected for funding for the period May 2000 through November 2003. The primary responsibility under this grant is to support the Lawrence Berkeley Laboratory (LBL) personnel in the evaluation of spacecraft structural and shielding materials by supplying a version of the neutron spectrometer suitable for accelerator tests. The first experiments were conducted in the first quarter of 2001 at Brookhaven National Laboratory (BNL). These experiments will collide high-energy heavy ion beams with standard and novel spacecraft materials and the spectrometer will measure the neutron energy spectrum produced as a result of these collisions. A secondary responsibility for this grant is to continue development of the modeling effort in a manner that is useful for materials science experiments as well as for assessment of astronaut biological radiation risk. The NES project team's work on shielding materials shows that polyethylene is an effective neutron shield. The team has found that for fast and high-energy neutrons, four inches (10 cm) of polyethylene is necessary to make a significant reduction in the neutron flux. For the fast (10-20 MeV) neutrons, a reduction of a factor of 3 was indicated while for the high-energy neutrons (20-600 MeV), a factor of 4.5 was determined.

<u>Project 3</u>: Miniature Time-of-Flight Mass Spectrometer
PI: R. S. Potember, Ph.D.

A high-resolution miniature TOFMS, already under development for other purposes, has been adapted for space flight. This instrument has the potential to identify and quantify a wide variety of biomarkers to support biomedical research and medical care. It is a rugged device that will unambiguously identify samples containing many compounds and be less than one cubic foot in size, weigh less that 5 kg, and require less than 50 W of power. Its applications include: analysis of breath, body fluids, products of infection, and perhaps DNA repair products and DNA mutations. Identification of compounds with mass ranges from under 100 to more than 10,000 amu has been demonstrated. While the instrument has a wide range of usage, the initial focus of the project is on the analysis of a variety of biological compounds in fluids although the instrument can be adapted to handle samples of various types. As currently configured, this instrument is of special value to the Bone Demineralization/Calcium Metabolism Team and the Muscle Alterations and Atrophy Research Team as well as being useful for gathering data on a variety of other experiments for the other Research Teams.

Accomplishments:

- Prototype Hardware

A major objective of this project was the design and development of a mass spectrometer *system architecture* that can be utilized for diagnostics based on complex, non-volatile biomarkers species. An orthogonal extraction time-of-flight mass spectrometer (TOFMS) analyzer, incorporating a dual matrix-assisted laser desorption/ionization (MALDI) and electron ionization (EI) source, was successfully completed and demonstrated. This novel instrument greatly expands the spectrum of biomarkers that can be measured by incorporating the capability of electron impact ionization with the previously demonstrated MALDI measurements. A prototype of this instrument operating out of a suitcase has been demonstrated.

- Detection and Analysis

The TOFMS has demonstrated the detection and analysis of urine biomarkers such as insulin-like growth factors (IGF-I), urinary 3-methylhistidine, estradiol, creatinine, and trivalent hydroxypyridinium cross-links. Measurement of such materials is important to both the Bone and Muscle Teams. The detection of compounds and biomarkers in both blood and saliva has also been demonstrated. Using a separate collection system, the breath from human subjects has also been analyzed.

During the period, the project team has designed and built a portable gas chromatograph-mass spectrometer (GC-MS) system. The GC-MS system will allow the monitoring of spacecraft for chemical and biological contaminants in addition to the analysis that can be performed on human fluids. The team completed studies on oxidative stress biomarkers for early detection of oxidative damage to DNA including detection at needed physiological monitoring levels. A study of Zolendronate (a bone loss countermeasure) has begun.

Project 4: Improved Bubble Detection for EVA
PI: J. C. Buckey, Jr., M.D.

The objective of the Improved Bubble Detection for Extra-Vehicular Activity (EVA) project is to improve EVA efficiency and safety through the *in-vivo* validation of two unique ultrasonic bubble-sizing and detection instruments that exploit bubble resonance (not Doppler) to transcutaneously detect and size intravascular and extravascular bubbles (stationary or moving) *in vivo*.

NASA presently utilizes in-suit intravascular bubble detection based on Doppler ultrasound as an early warning for the development of decompression sickness (DCS). Doppler-based systems, however, can only detect moving, relatively large bubbles and provide little information about bubble size. The ability to size bubbles, detect stationary bubbles, and detect bubbles smaller than conventional Doppler-based systems may provide important information for early DSC detection and prevention. Creare Incorporated, under two large projects for NASA, has developed two ultrasonic bubble sizing and detection instruments intended for transcutaneous detection and sizing of: (1) intravascular bubbles in the size range of 30-200 μm, and (2) extravascular bubble detection and sizing in the size range of 1 to 10 μm. The intravascular bubble-sizing instrument has been validated extensively *in vitro* using tissue phantoms that accurately mimic transcutaneous operation, and it has been successfully applied in a preliminary *in-vivo* trial. The extravascular bubble-sizing instrument is currently under development and has already demonstrated an ability to detect bubbles down to 1 μm in size *in vitro*. The instrument is presently being tested and optimized *in vitro* using a tissue phantom to simulate transcutaneous tissue bubble detection. Although these instruments have both been tested extensively *in vitro* and some preliminary but encouraging *in-vivo* work has been conducted with the intravascular bubble detection device, the potential for *in-vivo* applications of these instruments has not been fully explored nor have they been fully validated *in vivo*. The goal of the current project is to utilize these instruments to validate and optimize their performance *in vivo* and to begin to address several important long-posed DCS research questions.

One longstanding DSC concept is that gas phase nuclei exist normally in tissues before and after decompression. However, current Doppler-based monitoring techniques only allow for intravascular detection of relatively large bubbles, and as a result, little is known about the fundamental development of these bubbles. If, in fact, nitrogen bubbles normally exist in tissue and could be detected there, this instrument offers the potential to monitor DCS in a novel way, and potentially monitor the growth of disappearance of bubbles during decompression, recompression, or during oxygen pre-breathe. Such a capability could greatly enhance our ability to: (1) understand DCS, (2) detect the earliest stages of DCS, and (3) improve the efficacy and efficiency of strategies for mitigating the risk of DSC such as oxygen pre-breathing.

Accomplishments:

- Instrument Development

A dual-frequency ultrasound bubble detection instrument is under development. Bubbles insonified at two different frequencies act as nonlinear mixers and generate signals at both the sum and differences of the two frequencies. It has been shown that the signals (sum and difference) are enhanced if one frequency corresponds to the resonant frequency of the bubble. This phenomenon should allow sizing of the bubbles. Two detection techniques are being explored: (1) single pulse (analyze FFT from a relatively long-duration signal) and (2) multiple pulse (analyze undersampled signal from multiple short-duration pulses). The team has shown that the single pulse method has greater sensitivity the while multiple pulse technique offers greater frequency and spatial resolution.

- Analysis (*in vitro* and *in vivo*)

In general, sum signals are detected when bubbles are present and are absent when bubbles are not present. Strong sum signals have been observed in excised tissue. Sum signals have been consistently detected at certain anatomical locations (e.g., the hip). Initial studies indicate no significant time dependence of sum signals occur with both adynamic and decompression thickness. Significant progress has been made in the creation of bubbles in gelatin as a tissue simulate.

<u>*Project 5*</u>: Scanning Confocal Acoustic Diagnostic (SCAD) System for Bone Quality Assessment
PI: Y-X. Qin, Ph.D.

The goal of this project is to develop a new technology for monitoring bone quality of humans on Earth and during long-term space missions. This will lead to a better understanding of the progressive adaptation of bone loss in both aging populations and astronauts subject to microgravity. The principal objective of this project is to develop a portable scanning confocal acoustic diagnostic (SCAD) system capable of generating non-invasive, high-resolution ultrasound (US) attenuation and velocity maps of bone, and thus determining the relationship between ultrasound parameters and bone mineral density (BMD), bone quality, and other bone physical properties (i.e., stiffness and modulus). This system is relevant not only for ground-based determination of bone's physical properties, but can effectively be used in the space environment to determine subtle changes in density and strength during extended flights. In the proposed work, we will validate the structure and density information detected by SCAD using μCT and mechanical testing methods in *ex vivo* animal models. Correlations to *in vivo* DEXA data derived from humans will also be made. The system can monitor the degree and risk of bone loss in space and on Earth, and serve as a major step towards clinic usage as an early diagnostic tool for osteoporosis.

Accomplishments:

During this period, the research team was focused on technology development of the SCAD system and on determining interrelationship between ultrasound determined parameters and micro BMD and architectural parameters in a quantitative manner. Bone quality is predicted via the correlation between SCAD determined data and μCT identified BMD, porosity, trabecular space and trabecular width, as well as modulus using a large number of trabecular bone samples.

- Instrument Development

An experimental SCAD system has been successfully implemented, which is capable of generating non-invasive, high-resolution ultrasound attenuation and velocity maps of trabecular and cortical bones for predicting the risk of osteoporosis and fracture (U.S. patent pending). Spatial distributions of ultrasound parameters, i.e., ultrasonic attenuation and velocity, in the focal region in the trabecular bone can be measured and calculated, and thus it can be converted to an image, e.g., gray scale or virtual color. These new methods represent a major advance in investigating the mechanical properties of materials by utilizing confocal ultrasonic technology at appropriate frequencies. In addition, the ultrasound resolution and sensitivity are significantly improved over current ultrasound approaches.

A 3-D ultrasound scanning system consists of a pair of focused ultrasonic transducers (transmitting and receiving), digitally controlled moving stages, an ultrasonic wave generator unit, a preamplifier unit, and data acquisition unit with hardware. Ultrasonic scanning is program-controlled by a custom-written computer algorithm. The ultrasound propagates through tissue via water or acoustic gel. The converged beam can be as fine as 0.3 mm in diameter, through which most of the acoustic energy passes through the region of interest within the focal region of the trabecular bone. Thus, the influences of soft tissue, cortical bone and irregular shape surfaces can be greatly reduced. The resolution of the beam can be adjusted up to 0.1 mm or less for each incremental step. In this confocal scanning mode, ultrasound parameters, i.e., BUA and UV, can generate a spatial acoustic map at the region of interest.

It is critical that acoustic map can be achieved in a fast scanning mode, i.e., testing bone quality during the space mission. With new design using dedicated CPU board and micro-controller, acoustic scan can be achieved in a continuous matter, which reduces the scanning time more than 10-fold compared to initial design. The scan time for a 2-D regional map is dependant on the scan resolution and the moving stage speed and digital response. For example, a 40 x 40 pixel 2-D array requires approximately 3 minutes of scan time, which originally required more than 30 minutes to complete the same scan.

The system, through the use of ultrasound confocal scanning mitigates the difficulties resulting from current ultrasound apparatus. In particular, focusing energy at a confocal point increases the sensitivity of a received signal, thereby reducing the noise due to the interaction of the soft tissue with the cortical shell and thus increasing the resolution. The device then makes it possible to make a highly reliable prediction of the material properties and density of a specimen through analytical and experimental calculation and correlation. The generated image of both ultrasound attenuation (UA) and velocity (UV) will typically comprise of discrete elements (pixels) each having specific values relating to image data at the individual part of the bone. From the image data, bone mineral density (BMD) and stiffness can be calculated. A set of computer algorithms was developed including the functions to calculate the interrelationship between acoustic parameters, the bone stiffness and density in a region of interest using linear and/or non-linear regression analyses.

- Bone Structure Determination

It is hypothesized that musculoskeletal disorders, e.g., osteoporosis, change not only the structure and the mineral density (BMD), but also the modulus and stiffness of bone. Advents in ultrasonic techniques provide an intriguing and a physical modality for characterizing not only the structural but also the material properties of bone in a manner of non-invasive, non-radiation, non-destructive, safe and relatively accurate. These changes in bone properties can be evaluated using the combination of micro-CT, mechanical testing and ultrasound mapping. While ultrasound provides only the acoustic wave propagation parameters when waves pass through the specimens, it becomes essential to propose a relationship between detected acoustic signals and bone properties. As an initial database, SCAD determined US velocity and attenuation are correlated with micro-CT identified BMD, porosity, trabecular thickness and trabecular space, as well as material bulk modulus determined through *ex vivo* animal bone tests.

A total of 61 sheep trabecular bone cube specimens (1 x 1 x 1 cm), were harvested from the distal femoral condyle. These were scanned in three orthogonal directions: longitudinal, med-lat and ant-post to determine UV and BUA. In comparison, bone's trabecular mineral density was determined by micro-CT measurements with a spatial resolution of approximately 30 micron ($n = 17$). Bulk mechanical modulus of the cubes was determined by a contact compressive mechanical testing in a MTS machine in all three orthogonal directions ($n = 44$). To predict bone's structural and strength properties, a series of regression analyses were conducted between the results of μCT determined BMD, and stiffness, and the results obtained from the ultrasound measurements.

Through a micro-CT 3-D reconstruction, a number of parameters, such as the total volume (TV), bone volume (BV), bone mineral content (BMC), and BV/TV, were determined. These data show that the ratio of BV/TV in the normal group was 54.48 ± 2.3% and 49.45 ± 3.5% in the osteopenia group. These results have demonstrated a spatial difference among the samples, which is difficult to detect by normal ultrasound methods.

<u>Project 6</u>: Heavy Ion Microbeam and Micron Resolution Detector
PI: V. Radeka

The use of high-energy microbeam provides a unique way to control the number of particles traversing individual cells and localizing the dose within the cell. High-energy heavy charged particles transfer their energy to biological organisms through high-density ionization and excitation along the particle track even with uniform irradiation. This characteristic of microscopically non-uniform dose delivery is expected to induce complex DNA damage and mutagenesis. This is contrasted to the relatively uniform dose delivery produced by gamma rays or electron beam irradiation. To investigate the distinct biological effects of heavy ions, especially to determine the effects of occupational and environmental exposure of very low doses of heavy charged particles (e.g., since virtually no cells receive more than one traversal cosmic ray HZE particle in its lifetime in a spaceflight environment), one approach is to select cells with the desired exposures from a randomly irradiated population.

Therefore, the goal of the Heavy Ion Microbeam/Detector project is to design and test a high-energy microbeam apparatus and a micro-resolution solid-state detector for space radiobiology studies. Such a facility permits heavy-ion radiobiology to address specifically the impact of signal transduction between cellular compartments as well as issues related to intercellular communication at limiting low fluences where not all the cells in a population have been traversed by even a single particle. Moreover, a high-energy ion microbeam will permit researchers to address an important unanswered question: whether neurons that survive traversal by HZE particles develop changes as a late consequence of the damage they incurred. Therefore, these low-fluence studies promise to aid in our understanding of the consequences of exposure to high-LET radiation such as encountered in the space radiation environment. The project involves the development of two major tools:

1. A microbeam of heavy ions (e.g., iron) at energies higher than at existing microbeam facilities (up to 3 GeV/nucleon). The microbeam would have a sufficiently small diameter (about 10 micrometers) to localize the ions to a single cell.

2. An electronic position sensitive detector for heavy ions with a position resolution better than 1 micrometer, to localize the position of ion impact within a particular region of the cell.

These developments will advance significantly the state-of-the-art of high-energy heavy ion microbeams and of high-resolution heavy ion detectors. For the cell studies employing these tools, the necessary infrastructure will include a micropositioning stage with a microscope and auxiliary detectors.

Accomplishments:

- Detectors

Various detector designs were evaluated including double-sided strip detectors, pixelated detectors, and the alternating stripixel detectors (ASD). The stripixel detector was selected as the most promising approach for making a high-resolution detector. The ASD consists of individual pixels alternately connected by X and Y readout lines (strips). The advantages of the stripixel detector are:

(1) Both the pixels and strips can be made with a very small pitch in both directions (few micrometers). A few micrometer pitch (8-9 μm) allows submicron position resolution in two dimensions.
(2) The narrow strips (2 μm) produce low leakage currents and capacitance.
(3) The ASD also have flexibility to work with various readout schemes.

The simulation of the ASD chip design has been completed and the first prototype detector has been fabricated. While not completely functional, the first chip demonstrated that the desired patterning and resolution of features could be achieved. The large area test structures were functional. Some interconnection problems (opens) existed between first and second level metal. A new double-level metal process was developed that remedied the open contact problem.

A second batch of detectors is approximately 70% finished. It is anticipated that the detector chips will be fully functional. A 16-channel, low noise readout has also been designed and has begun fabrication.

<u>Project 7</u>: Design of a Dynamic Exercise Countermeasures Device (DECD)
PI: B. L. Davis, Ph.D.

The objective of this study is to design and develop an exercise device that primarily counteracts microgravity-induced bone loss and muscle atrophy. Secondary benefits will include alleviating some of the problems associated with vestibular and cardiovascular adaptations to microgravity. This dynamic exercise device is based on data previously collected under NASA grant NAGW-5006.

The DECD will be designed and constructed by Foster-Miller Incorporated. The assembly is designed as an exercise machine that allows the subject to simulate jumping in a microgravity environment without subjecting the surrounding vehicle structure to any significant impact loads. The assembly configuration is based on the conservation of the momentum principle whereby the subject "jumps" on a platform with mass similar to that of the subject. Both the subject and the platform are mounted on two coaxial support rails. They are both free to move relative to each other along these rails. The subject and the platform are connected by a pair of sleeved adjustable force springs. These springs are tensioned to produce a force that approximates the subject's body weight in a gravity environment. The subject is restrained on a torso support carriage. He places his feet on the push-off plate and pushes the counterbalance assembly away by straightening his legs. This stretches the force springs and simulates standing in a gravity environment. The subject then bends his knees and "jumps" off the platform. This jumping force causes the guided subject and the guided counterbalance assembly to separate.

The two masses, traveling in opposite directions, will be decelerated by the force applied by the interconnecting adjustable force springs. The deceleration rates will be proportional to the masses. When motion has stopped, the two masses will accelerate towards each other. The subject will "land" on the platform and soften the landing force by bending his knees. Both moving masses will decelerate to zero. This is equivalent to jumping in a gravity environment. This jumping cycle and the primary forces generated and reacted within the exercise machine assembly are balanced and isolated from the exterior environment. This arrangement will not be sensitive to mass differences between the loaded carriages. When subjected to the same force, both will have the same momentum with compensating differences in accelerations and velocities.

The primary strength of this project is that the DECD targets multiple systems of the body that are adversely affected by prolonged microgravity. The exercise countermeasure device that we are developing will provide physical stimuli to bones, muscles, the cardiovascular system and, most likely, the vestibular system. Another strength of the project lies in its simplicity. Astronauts will perform jumping exercises while they are tethered to a support platform. The principle of conservation of momentum dictates that when an astronaut pushes off the platform, he/she will experience a "flight" phase followed by an impact phase when "landing" occurs and there is contact with the support platform. The device is being designed with key considerations for mass, and for this reason the support platform will consist of an empty chamber that will be filled once the spacecraft has reached its orbit, and minimizing unbalanced forces and vibrations that are transmitted to the spacecraft.

Using the DECD: (1) astronauts will be able to exercise without the need for uncomfortable harnesses (since we generate the same forces under the feet with tether forces of 50% bodyweight as we do with 100% bodyweight tensions), (2) the hardware will be considerably lighter than the treadmill flown on previous missions (60 kg compared with 320 kg), and (3) future research will need to focus on the in-flight benefits of jumping exercises versus high frequency vibrations that are applied through the undersurface of the feet.

Accomplishments:

Significant progress on the DECD has been made. The design and fabrication of the second (or working) prototype is nearly complete. The selected dynamic exercise countermeasure device (DECD) configuration has been sized for a user population with body weights between 54 and 89 kg and standing heights between 162 and 175 cm. The device measures 305 cm in length, 89 cm wide, and 47 cm tall. Estimated empty weight is 60 kg. The general arrangement includes a pair of side rails positioned to be coplanar with the combined user/carriage center of gravity and the loaded platform center of gravity. The platform tank is being sized to achieve a platform-loaded mass of 82 kg. The DECD includes a load adjustment feature in the form of a hand crank and indicator which will allow the user to pre adjust the standing load force experienced between user and platform between 40% and 60% of the user body weight. A total of four shock cords each with a free length of approximately 460 cm long are being used to develop the standing force. Shock testing is currently underway to select the optimum length of shock cord required to satisfy the specified load range.

<u>*Project 8*</u>: Space Qualifiable MRI System
PI: I. N. Bankman, Ph.D.

The objective of the Space Qualifiable MRI System project is to develop a proof-of-concept engineering model of a Magnetic Resonance Imaging (MRI) system for small animal models and possible astronaut limbs that can be space qualified. Small animal MRI systems, although commercially available, are too massive to be considered for spaceflight, with masses >1000 kg and power requirements of >5 kW. Availability of a flight qualified MRI could especially benefit the study of physiological alterations in the space environment and the development, verification, and maintenance of countermeasures. The countermeasure development efforts of the following NSBRI teams would be significantly enhanced: Bone Loss, Cardiovascular Alterations; Muscle Alterations and atrophy; Neurovestibular Adaptation; Nutrition, Physical Fitness and Rehabilitation; Radiation Effects; DNA Damage and Repair, and Smart Medical Systems. This will establish a new era in space physiology research complementing and evaluating the effectiveness of the hind limb suspended mouse and rat models and human bed rest studies that are routinely carried out on Earth. Frequent MRI scanning of mice and rats in space is especially important to many of the research teams for understanding the basic processes at work.

The major goal of this project is to develop an engineering model of an MRI system for human limbs and small animals, specifically mice and rats, to demonstrate that a flight qualified system can be fabricated with the following characteristics:

- Field strength >1 Tesla and perhaps as high as 1.5 Tesla.
- Field inhomogeneity ≤8 ppm over spherical imaging volume of 10 cm diameter and ≤10 ppm out to 15 cm.
- Imaging of small animals (mice and rats).
- Standard resolution mode giving a resolution of 234 microns over a spherical imaging diameter of 6 cm for mice and rates.
- Higher resolution mode giving a resolution of 117 microns over a spherical imaging diameter of 6 cm for mice and.
- Mass <150 kg.
- Average power in standby mode <1 kW and during normal use <1.2 kW.

The proposed design is a compromise between field strength, imaging volume, system mass, system average power, and the ability to image small animals with sufficient resolution.

Accomplishments:

The MRI Project just began in July of 2003, after a change of PI and some refocusing of project goals. Currently, the project is conducting a detail trade-off study between image resolution and both the magnet bore size and strength subject to a weight constraint of less than 150 kg.

General Team Accomplishments:

The NSBRI Technology Development Team is characterized as an integrated, multidisciplinary group chartered to develop systems, instrumentation, devices, and algorithms. The accomplishments noted above provide a clear demonstration that this objective has been achieved. In addition to this, the project teams have demonstrated unique capabilities of being able to structure and accomplish complex applied research and development. An article describing the Technology Development Team activities was published in *Radiation Protection Dosimetry*. Some of the characteristics and accomplishments that cross project boundaries are:

- The capability to successfully conduct rapid system prototyping.

All of the Technology Development Team projects were successful in accomplishing the goal of developing and demonstrating prototype system implementations. A number of patent disclosures and/or applications have resulted from the developments. The ability to support the development of practical and useful tools in support of basic research requirements is a necessary element of a successful undertaking such as the NSBRI.

- The capability to transition developments to practical embodiments.

As an extension of the prior item, it is not sufficient to develop unique, one-of-a-kind prototypes. The developments must have practical means of supporting the basic research efforts by providing reliable and robust tools. The Technology Development Team projects have successfully demonstrated the ability to transition their developments to the real-world environment. For example, the AMPDXA scanner is ready to support human testing and commercialization efforts are underway. The SCAD system is ready for human testing and a prototype dynamic exercise device has been built.

- The capability to network and collaborate with NASA, the medical community, etc.

All of the Technology Development Team projects have established close and on-going interactions with NASA and the medical community. The interactions were initiated during the project proposal phase to assure that the intended development addressed a current space issue and was founded in a practical medical basis. The interactions have experienced positive growth and expansion throughout the research and development cycle. The result of the networking is that the resultant development products have validated utility to the space and medical communities. And, the networking within the communities has provided very good exposure and visibility for other applications and opportunities. A Technology Working Group meeting was held in January at the NSBRI retreat. At this meeting, over 35 opportunities for technology and instrument development were identified.

- The capability to produce quantifiable results to support countermeasures research.

The basic research programs of the NSBRI are charged with developing and evaluating countermeasures to the effects of long endurance exposure to microgravity. This effort requires that cause and effect relationships be identified and characterized. Proper characterization mandates that empirical data be referenced to a standard and be quantitative in nature. All of the Technology Development Team projects have achieved a level of standardization and quantitation that is necessary to support the basic research initiatives. In fact, some of the engineering models that have resulted from the team's activities exceed the accuracy and precision found in existing clinical and commercial systems (e.g., the AMPDXA and the SCAD).

Implications of Accomplishments

The seven active NSBRI Technology Development Team projects are making significant progress against their development goals. The three continuing projects have operating instruments, while the relatively new projects are in various phases of instrumentation development. For example, the two AMPDXA instruments (LTB and CTS) are operational and the CTS is being readied for human trials. In addition, commercialization discussions are underway to transfer the technology to industry. The neutron spectrometer is being readied for a high altitude balloon flight after completing several successful aircraft flight tests. The TOFMS has identified with high sensitivity several biomarkers associated with bone and muscle loss. The heavy ion microbeam and detector system has been designed and the detector fabricated. When completed, this resource will address several very current and significant issues in cellular biology. The SCAD system is operational and is performing correlation studies between measurements in the extremities and the weight-bearing bones. The bubble detection project has developed prototype equipment that has detected microbubble formation at various nucleation sites within the body. The DECD is in its second prototype design phase. Each of the projects and prototype instruments is addressing the major goals of the Technology Development Team, the NSBRI, and NASA by either developing research tools that facilitate the measurement and analysis of critical parameters necessary for the research of the other NSBRI teams or creating direct countermeasures to the risks encountered in long-duration spaceflight.

The Technology Development Team is constantly on the alert for technological developments and advancements (Goal 1) that will have impact on both the NSBRI and space life science research. For example, working closely with the Bone Team, the Technology Development Team was able to identify two major impediments to the development of countermeasures for bone demineralization: understanding of the bone mineral loss process and being able to monitor the instantaneous conditions of the subjects' bones. The TOFMS (Project No. 3) has been adapted to monitor the biomarkers for bone loss. While the TOFMS was developed under DARPA funding for solids analysis, newly invented methods of sample preparation and fixing techniques has allowed its applicability to biological specimen analysis. Historically, space-based monitoring of such biomarkers has typically relied on collection of specimens (urine, blood, etc.) and then storage of the specimens until Earthly return. Specimen analysis may, under good conditions, be completed many months after completion of the mission, but certainly does not afford the ability to provide closed-loop monitoring and control of countermeasures (Goal 2).

The AMPDXA project (No. 1) and the SCAD project (No. 5) specifically address the monitoring issue. Both these projects have completed engineering model instrumentation developments (Goal 2) and have demonstrated the ability to provide quantitative information that is critical to the current and future research of the Bone Team. These devices have been designed to be directly adaptable for in-space use. Size, weight, and power are currently, or soon will be, appropriate for routine launch and regular use on-orbit or in missions beyond Earth. Using advanced automation techniques (Goal 1), these devices and their associated analysis methods can be operated by individuals with very little training. Thus, the devices have broad utility in both space- and Earth-based applications.

The bone demineralization conditions that astronauts experience in space are similar to those that exist in clinical populations (e.g., age-related osteoporosis, quadriplegic, etc.) on Earth. Thus, the research supported by the AMPDXA, SCAD, and TOFMS is expected to have a direct positive influence on health care delivery on Earth (Goal 3). In addition, the technology itself has demonstrated better performance than commercially available devices. In particular, commercialization (Goal 4) of a clinical version of the AMPDXA is being pursued that has great potential to improve screening and treatment for age-related osteoporosis.

Muscle alteration research faces the same challenges of loss mechanism determination and monitoring as noted above for bone. Both the AMPDXA and TOFMS provide the same capabilities (i.e., monitoring and biomarker determination, respectively) in support of risk reduction for muscle as they do for bone. Advanced AMPDXA muscle algorithms (Goal 1), coupled with a radical new x-ray source (Goal 1), offer a promise of similar precision measurements of muscle as has been demonstrated for bone. The DECD (Project No. 7) offers the potential to directly countermeasure muscle loss in space (Goal 2).

Exposure to radiation in space is a threat that can lead to an increased risk of cancer and DNA damage. A significant portion of the exposure, between 30-60%, results from neutron sources that are extremely difficult to monitor, let alone characterize, in real-time. The absence of a portable, quantitative, real-time neutron spectrometer results in an exposure safety risk for astronauts (Goal 1). The Neuron Energy Spectrometer Project (No. 2) is developing a spectrometer (Goal 2) that can supply information on the neutron environment to the Radiation Effects Team in support of assessing radiation damage and cancer risk. The prototype of this unit is operational and has just completed several flight tests on F15 or F18 aircraft as well as long-duration, high-altitude balloon flight. The Ion Microbeam Project (No. 6) will address radiation damage at the cellular level.

Orthostatic intolerance can result in syncope when an individual is subjected to gravitational influence after exposure to microgravity. This situation can pose severe risks to astronauts who have to execute unassisted emergency procedures or extraterrestrial landings. The need to predict, prevent, or control orthostatic intolerance and its effects is significant to the space program. Both the TOFMS and the MRI project (No. 8) have the ability to provide near real-time monitoring of parameters related to orthostatic intolerance. The TOFMS can detect various heart-related biomarkers and the MRI will be able to monitor soft tissue, including vein and artery blood volumes and fluid shifts, in animals and potentially on the extremities of the astronauts.

To identify and appropriately fund these pipeline projects requires constant interaction between the NSBRI research teams and the Technology Development Team. To promote this integration, which satisfies much of Goal 5, the Technology Development Team established the Technology Working Group (TWG) as a formal mechanism for this liaison. Meetings of the TWG have been conducted frequently with expanded participation from academia, industry, and government. In addition, Technology Development Team participation in the annual retreats of the other teams also fosters cooperation and the synergism necessary to identify the technical requirements (Goal 1). Such input from NSBRI research teams, coupled with strong industrial and academic input, allows the Technology Development Team to develop calls for research that address technological solutions for the risk factors associated with long-duration spaceflight that are in concert with the established research goals of the other NSBRI teams. Part of the strategic growth plan for the Technology Development Team is the ability to direct key technology development efforts in addition to or in conjunction with the projects received in response to the research announcements. Such responses may leave gaps in the envisioned technology development requirements. A recent meeting of the TWG identified over 35 instruments or technology development needs of the space research community that are not currently being addressed by the NSBRI Technology Development Program. These gaps offer opportunities to foster important research that could accelerate the overall space effort. Support sources for such selected top-down driven research will have to be developed.

UB June 28, 2002

TO: U/Associate Administrator for Biological & Physical Research

FROM: UB/Acting Director, Bioastronautics Research Division

Chair, NSBRI Strategic Plan Peer Review Panel

SUBJECT: Completion of Peer Review of National Space Biomedical Research Institute (NSBRI) Strategic Plan

In their November 27, 2001 "passback," the Office of Management and Budget directed NASA to conduct a peer review and evaluation of NSBRI's Strategic Plan prior to providing any additional funds to the NSBRI. The December 2000 Site Visit of the NSBRI, conducted by the NASA Chief Scientist, also recommended that the NSBRI should prepare forward-looking Strategic Plan for NASA's review. NASA Headquarters received NSBRI's Strategic Plan and supporting documentation on May 28, 2002. This Strategic Plan and other background documents were provided to the members of a peer review panel chaired by Judith Vaitukaitis, M.D., (Director of the National Institute of Health's National Center for Research Resources). The members of the review panel are listed below.

Steve Beckwith, Ph.D., Director, Space Telescope Science Institute
Carolyn Huntoon, Ph.D., Former Director, NASA Johnson Space Center
Carol Scott-Conner, M. D., Ph. D., Head, Surgery Dept., University of Iowa
James Snow, M. D., Former Director, National Institute of Deafness and Communication Disorders
Frank Sulzman, Ph.D., Former Deputy Division Director, Life Sciences, NASA HQ
Judith Tintinalli, M. D., M. S., Chair, Emergency Medicine Dept. University of North Carolina, Chapel Hill
By telecon: Allan Tobin, Ph. D., Director, Brain Research Institute, UCLA (Chair, 2000 Chief Scientist NSBRI Site Visit Review Panel)

The charter for the review panel is enclosed as Attachment #1. The review panel met in Washington DC on June 10 –11, 2002 to evaluate the NSBRI's Strategic Plan. The consensus report of the committee is enclosed as Attachment #2. This report was provided to the NSBRI, which, in turn, provided a response plan (Attachment #3) back to NASA on June 21. NASA Johnson Space Center (JSC) also prepared a response (Attachment #4) to those panel recommendations that were directed to NASA as well as to the NSBRI. Both responses were given to the review panel with requests for comments or suggestions regarding the adequacy, appropriateness, or completeness of the NSBRI and NASA response plans. Four members of the review panel responded with written comments. On June 26, I held a teleconference with the Panel Chair to discuss the response plans and the panel member comments. Dr. Vaitukaitis agrees that the NSBRI and NASA JSC were responsive to the recommendations of the review panel. Her concurrence is provided below.

Some additional comments and suggestions arose during the panel member's review of the NSBRI and NASA JSC response plans. The first suggestion pertains to the term of appointment of the Director. It was noted that the recurrent one-year appointment of the Director with annual Board approval may be a significant deterrent for recruiting outstanding candidates. It was suggested that the NSBRI consider, say, appointing the Director for five years, with the first year or two being a conditional appointment so that the individual can be readily removed for lack of acceptable performance. One year may be insufficient for a provisional appointment to assess the creativity and leadership skills of the Director. It takes three to five years, and a Director willing to make difficult decisions, to develop strong programs. A longer tenure will not only provide continuity but also more likely provide strong leadership from an outstanding Director who holds a five-year renewable position. Second, some members of the panel wanted to reiterate and punctuate the panel's recommendation that the Institute needs to make real and measurable progress towards developing active interventions at higher Countermeasure Readiness Levels (CRLs). The NSBRI should develop tangible performance metrics in order to assess their progress in transitioning toward higher CRLs.

In general, it was the opinion of the panel members that NSBRI had fully and realistically addressed their concerns and recommendations and had put forth a response plan that would help NASA develop effective countermeasures for human space flight.

A number of the review panel's recommendations can only be accomplished over time. I will work with JSC and the NSBRI to ensure that the committee's recommendations are considered in good faith in decisions made over the upcoming years. The recommendation that "NASA should increase and stabilize the NSBRI budget" will require changes to our current plans. We should take these recommendations, together with the results of the Research Maximization and Prioritization (REMAP) task force, into account in our budget discussions this Summer.

Concurrence:

Guy Fogleman, Ph.D. Acting Director Bioastronautics Research Division	Judith L. Vaitukaitis, M.D. Director, National Center for Research Resources National Institute of Health

Enclosures

cc:
JSC/AA/J. D. Howell
SA/J. A. Rummel

Appendix E

Addendum

National Space Biomedical Research Institute
Annual Scientific and Technical Report
FY 2002

The following pages include a replacement index page for the Research Team Program Reports (Appendix F) and the Bone Loss Team Program Report received on November 25, 2002.

National Space Biomedical Research Institute
Research Team Program Reports
FY 2002

CONTENTS

Annual Report NSBRI Bone Team 2001-2002

Nov. 24, 2002

Team Leader: Jay R. Shapiro, M.D.
Uniformed Services University of the Health Sciences
Department of Medicine, A3060
4301 Jones Bridge Road
Bethesda, MD 20814-4799
Phone: 301-295-3600
FAX: 301-295-3557
jshapiro@usuhs.mil

Associate Team Leaders:
Susan Bloomfield, Ph.D., FACSM
Texas A & M University
College Station, TX 77843-4243
Phone: 979-862-1181
FAX: 979-847-8987
Sbloom@tamu.edu

Mitchell B. Schaffler, Ph.D.
Department of Orthopedics, Box 1188
The Mount Sinai School of Medicine
One Gustave L. Levy Place
New York, NY 10029
Telephone: 212-241-1625
FAX: 21-426-7750
Schafm01@doc.mssm.edu

TEAM PROJECTS

Leptin as a Regulator of Bone Formation in Microgravity Bone Loss:

Gerard Karsenty, M.D.
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030
Phone: 713-798-5489
FAX: 713-798-1465
Karsenty@bcm.tmc.edu

Therapeutic Modulation of Systemic Glucose-dependent Insulinotropic Peptide Levels to Counteract Microgravity-induced Bone Loss

Carlos M. Isales, M.D.

Institute of Molecular Medicine & Genetics
Medical College of Georgia
1120 15th Street/CB2803
Augusta, GA 30912-3260
Phone: 706-721-0692
FAX: 707-721-7915
Cisales@mail.mcg.edu

Receptor Countermeasures to Bone Loss in Microgravity

Carolyn L. Smith, Ph.D.
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030
Phone: 713-798-6235
FAX: 713-790-1275
Carolyns@bcm.tmc.edu

Muscle Bone Imbalance After Non-weightbearing

Susan Bloomfield, Ph.D., FACSM
Texas A & M University
College Station, TX 77843-4243
Phone: 979-862-1181
FAX: 979-847-8987
Sbloom@tamu.edu

A Biomedical Countermeasure for Disuse Osteopenia

Clinton T. Rubin, Ph.D.
Center for Biotechnology & program in Biomedical Engineering
Psychology-A Bldg, 3rd Floor
State University of New York at
Stony Brook, 11794-2580
Phone: 631-632-1188
FAX: 631-632-8577
Clinton.rubin@sunysb.edu

Resorption Suppression and Bone Health in Disuse Bone Loss

Mitchell B. Schaffler, Ph.D.
Department of Orthopedics, Box 1188
The Mount Sinai School of Medicine
One Gustave L. Levy Place
New York, NY 10029
Telephone: 212-241-1625
FAX: 21-426-7750
Schafm01@doc.mssm.edu

The Effect of Microgravity on Fracture Healing/Ultrasound as a Possible Countermeasure

Mark E. Bolander, M.D.
Orthopedic Research
Mayo Clinic
200 First Street
Rochester, MN 55905
Phone: 507-284-2266
FAX: 507-284-5075
Bolander.mark@mayo.edu

Defining and Preventing Bone Loss: A Microgravity Model

Jay R. Shapiro, M.D.
Uniformed Services University of the Health Sciences
Department of Medicine, A3060
4301 Jones Bridge Road
Bethesda, MD 20814-4799
Phone: 301-295-3600
FAX: 301-295-3557
jshapiro@usuhs.mil

Prevention of Microgravity-Induced Stone Risk by KmgCitrate

Joseph E. Zerwekh, Ph.D.
Department of Internal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd
Dallas, TX 75390-8885
Phone 214-648-3872
FAX: 214-648-2526
Joseph.zerwekh@emailswmed.edu

I ABSTRACT

The NASA Critical Path roadmap for Bone includes four areas of primary concern for astronaut health and mission success: 1) progressive bone loss, 2) quantifying fracture risk and promoting fracture healing, 3) connective tissue injury affecting ligament, tendon, and intervertebral disc, and 4) renal stone formation. The delay in the return of bone mass following return to earth's gravity is also of concern because of the potential short-, and long-term impact on skeletal integrity as Astronauts age. These concerns are as applicable to the health of individuals on earth as they are to Astronauts during and after spaceflight.

The development of effective countermeasures to each of the Critical Path factors depends on an understanding of the complex mechanisms that promote bone loss during prolonged exposure to weightlessness. To achieve this goal the Bone Team program includes both basic (CRL level 2) and applied (CRL levels 6) research studies involving nine principal investigators and their collaborators. During the past year efforts have been made to expand interactions between team members as well as with counterparts at the Johnson Space Center with the goal of achieving operational status for certain of these projects.

Each principal investigator has reported significant research advances aimed at countermeasure development and testing during the past year.

- The Karsenty group (Baylor) has demonstrated that the sympatheteic nervous system is the mediator of leptin anti-osteogenic function and that β–blockers, a class of sympathetic nervous system inhibitors, can prevent the occurrence of osteoporosis in ovariectomized mice.

- Isales (Univ. Georgia) has utilized experiments involving three models: (1) Human; a pilot cross-sectional study taking forty normal volunteers and measuring a number of hormones including GIP and bone density, found that GIP levels were positively correlated with BMD. Also, over expression of GIP in transgenic mice is associated with increased bone density.

- Hormonal regulation of bone cell differentiation and bone resorption has been advanced by the finding that the vitamin D agonist EB 1089 increases cancellous bone mass without causing hypercalcemia. Also, that the SERM raloxifene increases bone mass in male rats. (Smith, Weigel , Baylor)

- Bolander (Mayo Clinic) reports expected rates of fracture healing in hindlimb suspension rats vs controls. However, the smaller fracture calluses observed in HLS animals was associated with decreased formation of subperiosteal bone and cartilage.

- Bloomfield (Texas A & M) have developed an animal model to study muscle and bone reconstitution after mechanical unloading. Results indicate that following mechanical unloading there is a significant mismatch of bone strength

when muscle strength has fully recovered. This will which will permit testing of countermeasures PTH and growth hormone.

- Schaffler (Mt. Sinai) has observed that the bisphosphonate risedronate may not fully protect against bone loss in the immobilized limb- canine model of disuse osteoporosis

- The response to a countermeasure will in part and a potential countermeasure, vibratory mechanical loading, has been investigated by Rubin et al. (Stony Brook) who have explored the activation of bone genes responsible for the maintenance of bone mass following the use of vibratory mechanical stimuli (Rubin).

- The Rubin group has received funding for the development of a prototype vibrational instrument suitable for flight testing.

- Studies in spinal cord injury subjects confirm the utility of this model as a surrogate for bone loss experienced during spaceflight (Shapiro, Uniformed Services University). Radiographic studies point to deficient periosteal bone formation in weightlessness . Bisphosphonate treatment is a potential countermeasure to bone loss. Zoledronate, a novel potent IV bisphsdophonate, is being administered to spinal cord injury subjects in a double blind placebo controlled study.

- Zerwekh (Texas Southwestern, Dallas) has used chronic bed rest to demonstrate the effectiveness of KMgCit in lessening the risk of renal calculi in healthy volunteers.

II INTRODUCTION

Function of the musculoskeletal system is uniquely dependent on Earth's gravity. Although the remarkable adaptive ability of humans to the microgravity environment has allowed astronauts to maintain overall function, the musculoskeletal system rapidly degrades once the force of gravity is removed. Muscle atrophy has been documented by biopsy after 11 days in flight. Muscle strength is significantly impaired. This loss of mechanical strain rapidly indices cortical and trabecular bone loss, which increases the risk of fracture. The mechanisms relating muscle loss to increased bone resorption are unknown.

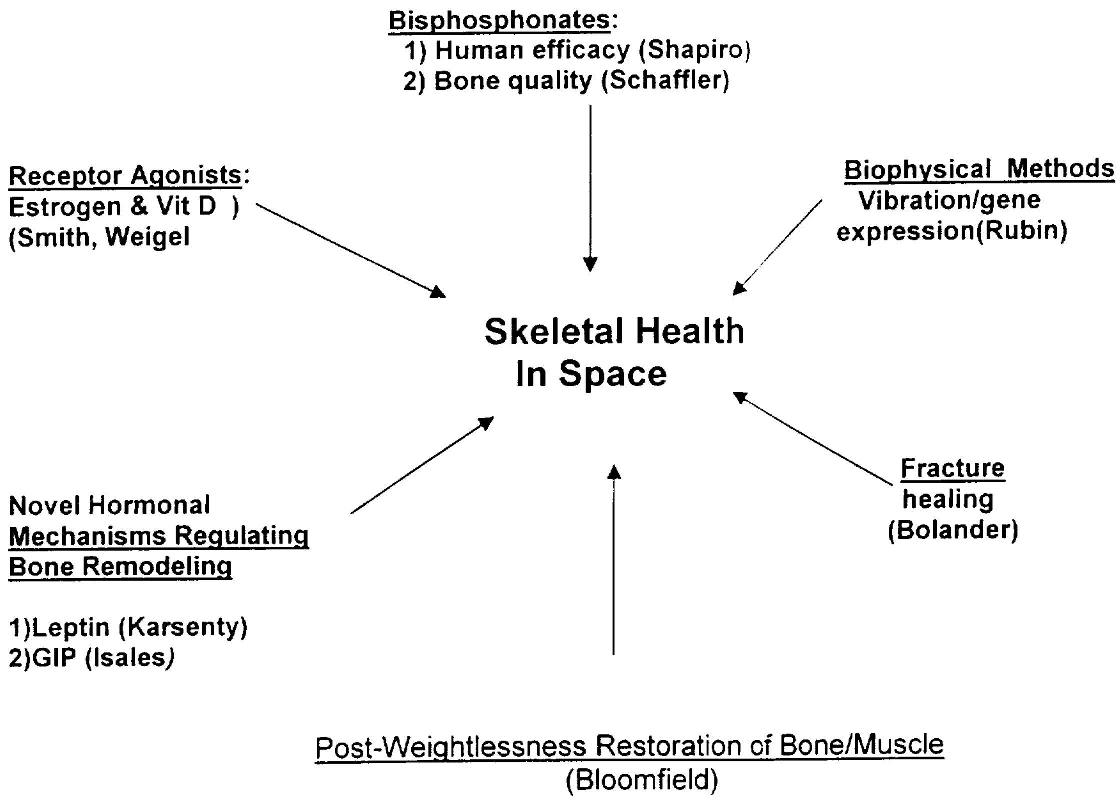
American and Russian studies have demonstrated that bone loss during flights lasting 4 to 6 months approximates 1-2% per month. However, researchers have reported the range of bone loss in Mir cosmonauts varies from 0% to 24% per month when measured by pQCT technology in cancellous and cortical bone in the tibia. Bone loss of this magnitude has been observed in human bed rest studies and in recently individuals following spinal cord injury (vide infra). The loss of bone mass compromises bone strength, and increases the risk of fracture. Attempts are in progress to model the risk of fracture after extended duration spaceflight as might occur on the Mars surface. It is likely that fracture risk would increase 2.5 fold for each decrease of 1 standard deviation (SD) from the young adult peak bone mass. After a 6 month voyage a 15% loss of bone in the femur neck could represent a 5-10 fold increase in fracture risk for astronauts starting to work on the surface of Mars.

We have virtually no information about the healing processes that would follow a fracture or tissue-based measures such as the application of growth factors that could be used on-site to promote fracture healing. A related issue involves the appropriate orthopedic measures for treating the fracture. We know that flight crews commonly experience back pain secondary to altered intervertebral disc mechanics during weightlessness. The Bone Team has not been successful in advancing research about back pain after microgravity exposure, nor is research involving the cartilage response to microgravity being currently funded by NSBRI. This reflects a paucity of laboratories focused on this question. A countermeasure for the prevention of renal calculi is now under study, and this parallels investigations in renal stone prevention being carried out by Astronaut Peggy Whitson in the ISS.

The NSBRI Bone Loss Team aims to: 1) advance our understanding of the mechanisms involved in bone loss and connective tissue injuries, and, 2) the group aims to develop an effective countermeasure to bone loss. Countermeasures utilized by NASA to date, including in-flight exercise regimens and novel exercise hardware, dietary and vitamin supplements, and pre-flight conditioning, have not prevented bone loss during long duration flights. Exercise regimens and exercise instrumentation are currently being tested in-flight on ISS. Pharmacological interventions are also under investigation but have not advanced to operational status pending the outcome of earth studies. It is anticipated that an effective countermeasure program to prevent bone loss will combine resistive exercise and an anti-resorptive pharmacological agent. Other agents may be more suitable in the future.

As discussed below, progress in these areas will require a better understanding of the basic mechanisms that alter bone cell function in a microgravity environment. The current Bone Team research program includes basic and applied research targeted at countermeasure development. As a group, the projects focus on issues relevant to mechanisms of bone loss, fracture healing, the problem of the delay in recovery of bone strength after weightlessness, as well as, means that may be employed in the near future to mitigate the negative effects of microgravity on bone cells. It is obvious that research which is applicable to astronauts, will also be of use to earth-bound individuals in non-weightbearing situations (nursing home residents, the chronically ill, children and adults facing chronic immobilization following trauma).

III Research Program, Structure and Design



IV RESEARCH PROGRAM ACCOMPLISHMENTS

Publications related to these studies are indicated by ** at the end of each summary. Countermeasure Readiness Levels are indicated (CRL)

1. Karsenty (Baylor): Leptin as a Regulator of Bone Formation in Microgravity Bone Loss: CRL 3

This study demonstrates a leptin-dependent neuronal regulation of bone formation with potential therapeutic implications for osteoporosis during and after spaceflight. We previously showed that leptin inhibits bone formation by an undefined mechanism

Leptin produced by fat cells is a powerful inhibitor of bone formation. In the last year we have continued our work on the mechanisms whereby leptin inhibits bone formation. To that end we have identified hypothalamic neurons required for this function. We show that hypothalamic leptin-dependent anti-osteogenic and anorexigenic networks differ, and that the peripheral mediators of leptin anti-osteogenic function appear to be neuronal. We have shown that following leptin binding to its hypoathalmic receptors the mediator of leptin antiosteogenic action is of neuronal nature. We demonstrated that the sympatheteic nervous system is the mediator of leptin antiosteogenic function. Neuropeptides mediating leptin anorexigenic function do not affect bone formation. Leptin deficiency results in low sympathetic tone, and genetic or pharmacological ablation of adrenergic signaling leads to a leptin-resistant high bone mass. β-adrenergic antagonist increases bone mass and can prevent the occurrence of osteoporosis in in wild-type and ovariectomized mice. This could be of therapeutic use to increase bone formation in bone loss conditions. None of these manipulations affects body weight.

**S. Takeda, F. Elefteriou, R. Levasseur, X. Liu, L. Zhao, K. L. Parker, D. Armstrong, P. Ducy and G. Karsenty. Leptin regulates bone formation via the sympathetic nervous system, Cell (November 1), 111:305-317, 2002

2. Carlos M. Isales, M.D. Therapeutic Modulation of Systemic Glucose-Dependent Insulinotropic Peptide Levels to Counteract Microgravity-induced Bone Loss CRL 3

During the last year my laboratory has worked with the enteric hormone, glucose-dependent insulinotropic peptide (GIP), secreted from the small intestine in direct response to nutrient intake. Our hypothesis is that GIP might be an important hormonal link between nutrient ingestion and bone formation and that by therapeutically elevating GIP levels, coupled with strict dietary control, it will be possible to mitigate the impact of microgravity. Current experiments involve three models: (1) Human; we have done a pilot cross-sectional study taking forty normal volunteers and measuring a number of hormones including GIP and bone density. We found that GIP levels were positively correlated with BMD (rho=0.29, p=0.07). Fat mass was also evaluated and was found to be correlated with BMD (rho=0.16, p=0.02) & BMC (rho=0.20, p=0.003), while leptin was not significantly associated with BMD (rho=0.11, p=0.12) or BMC (rho=0.006, p=0.93). This study is now being extended to include 100 subjects which will permit subgroup analysis including race, gender and age. A second set of human experiments involves measurement of GIP levels under simulated microgravity in collaboration with Dr. Joe Zerwekh at UT Southwestern. So far only two samples have been processed so analysis of the results is pending. (2) GIP overexpressing transgenic mice were found to have a higher basal bone mass. These mice have an inducible metallothionein promoter. Interestingly, if they are fed zinc for a prolonged period of time (to induce expression) we can get down regulation of the GIP receptor and a drop in bone density. Nevertheless if these mice are placed on a low calcium diet they will not lose bone mass while control mice bone density will drop (see figure) (3) GIP receptor knockout mice. We obtained these mice from Japan where they were being used for studies on the role of GIP in Diabetes Mellitus type II. We have found that these mice have a 13% lower basal bone density that control mice. Taken together these data demonstrate that GIP plays an important role in coupling nutrient intake to bone formation. Whether GIP will be as effective in preventing bone loss associated with microgravity is not yet known and will be the focus of experiments in the 2003 funding cycle.

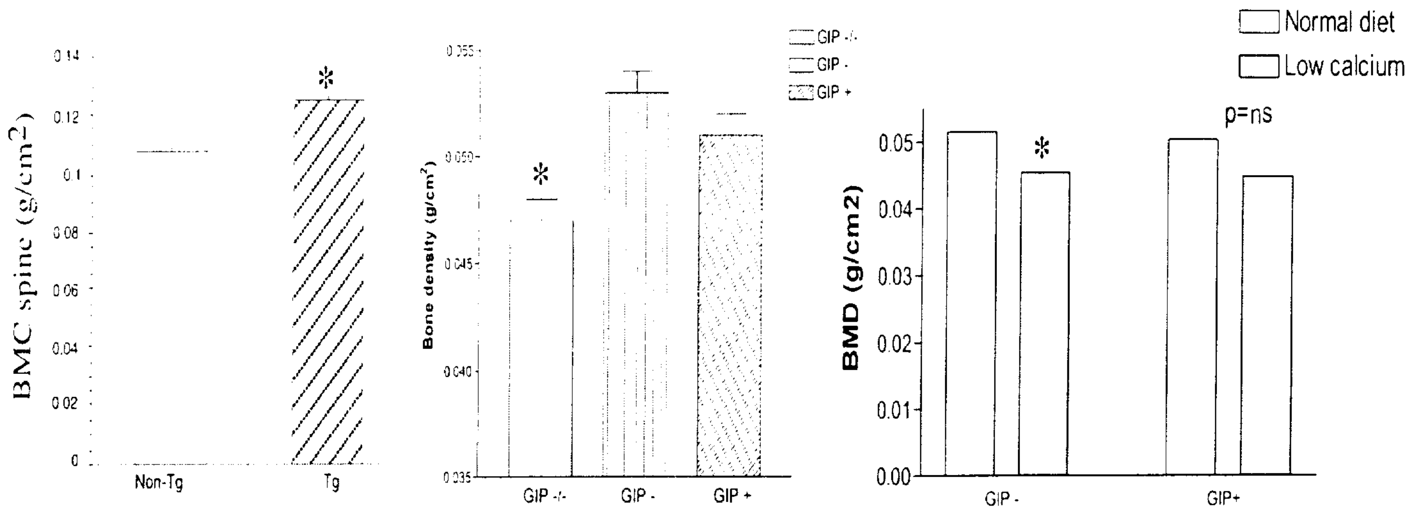


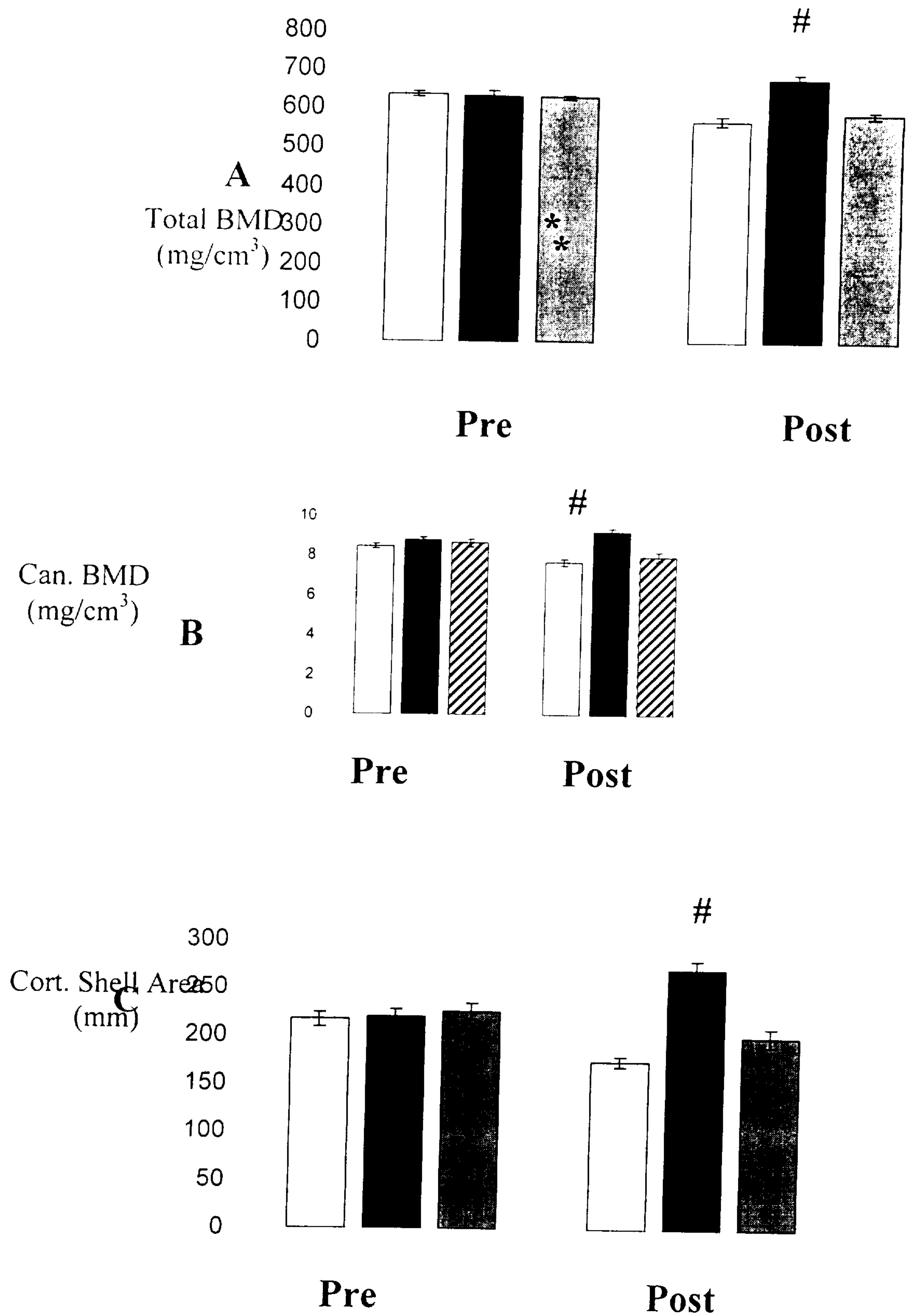
Figure legend: A: basal bone densities for transgenic GIP over expressing mice. Transgenic mice given zinc had receptor down regulation and lower bone density vs. controls before zinc. B: Bone densities for transgenic mice given zinc (notice receptor downregulation) or GIP receptor knockout mice. C: GIP overexpressing mice given zinc did not lose bone when placed on a low calcium diet.

3. Receptor Countermeasures to Bone Loss in Microgravity , Carolyn L. Smith, Ph.D., Nancy Weigel, Ph.D.(Baylor College of Medicine) CRL 3.

Receptor Countermeasures to Bone Loss in Microgravity (Smith, Weigel) Spaceflight is associated with decreased gonadal steroid levels and 25(OH) D and 1,25(OH)D2 levels. This study examines specific pharmacological alternatives, estrogen and vitamin D receptor agonists, as countermeasures to bone loss. These studies focus on novel vitamin D receptor agonists (VDR) such as EB189 and selective estrogen receptor modulator agents (SERMs) such as raloxifene. This study targets the ability of novel receptor agonists of the vitamin D receptor and estrogen receptor alone or in combination to modulate osteoblastogenesis, mature osteoblast function and osteoclastogenesis in vitro and in vivo. The study currently addresses these effects on preserving bone mass in the hindlimb suspended rat model of microgravity. Attenuation of disuse bone loss by estrogen and raloxifene in the hind limb suspended rat has been demonstrated. Altered osteoblast differentiation and preservatgion of bone mass during hindlimb suspension has been demonstrated using VDR agonists.

Hormonal alterations during spaceflight impact bone remodeling and potentiate bone loss. These changes assume greater significance as extended microgravity exposure is anticipated. Understanding the cellular mechanisms responsible for these changes are basic to defining and suggesting effective countermeasures to hormonal imbalance and thus bone loss. Flight testing with animal models is critical to correcting hormonal perturbations secondary to microgravity. This project addresses countermeasure development involves receptor agonists used during spaceflight to correct gonadal/vit D inbalance.

** SA Bloomfield, MR Allen, C Nolan, CL Smith, Attenuation of disuse Bone Loss by Estrogen and Ralixifene in Mature Male Rats. J Bone Mineral Res. 17: Suppl 1, S-433, 2002.



pQCT Analysis of Proximal Tibia. Total (A), trabecular (B) and cortical shell area (C) were measured at proximal tibia before and after 28 days of hindlimb unloading and treatment with vehicle (open bars), 1,25D (filled bars) or EB1089 (stripped bars) in five month old male rats. '*' indicates significance at $p<0.05$ from pre-suspension values, and '#' indicates significance at $p<0.05$ from vehicle treated post-suspension values.

4. The Effect of Hindlimb Elevation on Fracture Healing. Bronk, JT, Bolander, ME (Mayo Clinic) CRL 3.

Decreased bone formation in the microgravity environment could result in delayed healing and failure of the bone to return to normal strength at the conclusion of fracture repair. To address these issues we evaluated femoral fracture healing in rats undergoing hindlimb suspension. Ultrasound is the potential countermeasure evaluated for its effect on fracture healing.

Unilateral midshaft femur fractures were made in 180 six-month-old, male, Lewis rats using the Bonnares-Einhorn technique. All studies were approved by the institutional IACUC. Animals were randomly assigned to one of two groups (90 per group). The day after fracture rats in one group were made non-weight-bearing by hindlimb suspension (HLS). The remaining animals were allowed to bear weight normally (WB). Animals were sacrificed at one, two, three, five, seven, and nine weeks after fracture for histology (n=5/group) and at three, five, seven and nine weeks after fracture for mechanical testing (n=15/group). Weekly radiographs were obtained to assess callus formation and bone bridging.

The evaluation of weekly radiographs showed progressive callus formation in both groups. Calluses in WB animals were larger than in HLS animals at all times after fracture. Bone bridging was seen earlier on radiographs of HLS animals: at three weeks 60% of calluses in HLS animals were bridged compared with none in the WB group; at five weeks bridging was seen in all radiographs of HLS animals and in 70% of WB animals. At seven and nine weeks all HLS fractures appeared healed on radiographs. Force to failure, energy absorption and stiffness were equal in the two groups seven and nine weeks after fracture. Energy absorption was significantly increased in WB animals at three weeks, while force to failure and stiffness were significantly increased in HLS animals at five weeks.

Histologic analysis showed subperiosteal bone formation, chondrogenesis, and endochondral ossification in all calluses two and three weeks after fracture. Five weeks after fracture in WB animals the gap between the bone ends was filled with cartilage or a combination of fibrous and cartilage tissues. By nine weeks after fracture endochondral bone formation bridged the fracture gap in all WB animals. The smaller fracture calluses in HLS animals was associated with decreased formation of subperiosteal bone and cartilage.

Within the limits imposed by the schedule chosen for the histological studies, the histology data did not suggest a difference between HLS and WB animals in the initiation of subperiosteal bone and cartilage formation in the callus. Alternatively, histology studies did suggest either decreased formation rates and/or earlier termination of subperiosteal bone and cartilage formation in calluses from HLS animals, suggesting that HLS led to a decreased stimulus to form these tissues in the callus. Likewise, earlier completion of endochondral ossification in calluses from HLS animals appeared to be due to the smaller mass of cartilage undergoing endochondral replacement, but we cannot comment rule out a difference in the rate of endochondral bone replacement. We presume that differences between radiographs and histology in the number of fractures from WB animals with bridging bone at five weeks (70% vs 0%) are due to the presence of calcified cartilage in the fracture gap, which would not be seen on histology.

Relatively equal mechanical properties seven and nine weeks after fracture, together with bone bridging on histology, are consistent with complete healing of fractures in both treatment groups. Increased stiffness and force-to-failure in the five week HLS callus indicates that earlier formation of bridging bone at the fracture site increased the mechanical properties of the callus, even in calluses that were significantly smaller.

Based on these studies we postulate that repair of bone injury in hindlimb suspended animals is regulated differently than in weight-bearing animals. Hindlimb suspension leads to decreased cartilage formation and a smaller callus. Decreased cartilage formation did not, however, lead to decreased callus strength or to impaired fracture healing. Although less cartilage is formed, cartilage maturation is completed sooner after fracture, and those events that occur subsequent to cartilage formation, i.e. endochondral ossification and bone bridging, also occur sooner and are completed more rapidly. Indeed, earlier bone bridging in a smaller callus was associated with increased force to failure and increased stiffness (but not increased energy absorption) in the callus.

**The use of low-intensity ultrasound to accelerate the healing of fractures. J. Bone and Joint Surgery Am 83-A 259-270, 2001

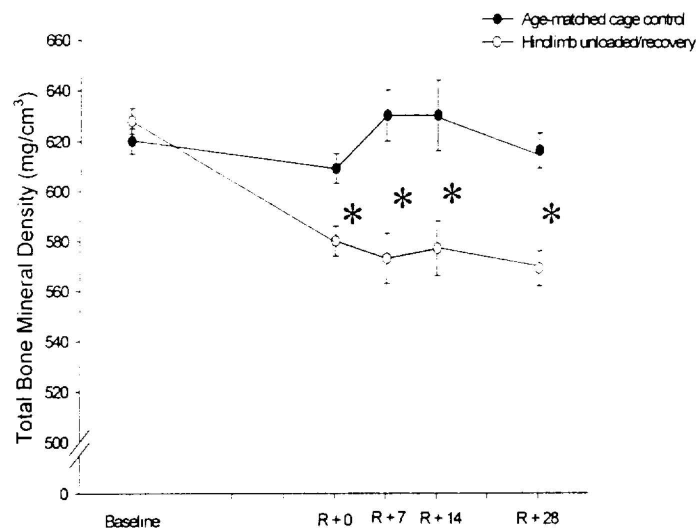
4. Muscle Bone Imbalance After Non-Weightbearing: Susan Bloomfield, Ph.D., (Texas A & M Univ.) CRL 3

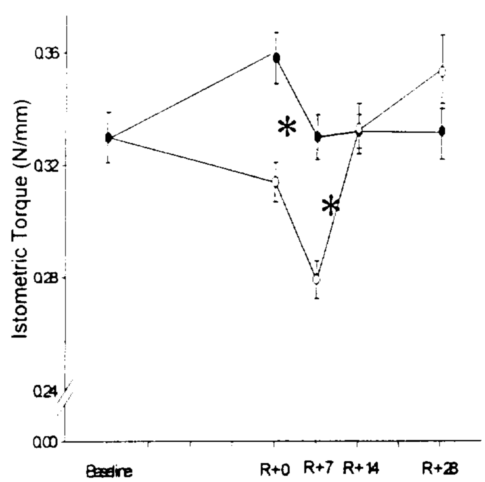
This study utilizes the hind limb suspended rat model to examine: 1) the time course of recovery of functional properties in a muscle bone pair of the hindlimb during reambulation after 28 days of skeletal unloading, 2) the mechanisms affecting the rate of recovery during periods of maximal mismatch between muscle and bone functional properties, 3) the effectiveness of two exercise regimens and a biomechanical intervention to promote return of bone strength during recovery, 4) the effectiveness of PTH treatment and growth hormone treatment as anabolic countermeasures during recovery.

The major findings thus far from our bone/muscle recovery project are depicted in the graphs below. In summary, proximal tibia total bone mineral density (BMD) and plantar flexor isometric muscle torque, the major muscle group inserting at the proximal tibia, are significantly reduced after 28 days of hindlimb unloading (HU). Although muscle strength is further depressed during the initial recovery period (R+7), it returns to control levels by R+14. Proximal tibia BMD, however, remains depressed through R+28, at levels similar to those after 28d of HU. This results in a significant mismatch of muscle:bone strength after R+14, when muscle strength has fully recovered. Ongoing studies are focused on using both mechanical (exercise) and pharmacological interventions to increase the rate of bone recovery, in an attempt to minimize the mismatch of muscle/bone following long-term unloading.

** Bloomfield SA, Allen MR, Hogan HA, Delp MD. Site- and compartment-specific changes in bone with hindlimb unloading in mature adult rats Bone 31: 149-157, 2002

** Allen MR, Bloomfield SA. Hindlimb unloading has a greater effect on cortical compared to cancellous bone in mature female rats. J App: Physiol 18: 2002 (epub ahead of print).





The major findings thus far from our bone/muscle recovery project are depicted in the above graphs. In summary, proximal tibia total bone mineral density (BMD) and plantar flexor isometric muscle torque, the major muscle group inserting at the proximal tibia, are significantly reduced after 28 days of hindlimb unloading (HU). Although muscle strength is further depressed during the initial recovery period (R+7), it returns to control levels by R+14. Proximal tibia BMD, however, remains depressed through R+28, at levels similar to those after 28d of HU. This results in a significant mismatch of muscle:bone strength after R+14, when muscle strength has fully recovered. Ongoing studies are focused on using both mechanical (exercise) and pharmacological interventions to increase the rate of bone recovery, in an attempt to minimize the mismatch of muscle/bone following long-term unloading.

4. Resorption Suppression and Bone Health in Disuse Osteoporosis : MB Schaffler, Ph.D. (Mt. Sinai Medical School) CRL 4

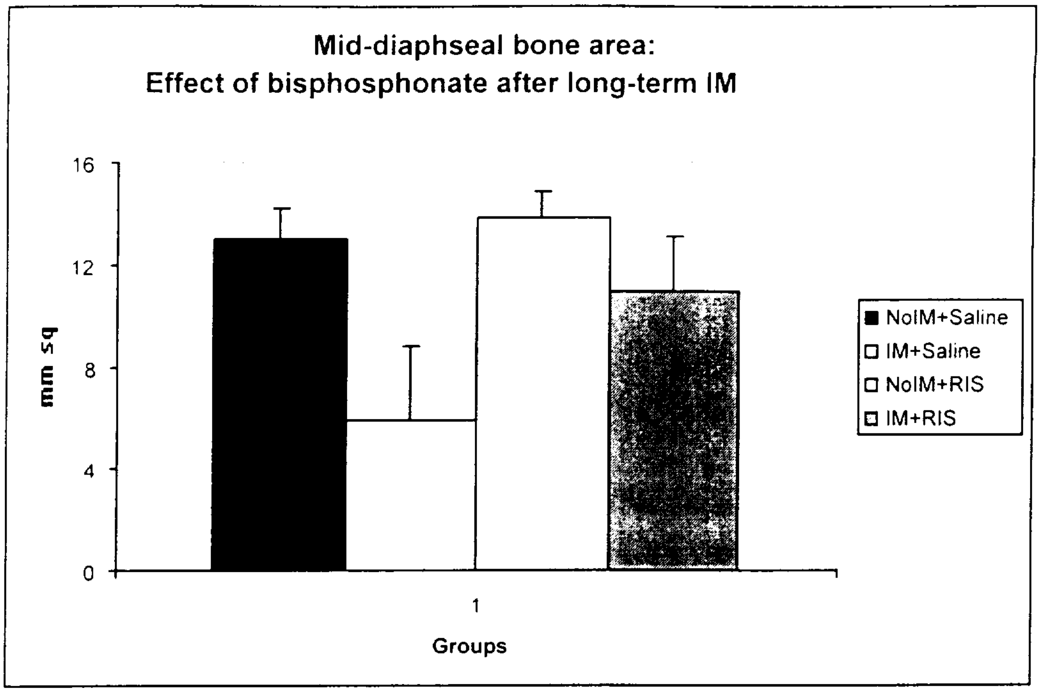
These experiments test the hypotheses that: 1) Long-term suppression of bone remodeling in disuse will successfully maintain bone mass, microarchitecture, stiffness and strength, but will result in compromised fracture resistance properties; and 2) Decreased mechanical usage in the presence of an antiresorptive agent results in loss of osteocyte integrity and accumulation of bone with impaired viability. In order to test these hypotheses, we have undertaken a series of long-term immobilization experiments, using a canine model with bisphosphonate treatment to prevent bone loss.

To date, we have completed the immobilization experiments for all animals. Single limbs immobilization experiments of 12 months duration have now been completed for retired breeder (N-32, 5-7 years old) Beagle dogs. The clinically-use bisphosphonate, risedronate, (Actonel, Proctor and Gamble Pharmaceuticals) was employed as the antiresorptive agent. Four experimental groups were examined: IM+RIS; IM+Vehicle; NoIM+RIS and NoIM+Vehicle. Bisphosphonate-treated animals were dosed at 1 mg/kg body weight; this dose is 5-10 times that used to prevent osteoporotic bone loss in humans. All in vivo experiments were recently concluded. In collaboration with Dr. Susan Bloomfield, at Texas A&M University, pQCT studies were recently completed for metacarpal bones. Histological, microCT and mechanical testing studies of bones are currently ongoing.

Key findings to date suggest that bisphosphonate treatment during long-term immobilization *attenuated, but did not eliminate bone loss*. The effect was greater in diaphyseal cortical bone, in which risedronate treatment resulted in approximately 15 percent loss of bone mass with long-term immobilization, compared to untreated, immobilized animals that almost 50 percent of their cortical bone mass. The data are summarized in Figure 1:

** Vashishth D, Gibson G, Kimura J Schaffler MB Fyhrie DP. Determination of bone volume by osteocyte population Anat Rec. 267: 292-5, 2002.

** Vashishth D, Verborgt O, Schaffler MB, Fyhrie DP. Decline in osteocyte lacunar density in human cortical bone is associated with accumulation of microcracks with age. Bone 26: 375-80, 2000



In cancellous bone of the epiphyseal-metaphyseal region, bone density declined 25% in risedronate treated, immobilized animals compared to approximately 50 percent decline in bone density in non-treated, immobilized limbs. Data from these studies suggests that the response of immobilized bones to bisphosphonates in more complicated than expected. Risedronate attenuated did not eliminate bone loss over the long term, as expected from metabolically driven bone loss (menopause, ovariectomy, glucocorticoids,etc). The precise reasons for this are unclear at this time.

6. A Biomedical Countermeasure for Disuse Osteopenia: Clinton T. Rubin, Ph.D. (Stony Brook) CRL 7

Vibrational mechanical stimulation increases bone mass in humans and rodents. Using the mouse as a model, it is clear that the genetic make-up of the animal is a strong determinant of their sensitivity to mechanical stimuli. Adult (16 week) female 16wk old C57BL/6J (low density), BALB/cByJ (medium density) and C3H/He (high density) mice were assigned to control, low-level mechanical stimulation, and disuse groups (n=13 each). Mice in the mechanically stimulated group were placed on a vibrating plate (45 Hz, 0.25g) for 10 min/d. Disuse animals were subjected to tail suspension. Four animals per group were culled 4d into the protocol for determining gene expression levels (semi-quantitative RT-PCR) while the remaining animals were sacrificed after 21d for the assessment of bone formation. Disuse failed to affect histomorphometric indices in C57BL/6J mice. In BALB/cByJ, mechanical stimulation increased bone formation rates by 34% ($p<0.02$), but bone volume was unaffected.

This increase in bone formation rate was primarily achieved by an increase in the ratio of double labeled surface to single labeled surface (+101%, $p<0.001$). Disuse in the BALB/cByJ mice suppressed bone formation rates by 48% ($p<0.01$), the ratio of double labeled surface to single labeled surfaced by 47% ($p<0.01$), and mineral apposition rates by 45% ($p<0.03$), resulting in trabecular bone volume that was 43% smaller ($p<0.01$) compared to control BALB/cByJ's. In contrast to the responsiveness of the skeleton of C57BL/6J and BALB/cByJ mice, no significant effects of mechanical stimulation or disuse were measured in tibial trabecular bone of C3H/HeJ mice.

7. Defining and Preventing Bone Loss: J.R. Shapiro (Uniformed Services University) CRL 7

The objectives of this program are: 1) to evaluate the spinal cord injured subject as a model for the rate and pattern of bone loss that occurs during spaceflight, and 2) to prevent bone loss with a new potent long-acting bisphosphonate, zoledronate. .Muscle loss in the femur is measured as is hip architecture by CT used in 3D finite element analysis of fracture risk. Zoledronate, a third generation bisphosphonate administered over 15 minutes has been shown to be effective for one year in published osteoporosis studies. This is a double blind randomized trial so that therapy effects will not be available until the study is un-coded.

Although only 50% of the study size has been entered, the results are significant to the extent that they show that SCI and microgravity exposure have similar effects on a number of measured parameters of bone. These are determined from DXA scans of the femur (T. Beck) and include femur cross sectional area, bone width as an indicator of periosteal bone growth, buckling ratio and section modulus and indices of bone strength. Muscle mass is measured by femur shaft CT. This shows muscle loss of approximately 2%/month in SCI in the mid femur which simulates bone loss during spaceflight.

The preliminary results indicate a deficient periosteal bone growth in subjects with decreased cortical thickness and bone loss seen in both SCI and Mir Cosmonauts. This pattern differs from that of normal aging. The study points to the putative role of periosteal bone formation as protective of fracture in subjects in weightless conditions. It is noted that depressed periosteal bone formation has been observed in rats following spaceflight. Decreased expression of bone matrix genes and growth factors has been observed in periosteal tissues recovered from rats following spaceflight. The results to-date, point to the need for defining new exercise programs and pharmacological agents to maintain periosteal bone formation and to diminish net bone loss.

**Shapiro JR. Patterns of femoral neck bone loss in spinal cord injury and spaceflight. J Bone Mineral Res. 17: suppl 1, S 434, 2002.

**Shapiro, JR, Gallaher, R, Schneider VS. Spaceflight and Bone Loss. Military Medicine (In press)

9. Zerewekh, J.: Prevention of Microgravity-Induced Stone Risk by KMgCitrate.: (UT Southwestern Medical Center at Dallas): CRL 7.

Renal calculus formation has occurred in cosmonauts, and this study addresses Critical Path Goal 4, Reduce risk of Renal Stone Formation. KMgCit is currently under consideration or in use for flight testing. KMgCit may offer additional benefits now under study in the bed rest model. Flight-testing is appropriate for this agent

The objective of this research study is: 1) to determine the effectiveness of potassium magnesium citrate (KMgCitrate) as a countermeasure to the propensity for stone formation and skeletal mineral loss sustained during spaceflight, 2) to evaluate the effect of KMgCit in averting the diminished muscle Mg and K concentrations that may occur during microgravity-related muscle atrophy, and 3) to assess the efficacy of KMgCit supplementation in reducing microgravity-induced increase in bone resorption and urinary calcium. These specific aims are studied in healthy volunteers on chronic bed rest for 5 weeks. Study phases include 1 week of ambulatory evaluation (A), 2 weeks of bed rest (weeks 2-6) (B) and 2 weeks of reambulation (weeks 7-8) (C). Subjects receive Relyte tablets, 3 tabs with breakfast, and 3 with dinner to equal 42 mEq K, 21 mEq Mg, and 63 mEq citrate. Placebo controls are included in the study design.

This study is in progress. Results of biochemical testing to date indicate significant increase in urine calcium, citrate, phosphate and magnesium which may be impacted by administration of KMgCit. Muscle biopsies during treatment are under study.

** Zerwekh J. Nutrition and renal stone disease in space. Nutrition, 18: 857, 2002

Summary and Directions: The Bone Team research projects will enter year 03 of the current funding cycle. The projects represent basic and applied studies, which range between CRL 3 and 7. It is anticipated that advancement in CRL will occur as soon as funding constraints are resolved and the schedule of flight opportunities is such as to permit consideration of animal or human testing of countermeasures. To this end, a Bone Team strategy document will be developed at the Bioastronautics meeting to be held in Jan. 2003 (Galveston).

Vibrational mechanical loading is currently in progress for flight implementation. Bisphosphonate treatment as a preventive measure for bone loss on 4-6 month flight is also a high priority issue.

Appendix G

National Space Biomedical Research Institute

RETREAT
January 14-17, 2002
Del Lago Conference Center
Montgomery, Texas

AGENDA

Monday, January 14

ALL PLENARY SESSIONS HELD IN TEJAS II

8:00 a.m.	Introductory Remarks	J. Sutton
	• Welcome	B. Alford
	• Retreat Objectives	J. Sutton
9:00	Bioastronautics Update	D. Williams
10:00	BREAK	
10:30	Neurovestibular Team Presentation	C. Oman
11:00	Neurobehavioral & Psychosocial Team Presentation	D. Dinges
11:30	Neurovestibular Team Posters	ROOM: TEJAS I
	Neurobehavioral & Psychosocial Team Posters	ROOM: TEJAS III
12:30 p.m.	LUNCH	
1:30	Smart Medical Systems Team Presentation	J. Sutton
2:00	Technology Development Team Presentation	H. Charles
2:30	Smart Medical Systems Team Posters	ROOM: TEJAS I
	Technology Development Team Posters	ROOM: TEJAS III
3:30	FREE DISCUSSION TIME - MOST PARTICIPANTS	
(3:30 – 5:00)	*Technology Development Working Group Meeting*	ROOM: TEJAS II
6:30	DINNER	
7:30	Critical Path Roadmap: Future Directions & Activities	J. Charles L. Leveton
8:30	Risk Estimation	J. Banfield
9:30	ADJOURN	

Tuesday, January 15

ALL PLENARY SESSIONS HELD IN TEJAS II

8:30 a.m.	**Education & Public Outreach Team Presentation**	**M. MacLeish**
9:00	**Education & Public Outreach Posters**	**ROOM: TEJAS I**
10:00	**BREAK**	
10:30	**Immunology Team Presentation**	**W. Shearer**
11:00	**Radiation Team Presentation**	**J. Dicello**
11:30	**Immunology Team Posters**	**ROOM: TEJAS I**
	Radiation Team Posters	**ROOM: TEJAS III**
12:30 p.m.	**LUNCH**	
1:30	**Human Performance Team Presentation**	**C. Czeisler**
2:00	**Nutrition & Fitness Team Presentation**	**J. Lupton**
2:30	**Human Performance Team Posters**	**ROOM: TEJAS I**
	Nutrition & Fitness Team Posters	**ROOM: TEJAS III**
3:30	**FREE DISCUSSION TIME**	
6:30	**DINNER**	
7:30	**TEAM LEADERS ONLY - Strategic Planning**	**J. Sutton, R. White & J. McPhee**
8:30	**TEAM LEADERS ONLY – Director's Meeting**	**J. Sutton**
9:30	**ADJOURN**	

Wednesday, January 16

ALL PLENARY SESSIONS HELD IN TEJAS II

8:30 a.m.	**International Activities: Reports from the Partners**	**R. White**
	• **DLR (Germany)**	**P. Gräf, R. Gerzer & F. Baisch**
	• **MEDES (France)**	**A. Pavy-LeTraon**
	• **Australia**	**A. Roberts**
10:00	**BREAK**	
10:30	**Bone Team Presentation**	**J. Shapiro**
11:00	**Muscle Team Presentation**	**K. Baldwin**
11:30	**Bone Team Posters**	**ROOM: TEJAS I**
	Muscle Team Posters	**ROOM: TEJAS III**
12:30 p.m.	**LUNCH**	
1:30	**Cardiovascular Team Presentation**	**R. Cohen**
2:00	**Integrated Human Function Team Presentation**	**M. Kushmerick**
2:30	**Cardiovascular Team Posters**	**ROOM: TEJAS I**
	Integrated Human Function Team Posters	**ROOM: TEJAS III**
3:30	**FREE DISCUSSION TIME**	
6:30	**DINNER**	
7:30	**Professional Development for Scientists & Engineers**	**J. Sutton & R. White**
8:30	**Data Archive Discussions**	**F. Vaughan & H. Winters**
9:30	**ADJOURN**	

Thursday, January 17

ALL PLENARY SESSIONS HELD IN TEJAS II

8:00 a.m.	**Space Mission Debriefing from Previous Shuttle and International Space Station Flights**	**D. Williams**
10:00	**BREAK**	
10:30	**Future Flight Activities on Shuttle & The International Space Station: The Reality**	**W. Paloski & L. Kuznetz**
12:30	**FINAL REMARKS**	
	ADJOURN	
	LUNCH	

Appendix H

REPORT ON EXERCISE WORKSHOP FOR NSBRI DIGITAL HUMAN MODELING CORE

Martin J. Kushmerick, M.D., Ph.D.

The workshop was held at the University of Washington on August 12 - 14, 2002. This report highlights the main points and is not a detailed set of minutes of the proceedings.

Workshop Goals and Expectations

The goals for the workshop were to integrate the current projects into a coherent simulation of human exercise, assess the strengths and weaknesses of the current approaches, and identify the requirements and road blocks for producing a model of astronaut exercise.

A textbook description of a simple bicycle exercise at one intensity for five minutes was selected for the first modeling activity; the details of the exercise are given in Appendix 1. The design for this workshop tested the ability of the interacting projects within the NSBRI integration core to make progress, from the particular simulations within each project, toward integration across projects and towards systems integration. The complete list of participants (not all of whom made presentations) is given in Appendix 2. In addition to the specific project presentations an equal number of presentations and discussions focused on strategies for integration, software designs and interconnectivity, and early work on the "whole body algorithm" at NASA.

Relevant papers on the role for large-scale integration in the work of NASA and NSBRI are references (3, 4). Two reviews of the data obtained from U.S. and Russian space missions are (1, 2). Leonard excerpted portions of drafts of his book on past work with the "whole body algorithm" and summarized selected Skylab data collected from various sources. Kushmerick has copies available for duplication but not for citation.

1. Convertino, V. A. Physiological Adaptations to Weightlessness: Effects on Exercise and Work Performance. *Exercise and Sports Sci. Revs.* 18: 119-166, 1990.
2. Convertino, V. A. Planning Strategies for Development of Effective Exercise and Nutritional Countermeasures for Long-Duration Space Flight. *Nutrition* 18: in press, 2002.
3. Srinivasan, R. S., J. I. Leonard, and R. J. White. Chapter 26: Mathematical Modeling of Physiological States. In: *Space Biology and Medicine: Humans in Spaceflight*, edited by C. S. L. Huntoon, V. V. Antipov and A. I. Grigoriev. Reston, VA.: American Institute of Aeronautics and Astronautics, 1996, p. 559 - 594.
4. White, R. J., and M. Averner. Humans in space. *Nature* 409: 1115-8, 2001.

Science Advances in Current Projects

Advances in modeling and experimentation relevant to the modeling were presented by the currently funded projects and set the stage for wide ranging discussions of strategies and tools for integrating organs from top-down (systems to components) and from bottom-up (molecules and cells to systems). Significant progress towards integration was made. In skeletal muscle cells Chase presented a 3 dimensionally correct model of a sarcomere linking cross bridge dynamics and Ca^{++} signaling with force output; a novel feature of this model was its inclusion of elastic properties of the myofibrillar filaments themselves, as well as the enzymatic rates of the proteins in the thick and thin filaments. Work in progress focuses on effects of ATP, ADP and phosphate, and Ca^{++} dynamics on force. Rice has a related model for cardiac muscle cells that included cooperative effects within each filament and accounted for the length dependency of force development critical to understand the mechanism behind Starling's Law. Kushmerick indicated how force can be integrated into a model of intracellular energetics dynamically. By varying the balance between energy supply and demand a quantitative prediction of sustainable power output emerged. The model can predict oxygen and susbtrate utilization from known reaction stoichiometry. Cabrera presented a model linking a lower limb skeletal muscle compartment to a whole body dynamic metabolism model of substrate and product fluxes. Next steps involve making all of these models for muscle interact from the resting state to exercise and back to baseline. In cardiac muscle cells, Bers and his co-investigators Puglisi, Shannon and Rice, demonstrated a working model of integrated ion channel action leading to cardiac cell function (LabHeart). The current model allows investigators to change parameter values during a simulation and to modify the kinetic equations describing the operation of any channel, even to modify them significantly to simulated skeletal muscle cells. Importantly this model allows simulation of calcium ion dynamics, which then will integrate cellular electrical activity with Ca^{++} control of contraction, energetics and metabolism. The inclusion of metabolic and adrenergic effects into a model of the heart was shown by McCulloch using algorithms he developed for simulations at the UCSD supercomputer center (Continuity). These simulations showed that a full 3D simulation of cardiac electro-mechanics was essential to get correct behavior of the organ. Simulations showed mechanisms regulating diastolic relaxation that are so important in increased cardiac output at high heart rates during exercise and showed specific ionic alterations that could lead to arrythmias. Coolahan used high-level architecture and IEEE 1516 standard simulation protocols to join simulations between Johns Hopkins and UCSD. Murphy in Coolahan's group described the software approach needed to make this integration successful. Feldman used cellular automata methods to simulate the integration of cardiac cells to organ in a medium fidelity simulation. This model also gave insights into electrical propagation and patterns of cardiac activation that generated arrythmias; T-wave alterans was specifically simulated. Heldt described the cardiovascular systems model developed at MIT (Roger Mark, PI, within the Cardiovascular Alterations Team). That model uses lumped hemodynamic parameters for each compartment and simulates heart rate and stroke volume as observed in tilt-table tests. The model accounted for the increased cardiac output and heart rate of exercise when interesting modifications were made. The large increase in flow to exercising muscle and the current baroreceptor reflex were insufficient to account for increased heart rate and cardiac output. Three new features (the "muscle pump", a shift in blood out of the abdominal region and a shift in baroreceptor operation to higher pressures) were needed.

<u>In summary</u>, the science advances in the projects had many features that fostered integration of component mechanisms and transfer of simulation algorithms among muscle cells and organs.

Strategies for Integration

In addition to these project-specific presentations, a number of presentations and discussions focused on strategies for simulation and integration. Coolahan emphasized the need for clear and consistent definitions of parameters and units among the models of interacting groups wanting to join simulations. He demonstrated the successful joining of three projects: his own, Andrew McCulloch's, and Roger Mark's. The discussion that followed indicated a relatively short path to join others, e.g. cellular energetics and whole body metabolism. Bassingthwaighte used his strategy of the "Physiome" to join blocks of metabolic networks to a large cellular model. He emphasized the need for available databases, adequately annotated and searchable, if researchers developing models are to use data for validation. He championed an "open source" strategy. Vicini brought his experience in modeling pharmaco-kinetics and -dynamics in the process of drug development to demonstrate many similarities with the processes the workshop is using to achieve an integrated digital human for NSBRI. Rosse outlined the approach taken by his research group to develop a logic and strategy for organizing anatomical knowledge out of anatomical data. Dan Cook outlined his "work in progress" of a graphical method for diagramming inter-relationships among components of systems, be they at the genomic or organ-system level. These "graphs" are actually object oriented programming modules that serve integration, database and searchable patterns and relationships in the database. At the end of the workshop Brian Davis brought together a set of convincing arguments for the inclusion of bone properties and dynamics into the analysis of exercise, both to enhance the analysis of exercise from the mechanical aspects, as well as to demonstrate the close mechanistic connections between muscle and bone properties to sustain and modulate bone properties.

In summary, many tools exist for modeling and simulation and are useful if not optimal for the work of the integrated human core. An ordered set of questions and concepts for integrating the many systems involved is not developed with the needed clarity for charting progress.

Current Exercise Results and Past Integration at NASA

Important contributions to past work at NASA in analyses of integrated human systems were spelled out by Leonard. The value of this work for our current goals was at least two-fold: it showed the enormous value to develop knowledge and understanding from heuristic models using lumped parameters, and it also demonstrated the value of this integration to account for measurements on astronauts and cosmonauts during a wide range of missions. Although not making a formal presentation, Convertino provided key insights on data available from missions at 0 G as well as ground based studies. He emphasized the wealth of information for both humans and animals that is already available for simulation and modeling but need analyses to develop an adequate understanding of the underlying systems, tissues and cellular relationships. Hagan described current NASA exercise protocols for ground-based training, the evolution of devices for exercise, the protocols used currently as countermeasures during ISS missions, and current understanding of these data in terms of astronaut performance. White emphasized that a major contribution would be made if a reduction in the time spent in exercise could be achieved by devising a more efficacious prescription for this countermeasure. During the current missions, astronauts typically spend 2.5 hours each day exercising to maintain their preflight health status.

In summary, to enable astronauts to spend more time in scientific duties, reducing the amount of daily exercise by optimizing its efficacy is a high priority. However, the specific exercise regime (frequency, intensity, duration and amount and kind of exercise) needed to maintain muscle function while traveling in space is not well determined. Currently, exercise training programs use individual heart rate at a particular exercise intensity as the main biomarker representative of performance. However, heart rate is not an ideal index of performance evaluation, especially due to cardiovascular alterations with space travel and inherent heart rate variability. Heart rate is not directly related to the local force and torque necessary to account for limb performance.

Revisions to Statements of the Problem and New Questions

The discussion throughout the workshop consistently showed that the overall goals for the integrated simulation and evolution of understanding of "exercise" as a countermeasure lacked sufficient specification on several levels. Some of the main classes of questions that need answering to make progress are:

- what aspects of the exercise currently practiced (intensity, duration, pattern, frequency, etc.) are causal in the astronaut's ability to walk off on landing and to pass the post-flight stand test?
- what are the physiologic and anatomic properties that are the primary and secondary components of the astronaut's ability to walk off on landing and to pass the post-flight stand test?
- what is the minimal physiological status to do emergency egress?
- what signals derived from exercise cause the clearly positive countermeasure effects of exercise? These are not likely to be the same for CM development for bone, muscle, cardiovascular and other system functional maintenance and rehabilitation.
- can one type of exercise be optimal for preventing loss of muscle mass and endurance, bone loss, orthostatic hypotension, cardiovascular system deconditioning and maintaining performance in case of an emergency? The likely answer is no, making the previous four questions even more obviously important, and analyses of their underlying components more urgent.
- are the right performance indices being used? How well do the physiological parameters as currently measured routinely during flight match with parameters used and important in the models? Discussion of these issues produced a clear need to develop surrogate parameters in the models that relate to current medical observations, and to workout model parameters that might be essential for integration that would need to be added to the list of current medical observations.

If we compile the proposed exercise model in the integrated manner visualized at the workshop, we will be in an excellent position to provide quantitative validation (or lack thereof) of what would otherwise be highly qualitative, cell-biological signaling pathways as they become known. We should have the short-term (order of minutes) model ready so that it can be used to address the unknown, long-term adaptation pathways. The exercise model would be used both to test the current physiological state of the "digital human" and as the stimulus for adaptation in silico.

The discussion on the methods for integration highlighted the need for clear definitions and units so that information between groups and their models can be properly connected. The need for an overarching "systems description" in terms of connected causal components became clear; this is essential before any details of the "digital human" can be worked out and integrated. A system description was provided to a certain extent by the "whole body algorithm" effort by NASA in the 1970's, and a new scheme is now needed to encompass the enormous expansion of biomedical knowledge since then.

Connectivity of Bone and Muscle

In a number of discussions the relationships among muscles and bones were thought critical for adequate responses of limbs to exercise prescriptions. The obvious interconnectivity among muscles, tendons and limb bones was pointed out, but equally obviously there is not a sufficient understanding to judge the effectiveness of current countermeasures to maintain and restore the preflight status of each. One critical difference between terrestrial (1G) locomotion and activities at 0G is the absence of storage of elastic energy in muscles and tendons at 0G. There are very few papers on this topic although the principles are well understood. These neglected topics need to be included in current modeling and research project plans and goals.

Further Questions Raised During the Workshop and Submitted Afterwards by Participants

Can we suggest more efficient exercise paradigms for training to meet specific performance criteria using the whole-body model of metabolic dynamics? Can this be accomplished by simulations of the dynamics of intracellular energetics, oxygen deficit and muscle lactate concentration assuming various work rate patterns?

Can the simulations indicate the rate limiting steps in the metabolic pathways which might be the stimuli for adaptation ? Are the absence (or diminution) of these same signals causal in detraining?

How can mechanical energy be transferred into models and simulations of human movement? What are the osteogenic stimuli thresholds for cancellous bone? And for trabecular bone?

What is the role of muscle tremor in maintenance of limb physiologic conditioning and is it altered at 0G? (the answer may be known but was not available at the workshop)

Besides identification of the signals involved in training and detraining, quantitatively what are the minimum stimulus thresholds to maintain each system?

What are the ratios of eccentric vs. concentric muscle activity profiles during orbital missions, as compared to similar activities and exercises on the ground?

Do changes in intracellular metabolite concentrations (specifically, ATP, ADP, Pi, H^+) affect exercise performance through direct effects (i.e., via changes in substrate concentration or product inhibition) on ATPases (actomyosin, Ca^{2+}-ATPase)? Many of these effects are known experimentally and this information can very usefully be incorporated into existing models and simulations to make predictions on altered performance.

The relationship between cardiac output and oxygen uptake at various exercise intensities is linear throughout the work rates examined in the Skylab series of studies. This relationship had a steeper slope at 1 g than at 0 g.

- What factors affect this relationship?
- Can exercise training alter the slope of this relationship at 1 g and at 0 g?
- Is the change in this relationship an adaptation or a mal-adaptation?

The dynamics of oxygen uptake at the onset of exercise and during recovery have been shown to be dependent on training status or degree of fitness. Alterations in muscle biochemical characteristics may alter the behavior of the pathways of ATP synthesis and thus the dynamics of certain metabolic processes resulting in marked changes in the dynamics of muscle oxygen consumption and energy output. Using changes in pulmonary oxygen uptake during exercise as a proximate variable representing changes in the rate of muscle oxygen consumption can allow us to evaluate the effect of changes in muscle metabolism on the time profile of oxygen uptake.

Do the training-induced changes in muscle enzyme activity in various metabolic processes affect the dynamics of muscle oxygen consumption (onset and recovery) during moderate intensity exercise? This question addresses the relationships between cellular properties and organ performance.

Are there any changes in efficiency after accounting for changes in muscle mass? This question addresses the possibility of both quantitative and qualitative differences in adaptation to training and detraining.

What can we do immediately after this workshop?

Get a detailed description of current aerobic and resistive exercises. Can we adequately simulate existing NASA exercise protocols with the devices used? We should start with ground-based data on humans and use animal results as a guide. Generate a new exercise regimen to which we can adapt our models and simulations. Validate the synthetic model with current ground-based data.

List characteristics of exercise devices used, and estimate force, motion and torque generated in the limb during exercise. Distinguish upper body and lower body exercise.

List the capabilities of the new physiological monitoring system to be installed in ISS. What parameters will be measured (workload, heart rate, cardiac output, blood pressure, tidal volume, oxygen uptake and carbon dioxide output), and with what frequency? Will there be comparable pre- and post-flight measurements? Identify gaps in current synthetic simulation with these activities and measurements.
Generate direct and surrogate parameters in models and simulations that map to the physiological and medical measurements.

Explain current modeling efforts and results to other projects in each of the teams. In particular raise the issues discussed in the workshop at the next meeting of the NSBRI teams for muscle, nutrition and rehabilitation, cardiovascular, bone and any other team interested. Plan on reconvening the principals from the workshop in approx. 6 months to assess progress.

In approximately six months, a new cycle ergometer and metabolic measurement system will be sent to the ISS to facilitate and improve monitoring of the exercise responses so that better evaluation of performance can be accomplished. This new measurement system permits determination of oxygen uptake and cardiac output in addition to the integration of heart rate measurements already provided by existing heart rate monitors. This equipment (cycle ergometer + metabolic measuring system) provides new opportunities not only to design exercise protocols (a variety of work rate functions) but also better methodologies and biomarkers to evaluate the astronauts' performance.

This report, along with individual presentations, has been posted to the Integrated Human Function section of the NSBRI secure website in a folder titled "Seattle Exercise Workshop."

Appendix 1

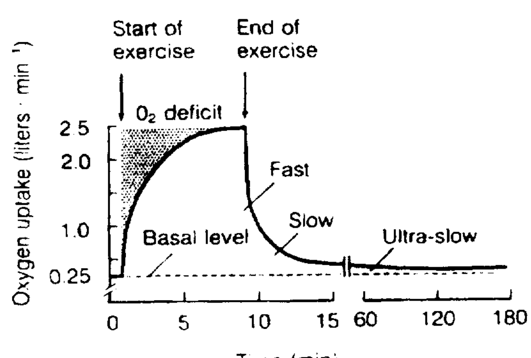
Design of the Exercise to be Simulated and Discussed at the Workshop, UW, Seattle 12-14 August 2002

History

We outlined a plan for a common activity for the six projects of the original Integrated Human Function Team, now a core function within NSBRI, to make a simulation of human exercise at the January 2002 NSBRI retreat. In early March 2002 we worked up a feasible project for this simulation. It would be a demonstration of the tools and approaches we have to integrate information, mechanisms and models. This plan was presented to the NSBRI External Advisory Board at its 12-13 March 2002 meeting and received strong encouragement. The workshop Aug 12-14 will review our work and plan for future progress towards integration mechanistic models at the cell level with an organ-level hierarchical structure.

Background information - basic primer on classical whole body oxygen uptake

The figure below is a schematic of an exercise in which a step increase in mechanical output begins at the start and abruptly ends at the end of exercise. The measured oxygen consumption at the mouth is given as oxygen uptake. To a first approximation the rate of increase in oxygen uptake from the onset of exercise and the rate of decrease during recovery after the end is monoexponential; this is not exactly correct, and the diagram emphasizes several components in the recovery phase.
[Figs from Astrand and Rodahl textbook on work physiology]

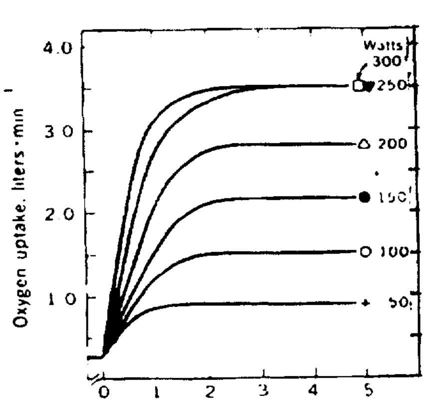


(a)

The diagram below shows two important features of exercise.

1. the steady state is achieved in about 2 - 3 minutes, and
2. oxygen uptake is graded in proportion to exercise intensity, i.e. the mechanical output.

The label to the right of each curve in the figure gives the exercise intensity measured in watts. For this average individual, the maximal exercise intensity is ~250 watts. Strenuous endurance training can increase the maximum oxygen uptake to the range of 5 L/min. High exercise intensities cannot be sustained very long (~10 min or so for moderate and a few min for near maximal) whereas lower intensities are sustainable for much longer duration, as everyday experience shows. We need to note that these rates of energy expenditures are superimposed on the basal metabolic rate, which for a 70 kg lean person is about 80 watts.



(b)

Initial Parameters for Simulation

Let's choose a moderate exercise intensity, 150 watts. Lets choose a duration sufficiently long that the muscle metabolism and energetics is definitely in a steady state; 3 minutes is just at the steady state, so 5 min to have a clear asymptote. However, the time constants in the cardiovascular simulation will be longer, so let's choose a longer time for both the initial resting control (5 minutes), exercise duration (5 minutes) and recovery (10 minutes). This is an impossibly long computation time for some projects. Thus we will have to decide and agree on intermediate points done with full simulation on the assumption that those states are replicated in steady states and can be interpolated during transitions.

Ideas on how we might proceed to accomplish this group demonstration project

Use the specific information on this particular description of an exercise as input perturbation from steady resting state to exercise and return for all of our models.

- put this metabolic load into the organ level heuristic model.
- heart electrophysiological models: for the two steady states (rest and exercise) and any interesting transitions.
- heart mechanical models: for the two steady states and any interesting transitions
- cross bridge models:
  - § skeletal muscle: basically consider episodic on/off duty cycle of about 150 msec on to simulate burst motor unit firing to calculate force produced per cross sectional area and ATPase cost
  - § cardiac muscle: two different work rates (rest at 70 bpm and cardiac output of 5 L/min and exercise) required to fit into the heuristic CV model
- muscle energetics model: simulate time course of intracellular high energy phosphates consistent with this exercise power output; predict O2 consumption using typical biochemical stoichiometries.
- whole body metabolism: sources for the metabolic load, and sinks for the products, CO_2 and lactate appropriate for the same exercise intensity and duration

Some quantitative inter-relationships among the metabolic quantities

Here we begin to deal with the stoichiometric relationships among ATP utilization, mechanical output, blood flow, cardiac output and oxygen uptake that are needed to connect the individual simulations to produce eventually the overall simulation. ***My view is that we will find the most difficult part of this project will be understanding and defining how each of our simulations made at various levels of complexity are interconnected.***

Resting oxygen consumption averages 0.25 liters of gas per minute for our standard 70 kg person; 0.011 moles of O2 per min using ideal gas law of 22.4 L/mole. Exercise at 150 watts requires 2 L/min; 0.089 moles O2/min above the baseline for a total of 0.1 mole/min from the first two figures. This is 8 times greater for the whole body, but more for the muscles. The reason is that muscle resting metabolic rate is so low, and most (>95%) of the increment in oxygen uptake in the body is due to increased uptake by muscle. Thus the increased blood flow to muscle primarily drives the increase in cardiovascular, respiratory and metabolic fluxes.

The units for intracellular energy demand and supply in the muscle are ATP units per kg of muscle, which can be expressed as molar concentration in intracellular water by (ATP units per kg of muscle)/0.7. ATPase flux in resting muscle is ~ 0.01 mM/sec; hard numbers for active muscle during exercise at 150 watts are not available, but we can estimate this to average 0.5 mM/sec above basal for a total of 0.51 mM/sec. Assuming oxidative carbohydrate metabolism, there are 6 moles of ATP synthesized per mole of oxygen used. Thus these ATP units translate into oxygen units: 0.1 mM O_2/min for basal and 5 mM O_2 per min for exercise for a total of 5.1 mM O_2/min.

To connect the info in the two previous paragraphs (whole body <-> muscle), we need to estimate the mass of active muscle. Assume it is 20 kg. From the calculations for ATP, 5.1 mM O_2/min times 20 = 0.1 mole O_2/min which agrees with the statement in the second paragraph in this section. The free energy available from ATP hydrolysis is on the order of 65 kJ/mole; 1 watt = 1 J/sec. A hydrolysis rate of 0.5 mM/sec works out works out to be 32 watts per kg active muscle, or 640 watts in the total body exercise. If no work were done, this would be the thermal load. The overall chemomechanical efficiency is on the order of 25% so this ATP hydrolysis rate could be converted into 160 watts of work measured on a bicycle ergometer. So the overall magnitude is in agreement given the assumptions made.

Appendix 2

NSBRI Integrated Human Function Exercise Workshop			
Names & Addresses	**Phone**	**Fax**	**Email**
Jim Bassingthwaighte Dept. of Bioengineering Box 357962 310D Harris Hydraulics Bldg. Seattle, WA 98195-7962	(206) 685-2005 (206) 685-2012	(206) 685-2651	jbb@bioeng.washington.edu
Don Bers Stritch School Of Medicine 2160 South First Ave. Maywood, IL 60153	(708) 216-1018 or 216-6107	(708) 216-6308	dbers@lumc.edu
Marco Cabrera 11100 Euclid Ave., RBC-380N Case Western Reserve Univeristy Cleveland, OH 44106-6011	(216) 844-5085	(216) 844-5478	mec6@po.cwru.edu
Stephen Carter University of Washington Dept. of Radiology Box 357115 1959 NE Pacific St., Rm AA-010 Seattle, WA 98195-7115	(206) 685-2693	(206) 543-3495	scarter@u.washington.edu
Bryant Chase Bio Unit One, Room 206 Florida State University Tallahassee, Fl 32306-4370	(850) 644-0056	(850) 644-0392	chase@bio.fsu.edu
Kevin Conley University of Washington Dept. of Radiology Box 357115 1959 NE Pacific St., Rm AA-010 Seattle, WA 98195-7115	(206) 543-3763	(206) 221-6515	kconley@u.washington.edu
Victor Convertino 3400 Rawley E. Chambers Avenue Bldg. 3611 Fort Sam Houston, TX 78234-6315	(210) 916-5633	(210) 916-5992	victor.convertino@cen.amedd.army.mil
Dan Cook Physiology and Biophysics University of Washington Box 357290 Seattle, WA 98195-7290	206 297-7794		raintown@halcyon.com

Jim Coolahan Applied Physics Laboratory 11100 Johns Hopkins Road Laurel, MD 20723-6099	(240) 228-5155 (443)-778-5155	(240) 228-5995	james.coolahan@jhuapl.edu
Brian Davis 29226 Cedar Road Pepper Pike, OH 44124	(216) 444-1055		davis@bme.ri.ccf.org
Andy Feldman Applied Physics Laboratory 11100 Johns Hopkins Rd MS2-234 Laurel, MD 20723-6099	(240) 228-5317	(240) 228-6904	andrew.feldman@jhuapl.edu
Donald Hagan Human Adaptation & Countermeasures SK2 Lyndon B. Johnson Space Center Houston, TX 77058	(281) 244-1122	(281) 483-2888	dhagan@ems.jsc.nasa.gov don.hagan1@jsc.nasa.gov
Thomas Heldt Building E25, Room 505 77 Massachusetts Avenue Cambridge, MA 02139	(617) 258-5406	(617) 258-7859	thomas@mit.edu
Martin Kushmerick University of Washington Dept. of Radiology Box 357115 1959 NE Pacific St., Rm AA-010 Seattle, WA 98195-7115	(206) 543-3762	(206-221-6515	kushmeri@u.washington.edu
Joel Leonard 400 Madison St., Ste #2103 Alexandria, VA 22314	(703) 549-2010	(703) 548-7795	joel-leonard@comcast.net jleonard@hq.nasa.gov
Andrew McCulloch Department of Bioengineering University of California-San Diego 9500 Gilman Drive La Jolla, CA 92093-0412	(858) 534-2547 (858) 822-1253	(858) 534-6896	amcculloch@ucsd.edu
Jancy McPhee NSBRI One Baylor Plaza, NA-425 Houston, TX 77030-3498	(713) 798-7412	(713) 798-7413	jmcphee@bcm.tmc.edu
Anouchka Mihaylova Department of Bioengineering University of California, San Diego 9500 Gilman Drive La Jolla, CA 92093-0412	(858) 822-2132	(858) 534-6896	amihaylo@bioeng.ucsd.edu

Sean Murphy Applied Physics Laboratory 11100 Johns Hopkins Road Laurel, MD 20723-6099	(240) 228-4299	(240) 228-5889	sean.murphy@jhuapl.edu
Jose Puglisi Dept of Physiology 2160 South First Avenue Maywood, Illinois, 60153	(708) 216-4054	(708) 216-6308	jpuglis@lumc.edu
Krishnan Radhakrishnan NASA Glenn Research Center Mail Stop 5-10 Cleveland, OH 44135	(216) 433-8483	(440) 962-3120	kxr32@po.cwru.edu
Michael Regnier Dept. of Bioengineering Box 357962 320 Harris Hydraulics Bldg. Seattle, WA 98195-7962	(206) 616-4325	(206) 685-3300	mregnier@u.washington.edu
Jeremy Rice T.J. Watson Research Center P.O. Box 218 Yorktown Heights, NY 10598	(914) 945-3728	(914) 945-4104	johnrice@us.ibm.com
Cornelius Rosse Dept. of Biological Structure University of Washington Box 357420 Seattle, WA 98195-7420	(206) 685-4707	(206) 685-6887	
Gerald Saidel Dept. of Biomedical Engineering Wickenden 410 Case Western Reserve University Cleveland, OH 44106-7207	(216) 368-4066	(216) 368-4969	gms3@po.cwru.edu
Thomas Shannon	(708) 216-6994	(708) 216-6308	tshanno@lumc.edu
Paolo Vicini Box 352255 AERL RM 241 University of Washington Seattle, WA 98195-2255	(206) 616-1133 (206) 685-3021	(206) 543-3081	vicini@u.washington.edu
Ron White NSBRI One Baylor Plaza, NA-425 Houston, TX 77030-3498	(713) 798-5906 (or 7412) At NASA: (281) 483-0274	(713) 798-7413	rwhite@bcm.tmc.edu

Appendix I

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

PROGRESS REPORT

May 24, 2002

TABLE OF CONTENTS

1. PREAMBLE

The National Space Biomedical Research Institute (NSBRI or "Institute") is a unique, non-profit scientific partnership with NASA that engages and coordinates outstanding researchers and educators to lead a national, team-based effort to develop countermeasures to reduce significant health risks associated with human space travel.

Progress of the NSBRI in achieving its goals, objectives and mission, as laid out in its Cooperative Agreement Notice (CAN; 9-CAN-96-01) with NASA, is available in the Institute's Annual Reports 1998, 1999, 2000 and 2001. The purpose of this Progress Report is to provide:

- A statement on the progress and status of the Institute with respect to the recommendations from the Site Visit Review Report of the National Space Biomedical Research Institute.
- An update of the research and education progress and accomplishments of the Institute since the 2001 Annual Report.

Some of the material in this document links directly to components of the Institute's Strategic Plan, which is being submitted to NASA along with this report. References to the appropriate sections of the Strategic Plan are provided.

The appendices contain supporting documentation concerning recent Institute progress and leadership. A compact disc is also enclosed that contains (a) briefings made in March 2002 by all of the Team Leaders to members of the External Advisory Council regarding their team's activities and progress in countermeasure development and education and (b) a movie of an interactive demonstration by the Smart Medical Systems Team, conducted in October 2001, which showcases NSBRI Team Leaders, Council and Board members, former astronauts, Johnson Space Center personnel, including flight surgeons, and students, using new enabling technologies for non-invasive human physiological monitoring and advanced medical care.

2. STATUS ON RECOMMENDATIONS FROM THE SITE VISIT REPORT OF THE NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

From November 28 to December 1, 2000, the NASA Chief Scientist conducted a review of the NSBRI and issued a Site Visit Report of the National Space Biomedical Research Institute, which concluded the following in the executive summary:

> *The committee was impressed by the scientific strengths of the NSBRI, by its progress in developing countermeasures, by its innovative scientific leadership and by its outstanding trainees. We recommend that NSBRI continue for its second five-year funding period. We commend NSBRI for providing added value both for the institute as a whole and for individual teams.*

It was recommended that under its new Director, the NSBRI should prepare a forward-looking strategic plan. A Strategic Plan has been developed and submitted to NASA together with this Progress Report.

Besides the delivery of a Strategic Plan, the Site Visit Report made 14 principal recommendations, which are listed below. Following the site visit, there was bilateral correspondence between the NSBRI and the Office of the NASA Chief Scientist regarding efforts made, or to be made, to address the recommendations (Appendix 1). In this section, the status of progress with respect to each recommendation is summarized. Actions have been taken to deal with **all** of the recommendations.

Recommendation 1. *We recommend that NSBRI continue to serve as a team-based organization, whose targeted mission is the development of mechanism-based countermeasures. We understand that NSBRI's primary goal is to move countermeasures from Countermeasure Readiness Levels (CRLs) of 2-3 to 6-7. The development of the critical path roadmap is also evidence of effective, focused interaction.*

Status: Agree. A unique value that the NSBRI brings to NASA's human space program is an integrated and coordinated team approach, involving some of the nation's most elite investigators and non-NASA resources, to solve complex biomedical problems related to long-duration space travel. The NSBRI therefore abides by this recommendation and continues to play an active role in the ongoing development of the Critical Path Roadmap (enclosed as a separate document; also see Strategic Plan Volume I, Section 3). A list of all peer-reviewed funded projects appears in Appendix 2 of this document. The strategies for moving the research projects and teams from CRLs of 2-3 to 6-7 are contained in Strategic Plan Volume II.

Recommendation 2. *We do not recommend that the NSBRI develop into a funding agency that dispenses R01- or NRA-like grants to outside investigators to work on low CRLs. Instead, we recommend that NASA Headquarters, in close cooperation with NSBRI and Johnson Space Center (JSC), extend and expand its targeted grant program to fund individual research grants that will address CRLs of 1-3.*

Status: Agree. See Status section of Recommendation 1 above. The NSBRI has worked in close cooperation with NASA Headquarters and JSC regarding new grant solicitations in countermeasure development appropriate for CRLs 1-3 (NASA Research Announcement program) and CRLs transitioning from 2-3 to 6-7 (NSBRI program). A joint NRA-NSBRI call for proposals issued in October 2001, NRA 01-OBPR-07, is testament to a coordinated effort in this regard. It should also be pointed out that while the NSBRI is not focused on CRLs 1-3, basic science advances have occurred at these levels, such as the discovery of the Atrogin-1 gene associated with muscle wasting (*Proceedings of the National Academy of Sciences* 98:14440-14445, 2001; Appendix 3). Achievements of this type are not unexpected given that scientific discovery targeted at one CRL range may indeed contribute to accomplishments at that range and/or levels below or above the selected range (N.B., "fast-track" NSBRI advances to operational CRLs 7-9 have occurred as well; see Strategic Plan Volume I, Sections 3 and 5).

Recommendation 3. *We recommend that NSBRI continue to make use of its extensive network of outside advisors, including its Board of Directors, its Board of Scientific Counselors, and its External Advisory Council. We note, however, that the striking and surprising lack of diversity of these boards effectively excludes many talented people from whose expertise NSBRI could well profit.*

Status: The NSBRI is honored to have, and continues to make use of, its distinguished and active Board of Directors, External Advisory Council, User Panel and Board of Scientific Counselors (Appendix 4). It is imperative that appropriate gender and ethnic diversity occur at all levels, including upper levels, of the NSBRI. This is a serious issue that the NSBRI has taken action on and will continue to address. At present, 17% of the Board of Directors, 19% of the External Advisory Council, 22% of the Users Panel and 11% of Board of Scientific Counselors are women. There is also ethnic diversity among these important panels. The NSBRI not only wishes to have good representation of women and minorities among its ranks, but it strives to be a benevolent leader in helping to reduce barriers that are endemic in our national scientific and engineering culture. Also see Status section of Recommendation 8 below.

Recommendation 4. *We were pleased by the ability of the NSBRI leadership to make "mid-course corrections" in its research agenda. We recommend that the leadership make the process of team leader* *selection more transparent, in order to avoid any appearance of cronyism. NSBRI's credibility and its effectiveness in recruiting new researchers will depend on management's ability to manage apparent or potential conflicts of interests, especially at the level of team leaders.*

Status: Agree. The hybrid NRA (or National Institutes of Health) and Department of Defense model of the NSBRI is innovative in that open peer-reviewed research is subsequently organized into teams, which are mission driven towards countermeasure deliverables.[1] The success of this model is clear (Sections 3 and 4, Appendix 3). Furthermore, it relies to a great extent on the ability of Team Leaders to act as effective scientists and managers. The team selection process that follows peer review, and criteria for Team Lead evaluation, with adequate protection from real or perceived conflict of interest, are critical management issues. The topic was discussed at the March 2002 meeting of the External Advisory Council and is addressed in Strategic Plan Volume I, Section 3. Part of the action plan is to establish an expert committee to review this issue in detail and provide recommendations to NSBRI senior management prior to the end of 2002. The current cycle of Team Leader support expires on September 30, 2003, with current grants ending on or after that date. This allows adequate time to implement a process that will achieve the highest level of fairness and integrity in the selection of teams and team leadership.

Recommendation 5. *Because of increasing potential for conflict of interest, we recommend that the selection process (following peer review) should be reexamined and reformulated.*

Status: Agree. See Status section of Recommendation 4 above and Strategic Plan Volume I, Section 3 for actions taken, and strategies going forward, that address this issue.

Recommendation 6. *We strongly recommend the establishment of a university-level education program – especially at consortium institutions – that takes advantage of the ability of space research to excite student interest in NASA's and NSBRI's long-term goals.*

Status: Agree. As described in the Strategic Plan Volume I, Section 4, an initiative for graduate and post-doctoral level training is to be carried out in coordination with the Institute's research and other educational programs. Moreover, members of the Industry Forum (Appendix 4.F) have expressed a willingness to financially support a portion of a university-level education program. The NSBRI wholeheartedly endorses this recommendation.

Recommendation 7. *To increase the pool of future space researchers, we strongly recommend increased support and coordination of NSBRI's educational programs. Additional funding should track the increase in NSBRI's budget. Rather than increasing educational activities in vacuo, we recommend significant integration of educational and research efforts, and we suggest future reviews include the evaluation of the plan and the accomplishments of this effort.*

Status: Agree. Activities have already been carried out in this regard that include, but are not limited, to the action listed under the Status section of Recommendation 6. The Strategic Plan outlines the Institute's plans to grow the Education and Public Outreach Program (Strategic Plan Volume I, Section 4) with an augmented budget.

Recommendation 8. *We strongly recommend increased attention to human resource issues at all levels of NSBRI employment, especially at upper levels.*

[1] The openness of the program is important. Appendix 5 lists NSBRI funding across 21 states, reflecting regional diversity and the result that solicitations are not restricted to consortium institutions.

Status: As stated in the Status section of Recommendation 3, action has been taken in this regard. Moreover, the NSBRI is proud that, based on merit, 26% of the Team and Associate Team Leaders are women (Appendix 4.E), with the leadership of the prestigious Education and Outreach Team belonging to an excellent and inspiring educator who happens to be an African-American female. Diversity is a component of the Institute's Cooperative Agreement Notice and Strategic Plan, and the Institute works hard to address human resource issues at all levels.

Recommendation 9. *In establishing future priorities, we urge NSBRI to consider the recent determination by NASA that radiation is the number one health-and-safety issue associated with deep space flight.*

Status: Agree. Plans to focus research efforts in high-priority areas, especially where the risks have high likelihood, high consequence and low mitigation status, are important activities for NASA and the NSBRI. This is discussed in the context of the Critical Path Roadmap in the Strategic Plan Volume I, Section 3. With respect to radiation, efforts have been under way to coordinate NSBRI investigators and resources within the larger framework of NASA's radiation initiative.

Recommendation 10. *We recommend that NSBRI consider the discontinuation or the reorganization of the new team for integrated human systems.*

Status: The Integrated Human Function Team was carefully reassessed in 2001 and formally discontinued in 2002. Peer-reviewed projects previously assigned to the team were reassigned to other teams, while maintaining central oversight of integration and modeling efforts among the teams. The efforts to integrate modeling across the Institute are described in the Strategic Plan Volume I, Section 5, and in the Strategic Plans for each of the current teams (Strategic Plan Volume II).

Recommendation 11. *NSBRI, JSC and NASA Headquarters should find ways of increasing the accessibility of relevant performance and medical data.*

Status: Agree. Considerable progress has been made in this area. There are strong ties between NSBRI investigators and personnel in the Office of Bioastronautics and the Space Medicine and Health Care Systems Office at JSC. Important and valuable performance and medical data are being made available, where appropriate. There is a working group involving the NSBRI, JSC and NASA Headquarters that brings together key personnel, including the NASA Chief Health and Medical Officer, to address medical requirements and evidence-based medicine. This is critical for developing and implementing a coordinated effort to best determine, prioritize and mitigate biomedical risks to astronaut health and safety. Cooperative activities in this area are outlined in the Strategic Plan Volume I, Section 5.

Recommendation 12. *We recommend that a NASA external review be scheduled for each individual team in year 5, and every 3-5 years thereafter.*

Status: Agree. Ongoing review of individual teams is important to assess the quality of the research, relevance to the needs of NASA and performance based on defined goals and measures. These criteria are espoused by the White House Office of Management and Budget. The NSBRI is an outstanding resource for NASA and review of its teams affords an opportunity to critically evaluate, coordinate and integrate NSBRI activities with other NASA programs and initiatives, thereby providing maximum benefit and impact for NASA and the American people. A review schedule for the 11 research teams and the

Education and Public Outreach Team (see Status section of Recommendation 7) is proposed in the Strategic Plan Volume I, Section 3.[2]

Recommendation 13. *We were not given adequate information to assess the budgetary needs of NSBRI for current and future years.*

Status: This recommendation is a statement of fact rather than a recommendation per se. Nevertheless, it is hoped that the present Strategic Plan, along with other materials being submitted by the NSBRI and JSC to NASA Headquarters, will provide a compelling case for the NSBRI budget to be determined, based on requirements, at an appropriate level above $10 M per annum.

Recommendation 14. *Absent any new strategic plan or any external review, the committee has no basis to endorse a large increase in funding.*

Status: The Strategic Plan sets forth a program and implementation strategy for outstanding biomedical research that will enable the Institute, in partnership with NASA, to achieve its mission and meet its objectives and goals as originally laid out in the Cooperative Agreement Notice. The Strategic Plan is submitted for external review.

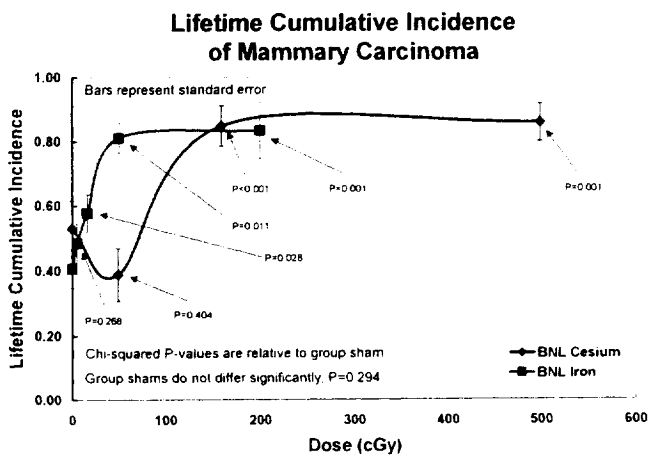
[2] In the joint NSBRI / JSC response letter (Appendix 1 of the accompanying Progress Report) to the NASA Chief Scientist, there was disagreement about the timing of the reviews, but not about having the reviews. The review schedule proposed in Section 3 of the Strategic Plan resolves this apparent (but not real) conflict of views.

3. SELECTED RESEARCH ACCOMPLISHMENTS

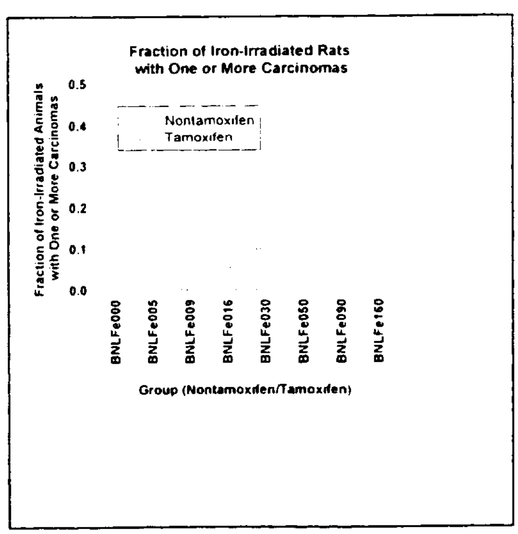
Significant progress in NSBRI countermeasure development was showcased at the Institute retreat in January 2002. This meeting involved more than 300 NSBRI investigators, students and NASA personnel from multiple Centers and Headquarters. Many of the advances and achievements have been presented at recent scholarly meetings, national committees and symposia, such as the Institute of Medicine Committee on Aerospace Medicine and Medicine in Extreme Environments in January 2002, and the National Space Symposium in April 2002. The NSBRI has matured to the point where research discoveries (Appendix 3) and proof-of-principle countermeasures are beginning to be delivered (Appendix 7). A survey of selected accomplishments is listed here to portray the depth and breadth of research progress and deliverables.

Countermeasure Development

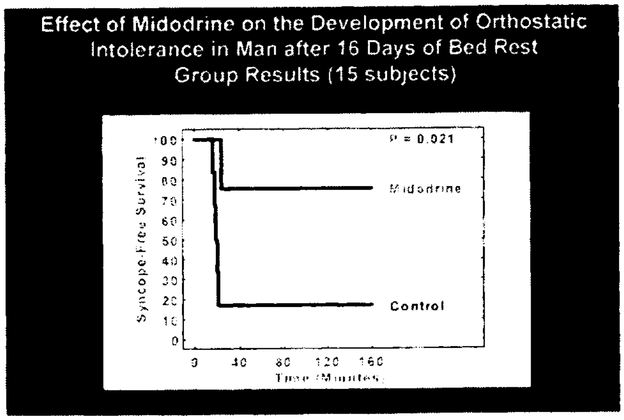
- Demonstrated that pharmaceuticals, such as tamoxifen, used after HZE exposure reduced the risk of cancer.



J. Dicello, D. Huso, et al: Recent results for first completed study of the risk of breast cancers in Sprague-Dawley rats. The maximum RBE is estimated to be about five or six times lower than the only previous value obtained for cancer in the Harderian gland of the mouse (Alpen et al).

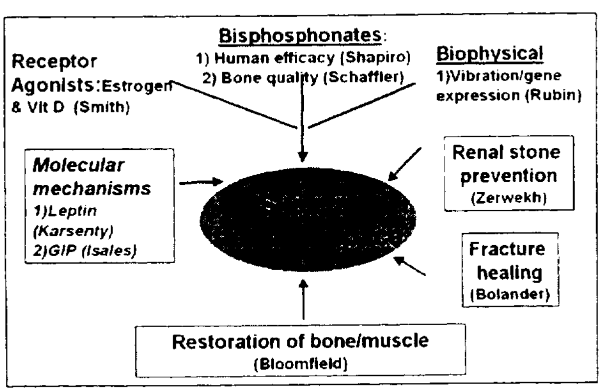


- Showed, in partnership with JSC, that midodrine reduces the incidence of orthostatic hypotension, after prolonged bed rest. Countermeasure development is in the flight-proposal stage. (Ramsdell, C. D., T. J. Mullen, G. H. Sundby, S. Rostoft, N. Sheynberg, N. Aljuri, et al. Midodrine prevents orthostatic intolerance associated with simulated spaceflight. *J Appl Physiol* 90:2245-2248, June 2001.)



R. Cohen, et al: *Midodrine is an alpha-sympathetic agonist that constricts both veins and arteries.*

- Demonstrated that pharmaceuticals, such as bisphosphonates, and exercise reduce bone loss in ground-based microgravity simulation studies. Flight proposal to test pharmaceuticals is in development.



J. Shapiro, et al: *Testing Zoledronate (Novartis - a third-generation bisphosphonate, used in osteoporosis) to inhibit bone loss in spinal cord patients, who experience similar patterns of bone and muscle loss as astronauts. Zoledronate exhibits a high level of counter-measure readiness.*

- Showed that vibration stimulation and mechanical loading affect bone mass and gene expression in bone. (Rubin, C. T, D. W. Sommerfeldt, S. Judex, and Y. X. Qin. Inhibition of osteopenia by low magnitude, high frequency mechanical stimuli. *Drug Discov Today* 6(16):848-858, August 15, 2001; and in Rubin, C. T., G. Xu, and S. Judex. The anabolic activity of bone tissue, suppressed by disuse, is normalized by brief exposure to extremely low magnitude mechanical stimuli. *FASEB J* 15:2225-2229, 2001.)

- Showed that intermittent exposure to bright light, when timed critically, greatly helps the body's internal, or circadian, clock and allows for better sleep time. (Dijk, D. J., D. F. Neri, J. K. Wyatt, J. M. Ronda, E. Riel, A. Ritz-De Cecco, R. J. Hughes, A. R. Elliott, G. K. Prisk, J. B. West, and C. A. Czeisler. Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights. *Am J Physiol Regul Integr Comp Physiol* 281:R1647-1664, November 2001.)

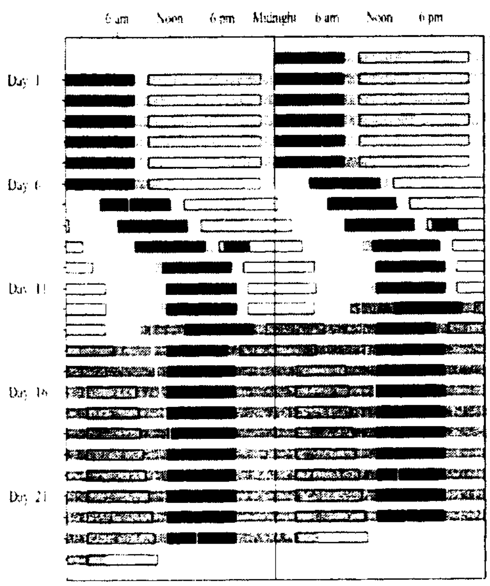
Data from STS-106:

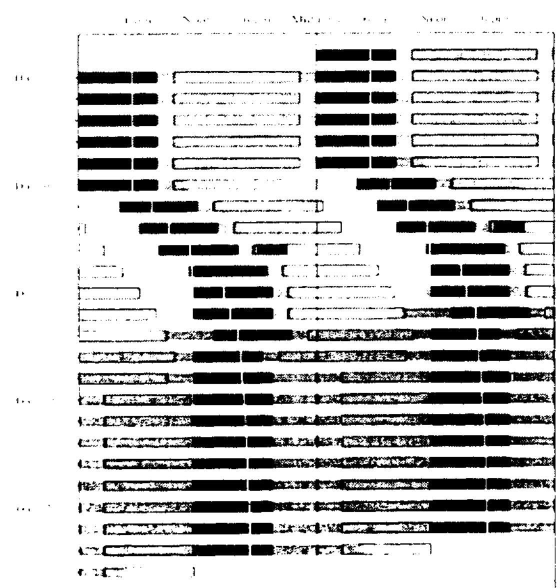
Evaluate Actual Schedule

Note: less than optimal performance predicted during launch, landing and much of wakefulness in space

Determine Optimal Schedule

Solution: Removing morning bright light exposure & increase evening bright light duration.





0 lux

50 lux (Space)

10 lux

150 lux

40 lux

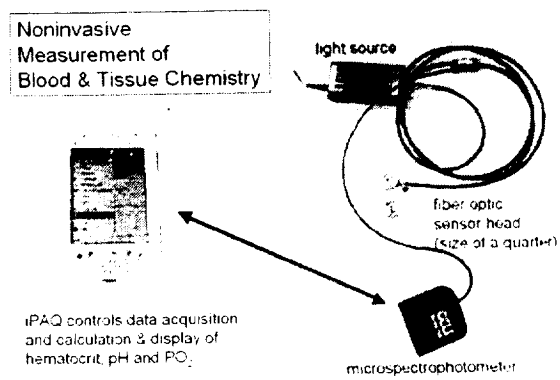
10,000 lux

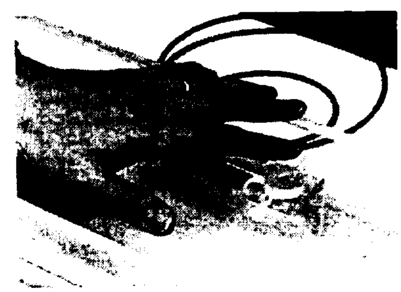
M. Jewett, et al: *Circadian Performance Simulation Software (CPSS) package.*

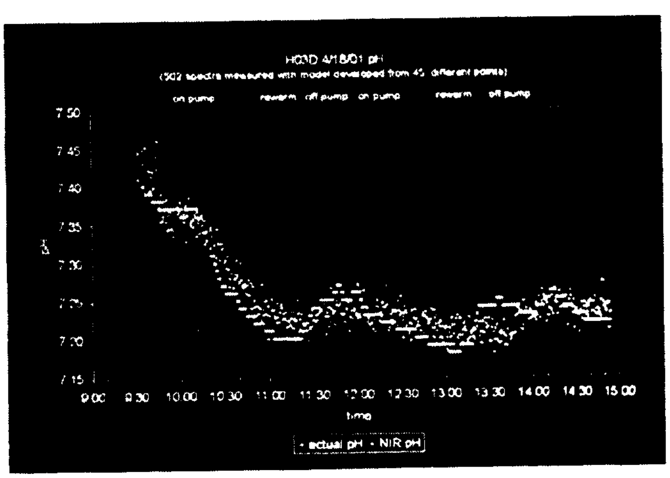
- Documented that nap time is less important than it had been thought to be if less than eight hours of sleep is sustained per day. (S. M. Doran et al: Sustained attention performance during sleep deprivation: evidence of state instability. *Archives of Italian Biology: A Journal of Neuroscience*, 139:253-267; and in D. Dinges, et al: Cumulative sleep loss in space flight: neurobehavioral consequences and countermeasures. Submitted to *Acta Astronaut*.

Technological Advances in Non-Invasive Health Care

- Developed a near infrared spectrum system to measure physiological parameters non-invasively.

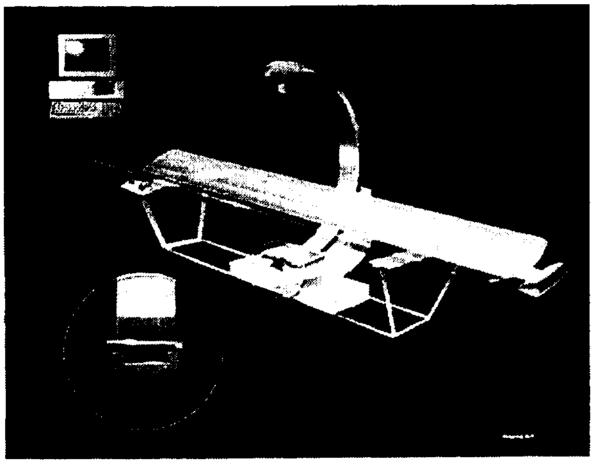




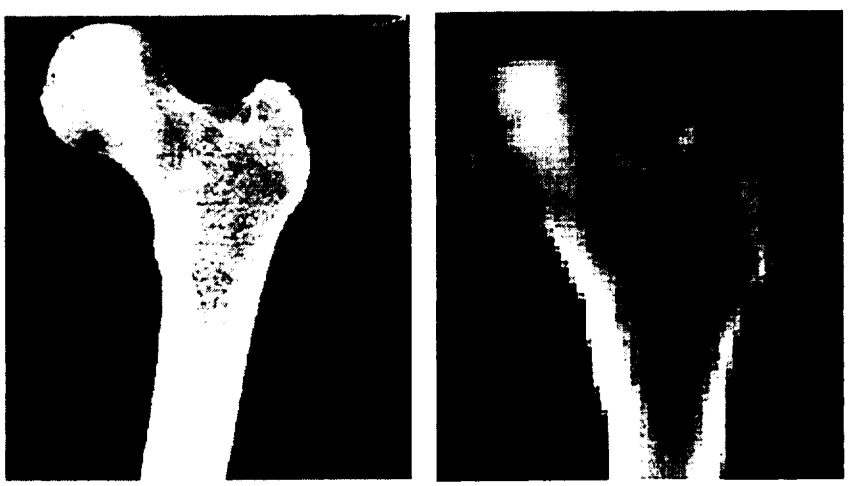


Drs. Babs Soller and Patrick Idwasi.

- Developed the Advanced Multiple Projection Dual Energy X-ray Absorptiometry (AMPDXA) Scanning System to measure bone loss. Clinical trials are now under way. (Charles, Jr., H. K., T. J. Beck, H. S. Feldmesser, T. C. Magee, T. S. Spisz, and V. L. Pisacane. Precision bone and muscle loss measurements by advanced, multiple projection DEXA (AMPDXA) techniques for spaceflight applications. *Acta Astronaut* 49(3-10):447-450, August-November 2001.)



Artist's concept of space-based protoflight Advanced Multiple Projection Dual Energy X-ray Absorptiometry (AMPDXA).



Comparison of AMPDXA, left, versus conventional DXA using same bone.

Patent Applications:

Charles, Jr., H. K., T. J. Beck, H. S. Feldmesser, T. C. Magee, J. A. Weiner, D. M. Lee, and C. E. Bennett. Method and apparatus for multiple projection dual energy x-ray absorptiometry scanning. JHU/APL File No. 1449-NSBRI, 2001.

Charles, Jr., H. K., T. J. Beck, H. S. Feldmesser, and T. C. Magee. Techniques for deriving tissue structure from multiple projection, dual energy x-ray absorptiometry. JHU/APL File No. 1784-NSBRI, 2001.

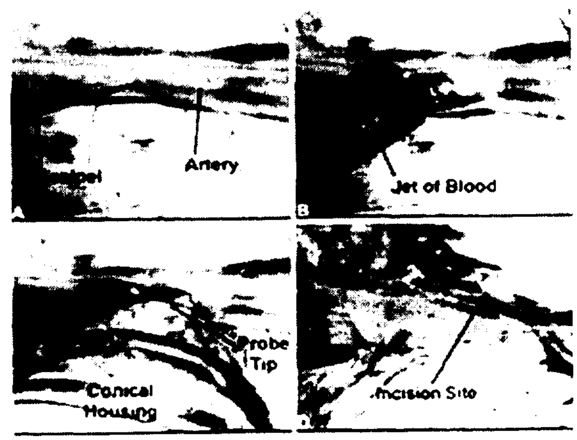
Invention Disclosure:

Charles, Jr., H. K., and T. J. Beck. Highly efficient and compact x-ray source employing a thin transmission target with spray cooling suitable for use in dual energy x-ray absorptiometry (DXA) and other x-ray systems, 2001.

- Refined the Microvolt T-Wave Alternans test as a non-invasive method to identify risk for cardiac arrest and sudden death during space flight. This technology has been cleared by the FDA and approved by Medicare for reimbursement. The device can be used on Earth in hospitals and emergency departments to predict cardiac arrhythmias and the risk of sudden death.

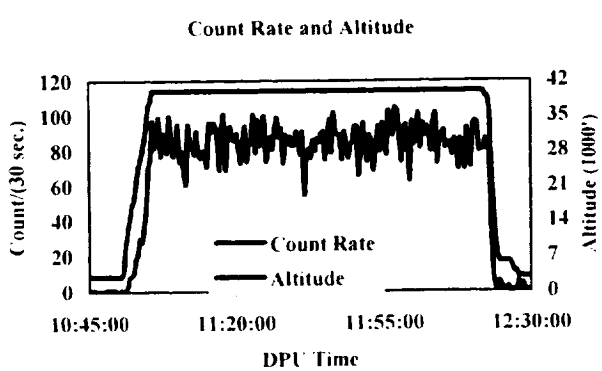
- Developed a small, lightweight ultrasound scanner capable of providing accurate prediction of bone physical properties and structural information for use in space flight. Instrumentation refinements completed allowing animal testing. (Lin, W., Y. X. Qin, and C. Rubin. Ultrasonic wave propagation in trabecular bone predicted by the stratified model. *Ann Biomed Eng* 29(9):781-790, September 2001.)

- Helped further development of a high-intensity, focused ultrasound (HIFU) system for hemorrhage control and destroying unwanted tissue or tumors. (Lafon, C., O. A. Sapozhnikov, V. A. Khokhlova, P. J. Kaczkowski, M. R. Bailey, and L. A. Crum. Use of a bovine eye lens for real-time observation of HIFU-induced lesion evolution. *Ultrasound Med Biol*, submitted.)



Technological Advances in Environment Monitoring

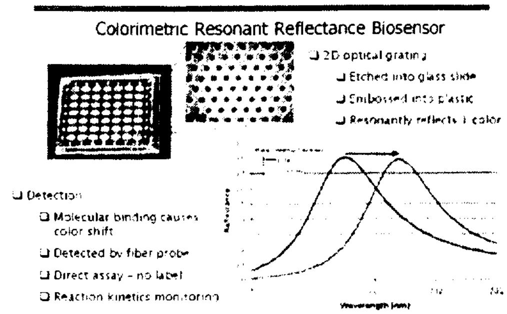
- Developed an engineering prototype of a neutron scanner for space operations that has already been flown in several aircraft at altitudes up to 40,000 feet. The device will next be flown at high altitude (90,000 feet) in a balloon flight for 20 hours.



[3]He tube count versus DPU time. Note that the count is the count rate integrated for 30 seconds. Right ordinate is aircraft altitude versus DPU time. Note the pilot had to contend with air traffic controllers on the approach leg of the trip.

- Developed biosensor for microbes and toxins that has application in the bioterrorism field.

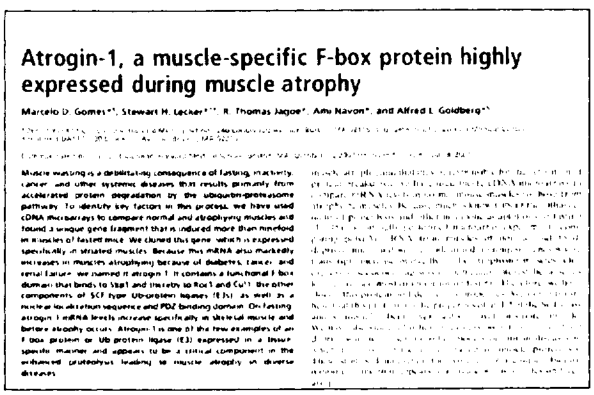
SRU Technology Platform



M. Klempner and B. Cunningham, et al: Real-time assessment of microbial environment for early detection, treatment and manipulation. Other applications include non-microbial sensing, such as proteins, toxins, pharmaceuticals. Project is under development with a start-up biotech company.

Basic Science Advances

- Discovered Atrogin-1, a gene that is highly expressed during muscle atrophy and is associated with protein degradation.


Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy

Marcelo D. Gomes, Stewart H. Lecker, R. Thomas Jagoe, Ami Navon, and Alfred L. Goldberg

Gomes, M.D., S. H. Lecker, R. T. Jagoe, A. Navon, and A. L. Goldberg. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proc Natl Acad Sci 98(25):14440-14445, December 2001.

- Discovered that altered blood flow and fluid flow in bone affects bone cells in ground-based microgravity simulation studies. (Bloomfield, S. A., H. A. Hogan, and M. D. Delp. Decreases in bone blood flow and bone material properties in aging Fischer-344 rats. *Clin Orthop* 396:428-457, March 2002.)

- Documented in ground-based research that space travel will lead to a weakened immune system. (Shearer, W. T. Contamination of the spacecraft environment: immunologic consequences. *Gravit Space Biol Bull* 14(2):7-14, June 2001.)

- Demonstrated in Antarctic studies that isolation and confinement leads to increased excretion and/or reactivation of latent viruses and a "turning off" of some of the immune system. (Shearer, W. T., B. N. Lee, S. G. Cron, H. M. Rosenblatt, E. O. Smith, D. J. Lugg, P. M. Nickolls, R. M. Sharp, K. Rollings, and J. M. Reuben. Suppression of human anti-inflammatory plasma cytokines IL-10 and IL1-RA with elevation of proinflammatory cytokine IFN-γ during the isolation of the Antarctic winter. *J Allergy Clin Immunol*, (5 Pt 1):854-857, May 2002.

- Found that reactivation of viruses is of concern under extreme conditions because they may be involved in cancer development, in addition to non-malignant disease. (R. A Vilchez, C. R. Madden, C. A. Kozinetz, S. J. Halvorson, Z. S. White, J. L. Jorgensen, et al. *The Lancet* 359:817-823, 2002.)

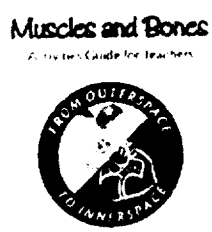
- Proved that chronic sleep restriction affects behavioral capability and the endocrine system. (Shearer, W. T., J. M. Reuben, J. M. Mullington, N. J. Price, B. N. Lee, E. O. Smith, M. P. Szuba, H. P. A. Van Dongen, and D. F. Dinges. Soluble tumor necrosis factor-alpha receptor 1 and interleukin-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol,* 107: 165-170, 2001.)

4. SELECTED EDUCATION AND PUBLIC OUTREACH ACCOMPLISHMENTS

Members of the Education and Public Outreach Team work with the various Institute research teams to inspire and communicate the excitement and importance of space life sciences to students, teachers and the general public. Several of the Education and Public Outreach Team achievements are listed here showing the variety of work being done and materials available. Another component of the Education, Training and Outreach Program of the NSBRI is the Communications and Outreach group, which is responsible for information dissemination to scientists and the public (Appendix 6).

Education and Public Outreach Materials

- Developed the first three in a series of educational materials for grades 4-6. Each guide highlights an Institute research area.



B. Thomson and N. Moreno, et al: *From Outerspace to Innerspace: Activity Guides for Teachers, Baylor College of Medicine.*

- Developed two problem-based, case study curriculum guides addressing sleep and circadian rhythms and neurovestibular function. These studies give students enough information to proceed with investigations but require them to undertake further investigation to solve the problem at hand. In partnership with the Harvard Medical School Teacher Institute, Morehouse School of Medicine created these guides for 5th through 12th grade teachers and students. (M. MacLeish, et al: *What's Up With Jose* and *Cecilia's Story,* Morehouse School of Medicine.)

- Created two teacher professional development programs including workshops, summer institutes and research experiences for middle- and high-school teachers. (R. James, et al: *Teacher Academy Project,* Texas A&M University; and R. Smith and C. Houston, et al: *Outreach Program for the Professional Development of Students and Teachers on Studies Related to Biomedicine in Outer Space,* Rice University and the University of Texas Medical Branch at Galveston.)

- Developed and evaluated a graduate-level curriculum to educate a generation of scholars in space life sciences. The course work is being adapted to the undergraduate level. (D. Newman, *Space Biomedical Sciences and Engineering Curriculum and Outreach Program*, Massachusetts Institute of Technology.)

- Created two student research programs allowing high school and college students to spend a summer working in research laboratories and explore the life of a research scientist. (A second focus of M. MacLeish, et al: *MSM Undergraduate Summer Research Program*, Morehouse School of Medicine. Also a second focus of R. Smith and C. Houston, et al: *Outreach Program for the Professional Development of Students and Teachers on Studies Related to Biomedicine in Outer Space*, Rice University and the University of Texas Medical Branch at Galveston.)

- Developed an opportunity where students in the University of Washington's Technical Communications program will have the opportunity to interview NSBRI researchers as part of a science writing course. Articles appear in the magazine *Northwest Science and Technology*. (D. Illman: *Northwest Outreach Program on Space Biomedical Research*, University of Washington.)

Appendices to the NSBRI Progress Report are available upon request.

Please contact the NSBRI at 713-798-7412 if a copy of the appendices is needed.

Appendix J

REPORT ON INSTITUTE ACTIVITIES

Jeffrey P. Sutton, M.D., Ph.D.

Board of Directors Meeting

Washington, D.C.

September 26-27, 2002

I. Overview

The past six months have been a busy and critical time for the Institute, with a ubiquitous and strong effort throughout the NSBRI community to work towards stabilizing our Institute, and ensuring that we have a bright and productive future in order to meet our mission as set forth by NASA.

II. Strategic Plan and Review

Strategic Plan Volumes I and II were completed over a seven-week period following the last Board of Directors meeting. They were delivered on time to NASA for external peer review, and then reviewed at a meeting in Washington on June 10-11, 2002. The strategic planning effort, including the response to the review, was collaborative and reflective of the cooperative partnership between the NSBRI and JSC. Special recognition and appreciation are extended to Bobby Alford, M.D., Ron White, Ph.D., General Jefferson Howell, Jr., David Williams, M.D., John Rummel, Ph.D., Judith Robinson, Ph.D. and the Team Leaders. The Institute is also appreciative of the Review Committee, chaired by Judith Vaitukaitis, M.D., who carefully evaluated the materials and gave in depth consideration to, and recommendations regarding, the strengths and shortcomings of our Institute.

As members of the Board of Directors already know, *Strategic Plan Volume I* presents a gap analysis between the Institute's current strategies and those needed to meet the objectives and goals of the Institute, as laid out in NASA Cooperative Agreement Notice 9-CAN-96-01 and subsequent augmentation guidelines. *Strategic Plan Volume II* contains the strategic plans for each of the eleven research teams, as well as the Education and Public Outreach Team. Both volumes are science driven and mission oriented.

Three other related documents were prepared as ancillary materials to the *Strategic Plan*. A *Progress Report* outlines the principle accomplishments of the Institute and summarizes how the Institute has addressed all recommendations of the 2000 Site Visit Report of the National Space Biomedical Research Institute. An *Executive Financial Summary* gives a baseline from which the budget contained in the *Strategic Plan* projects forward over five years. A *Presentation to Panel* booklet summarizes the *Strategic Plan* and related materials in the context of the Review Committee's assessment criteria.

The Review of the NSBRI Strategic Research Plan concludes that the Institute has made outstanding progress and that there is a need for adequate and stable funding. In particular,

> *The original budgetary discussions of an annual NSBRI budget of 50 million to 100 million dollars, in addition to the baseline Biomedical Research Program, would be appropriate to support research into the health risks associated with space flight. The need is urgent because health risks are likely to increase cumulatively.* (p. 8)

The Review is an important document containing critiques and recommendations on eleven topics. Matters pertaining to these topics were addressed in a joint JSC/NSBRI response to NASA HQ on June 21, 2002. On June 28, 2002, the Acting Director of the Division of Bioastronautics at NASA HQ, along with Dr. Vaitukaitis, wrote a letter to the Associate Administrator, Ms. Mary Kicza, of NASA's Office of Biological and Physical Research (OBPR) stating that the peer review of the NSBRI Strategic Plan had been successfully completed. Subsequently, on July 10, 2002, Ms. Kicza wrote to JSC Center Director, General Howell, stating that

> *The recommendation that 'NASA should increase and stabilize the NSBRI budget' will require changes to our current plans. We will take these recommendations, together with the results of the Research Maximization and Prioritization (REMAP) task force, into account in our budget discussions this summer.*

On August 29, 2002, the NSBRI received a letter from the JSC Contracting Officer informing the Institute that, for planning purposes, the NSBRI should presume a \$30 M total budget (\$29 M plus \$1 M for Advanced Medical Care Systems) for FY 2003 through FY 2007.

Going forward, it will be necessary to modify the *Strategic Plan*. Changes to *Strategic Plan Volume I* include, but are not limited to, addressing topics contained in the Review (e.g., Topic 2 – Team Leader selection, Topic 3 – productivity metrics, Topic 6 – bioinformatics), as well as providing updated budget projections based on NASA's budget for the NSBRI. The EAC should review a revised version of *Strategic Plan Volume I*, as well as the team strategic plans contained in *Strategic Plan Volume II*, in accord with the EAC responsibilities set forth in the 1997 *A Proposal for the Establishment of the National Space Biomedical Research Institute (NSBRI)*.

A key point to emphasize is the need for productivity and the generation of demonstrable countermeasures (see Section VI). As stated in the June 28, 2002, letter referenced above,

> *the Institute needs to make real and measurable progress towards developing active interventions at higher Countermeasure Readiness Levels (CRLs). The NSBRI should develop tangible performance metrics in order to assess their progress in transitioning toward higher CRLs.*

III. Scientific Progress

Investigators continue to make good progress on projects, although the 25% average reduction in research support has had an impact on productivity.

a. Selected Team Achievements

Dr. Bloomfield and Bone Loss Team colleagues at Texas A&M University have completed 91 hindlimb unloading experiments in rats showing that isometric torque and muscle mass recovers to pre-unloading values after 14 days of normal cage activity; whereas, total bone mineral density remains depressed by 7-10% through 28 days of normal cage activity (preliminary results published in *Bone*, 2002;149-157). The investigators are seeking the time interval of maximal mismatch between bone mass and muscle strength, in order to focus upcoming countermeasure experiments on that interval.

In related work, Dr. Goldberg and colleagues at Harvard Medical School and on the Muscle Alterations and Atrophy Team have focused on gene changes associated with muscle atrophy. Their earlier work showing dramatic increases in mRNA for the ubiquitin ligase atrogin-1 was reported late last year in *PNAS*. This has been followed by a recent paper (*Nature Medicine*, 2002;8:338-340), which offers new insights into pathways to reduce muscle atrophy.

On the Neurobehavioral and Psychosocial Team, Drs. Carter and Buckey, and colleagues at Dartmouth Medical School, have completed interviews with ten astronauts and cosmonauts from long-duration missions, and are using their data to help develop a computer-based system for self-diagnosis and treatment of psychosocial problems (*JAMA*, 2002;288:822). Dr. Wood at NASA/JSC discussed aspects of psychosocial challenges in the Antarctic winter environmental analog to space in *Highlights for Children* (September, 2002; circulation 2.5 million).

The Immunology, Infection and Hematology Team continues to make excellent progress in several areas: Antarctic winter human model of space flight; radiation and viral infection mouse model; human stem-cell monitoring post radiation; anti-orthostatic mouse model of microgravity; and microbial monitoring. Dr. Sonnenfeld and colleagues at Morehouse School of Medicine have demonstrated impaired resistance to gram-negative organisms in anti-orthostatic mice (*J Allergy Clin Immunol*, 2002;110:262-268) and Dr. Shi and colleagues at Robert Wood Johnson Medical School have shown increased expression of Fas/Fas L (apoptosis) on lymphocytes (blocked by anti Fas L) in the same animal model (*Brain Behav Immun*, 2002, in press).

Dr. Vazquez and Radiation Effects Team collaborators at Brookhaven National Laboratory are following 180 of the 498 C57B1/6 male mice exposed to acute doses of 0.15 to 4.8 Gy Fe ions and gamma radiation during the last NASA run (BNL-8, April 2002). The animals are being monitored to detect memory function alterations and changes in hippocampal biochemistry. These investigators have recently shown that doses as low as 0.25 Gy of heavy ions are able to up-regulate p53 within hours in human neural precursor cells and rodent glial progenitor cells (CG4). bFGF as a countermeasure is able to protect apoptosis induction in CG4.

Dr. Cohen from MIT and Dr. Meck from NASA/JSC, and their co-workers on the Cardiovascular Alterations Team, have complementary flight projects involving orthostatic hypotension. Both studies have completed the definition phase for flight study and Midodrine, as a countermeasure for post-flight orthostatic hypotension, has been used with good results in one astronaut. Interestingly, nearly all females, while only 50% of males, are tilt intolerant following simulated microgravity. The mechanisms are being investigated.

Scientists on the Smart Medical Systems Team and Technology Development Team continue to make advances on enabling technologies for countermeasures. The Sutton project has used SpaceDOCK, a new software program developed with a NASA flight surgeon, to evaluate performance in awake- and sleep-deprived subjects undergoing simultaneous brain fMRI and diffuse optical tomography (DOT) imaging (*NeuroImage*, 2002, in press). The results reveal objective measures of brain function obtained by a portable, non-invasive means (DOT), which is a technology desirable to the medical operations community. Also, in collaboration with JSC medical operations and Ames Research Center personnel, and with new (NSBRI leveraged) support from the Department of Defense, Dr. James Thomas of the Cleveland Clinic Foundation has been participating in wireless demonstrations of portable ultrasonography and transmission. The system is being developed for future physiological studies and medical care aboard the ISS.

At Johns Hopkins University, Dr. Charles has filed a provisional U.S. patent application related to his technology project on an Advanced, Dual Energy X-ray Absorptiometry (AMPDXA) Scanning System. Dr. Charles' work will be featured in an upcoming issue of *Advancing Microelectronics*, where the cover will illustrate the AMPDXA in a space setting.

b. Selected Inter-Team Achievements

There is clear evidence of added value across projects and teams. The Human Performance Team is using the theme of understanding light input to the circadian system to use light, which is already an operational countermeasure, in more effective ways. For example, Dr. Brainard from Jefferson Medical College, has made significant progress on optimizing the light spectrum to enhance performance. Since March 2002, the Team has 15 new publications, three papers in press, five manuscripts that have been submitted for publication, 51 presentations, eight new awards funded totaling $3.8 M and four new grant proposals that have been submitted.

Appendix I of this report contains an outline of an upcoming special issue of *Nutrition*, which is co-edited by the Team Leader and a co-investigator on the Nutrition, Physical Fitness and Rehabilitation Team. The issue involves 23 members throughout our NSBRI/NASA community and demonstrates the interdisciplinary expertise that the Institute brings to address important biomedical problems related to nutrition in space.

Similarly, the Neurovestibular Adaptation Team has an upcoming special issue of the *Journal of Vestibular Research* highlighting research findings on their team.

Projects from the former Integrated Human Function Team have been successfully re-assigned to other research teams and are being leveraged to support a NSBRI/NASA focus on exercise countermeasures. A *Report on Exercise Workshop for NSBRI Digital Human Modeling Core*, authored by Martin Kushmerick, M.D., Ph.D., summarizes the directions that the new Core is taking.

Principal investigators from three teams recently visited Germany to discuss ground-based research efforts. Also, an international initiative is being coordinated to advance studies in artificial gravity.

IV. NSBRI/NASA Coordination

There have been many changes in senior leadership positions at NASA HQ and JSC, and the NSBRI has been active to ensure that strong connections remain, and new ones are formed, with our NASA partner. The valuable role that the NSBRI has for NASA was evident in the plenary talk given by Ms. Mary Kicza at the September 2002 EAC meeting in Philadelphia.

The NSBRI continues to play a central role in the evolution of the Critical Path Roadmap. The Institute has also been participating in the **Risk Mitigation Collaborative Group**, headed by Jeffrey Davis, M.D., the new Director of the Space and Life Sciences Directorate at JSC and by Guy Fogleman, Ph.D., the Acting Director of the Division of Bioastronautics at NASA HQ. The Group examines, in part, biomedical risk reduction strategies for different mission scenarios, which include multiple factors, such as risk type, consequences, likelihood, current countermeasure readiness and crew health, safety and performance requirements. NASA participants include NASA's Chief Scientist, Shannon Lucid, Ph.D., Chief Health and Medical Officer, Richard Williams, M.D., and leaders from OBPR, the Office of Space Flight and JSC. The activities of this Group help determine the research priorities on the Critical Path Roadmap, and hence the NSBRI, whose research activities must be coordinated with NASA priorities and needs.

Another area where there has been increased coordination is in the solicitation and peer-review of NASA Bioastronautics and NSBRI proposals (see Section V).

NASA's budget to the NSBRI specifies funding for Advanced Medical Care Systems, where the NSBRI is to collaborate with JSC personnel on joint projects having direct operational need. Two projects are currently under development. One project concerns the design and testing of a space-adapted human patient simulator for training purposes. A second project refines non-invasive physiological sensors for astronaut exercise assessment and utilization.

V. New Proposals

On October 31, 2001, NASA released solicitation NRA 01-OBPR-07 on behalf of three programs, including the NSBRI. Fifty-one proposals were received by the NSBRI and subsequently underwent peer review along with the other NASA proposals. Twenty-five proposals were in the competitive range (a score of 70 or greater out of 100). Four proposals were transferred from NASA to the NSBRI. Representatives of NSBRI Senior Management attended the NASA selection meeting. All 29 proposals were reviewed for programmatic relevance by appropriate Team Leaders. A combination of peer-review score and relevancy categorized the proposals, which were then prioritized by the EAC for funding. Selection of new proposals will depend upon the FY 2003 budget.

Unlike past solicitations and reviews, the NSBRI shared many aspects of the solicitation-review-selection cycle with NASA. The process worked well in many respects. However, the NSBRI may wish to consider having the BSC have a direct role in overseeing the peer-review process for the Institute, rather than delegating the task to NASA. The rationale is that review of applied countermeasure research requires different panels than those reviewing basic R01-type research for NASA, and continuity in expert panel membership may serve the Institute better than ad-hoc panel composition.

In addition to research proposals submitted in response to the joint NASA/NSBRI solicitation, a proposal for a fellowship program was received from Morehouse School of Medicine. The establishment of an Institute fellowship program is a priority for FY 2003, if the budget will allow this program to be launched. The Morehouse proposal is being forwarded to the BSC for review.

VI. Countermeasure Productivity

A concerted effort is under way to have improved methods for tracking, evaluating and ensuring countermeasure productivity. A user-friendly electronic system for investigators to upload information, such as scientific articles, presentations, patent applications and collaborations with NASA scientists, is scheduled for completion by the end of 2002. The system will be used to generate project and team reports in a standard format, and it will allow management to better assess progress and implementation of current team strategies.

There is also a need to identify and foster the most promising projects that will deliver countermeasures of high priority and impact to NASA. In the initial NSBRI proposal, a Research Steering Committee consisting of a Chairperson and the Team Leaders was to coordinate projects. The Committee was to be expanded to include representatives from JSC. However, the Committee was short-lived and it is apparent that the Institute can benefit from a panel to help foster due diligence on promising projects. It is imperative that the Institute begins to have demonstrable countermeasure deliverables and "success stories."

After consultation with representatives from the Board of Directors, Team Leaders, Industry Forum and venture capital, User Panel, EAC, BSC and NASA, a **Committee on Research and Technology Transfer (CRTT)** has been formed (see Appendix II). The purpose of the Committee is to help determine what next action steps are most appropriate to "fast track" scientifically meritorious projects, that also have a high probability of success for countermeasure transfer and/or commercialization.

VII. Guidelines for Team Leadership

A draft document for NSBRI team leadership guidelines has been prepared and circulated to Team Leaders and to EAC members. The document is currently undergoing revision and should be ready for presentation to the Board of Directors at the next Board meeting.

VIII. Leadership Changes

Martin Fettman, D.V.M., Ph.D., Chairman of the EAC, will be stepping down from service on the EAC following the September 2002 Board of Directors meeting. His valuable leadership and contributions to the NSBRI over the years are greatly appreciated. We wish Dr. Fettman continued success in the future.

Lawrence Crum, Ph.D., from the University of Washington, has been elevated from Associate Team Leader to Acting Team Leader for the Smart Medical Systems Team.

IX. Budget

The President's FY 2003 budget for the NSBRI is $17.2 M, including $1 M for Advanced Medical Care Systems. The Senate markup of the President's FY 2003 budget identifies the NSBRI to receive $7.5 M above the President's FY 2003 budget. The budget now goes before the House. Dr. Alford and other members of the Board of Directors are to be commended for their outstanding efforts in working with Congress on behalf of our Institute.

NASA's acceptance of the NSBRI *Strategic Plan*, as the proposal for the second 5-year period of performance for the NASA Cooperative Agreement NCC 9-58, instructs the Institute to presume, for planning purposes, a budget of $30 M for FY 2003 through FY 2007 (Section II). The actual NSBRI budget from NASA will depend upon multiple factors, including the OBPR budget changes as a result of the Research Maximization and Prioritization (REMAP) Task Force recommendations, and Congress.

In July 2002, the REMAP Task Force reported to the NASA Advisory Council. The final REMAP report is available online at http://spaceresearch.nasa.gov/general_info/remapreport.html. The Committee was assembled to assist OBPR in establishing a prioritized program for its research portfolio. The highest priority areas in biomedical research include radiation health, behavior and performance, physiology (integrated and organ system physiology) and clinical/operational medicine. Many of the recommendations of the REMAP report encompass and endorse a NSBRI-like model for research, including goal directed programs, visionary strategies and an interdisciplinary organization aligned along research questions rather than disciplines.

X. Priorities Going Forward

- Implement an appropriate tactical plan based on the actual FY 2003 NSBRI budget. The priority areas are the ongoing research program, new proposals and the fellowship program.
- Continue to strengthen ties with NASA to enable high countermeasure readiness level research and transition to flight and operations, where appropriate.
- Refine mechanisms to foster and track countermeasure productivity and "success stories" within our program (e.g., CRTT).
- Reconstitute the BSC, augment and balance the EAC membership and re-engage the User Panel.
- Have *Strategic Plan Volumes I (revised) and II* reviewed by the EAC.
- Develop a solicitation for FY 2004 proposals, focused on countermeasure research that will allow the Institute to successfully meet its mission.

Appendix I

Special Upcoming Issue of *Nutrition*

NUTRITION
THE INTERNATIONAL JOURNAL OF
APPLIED AND BASIC NUTRITIONAL SCIENCES

Upcoming Issues

October Special Issue 2002

Nutrition In Space

edited by Joanne R. Lupton, PhD
Professor
and
Nancy Turner, PhD, CNS
Professor
from Texas A&M University
College Station, Texas, USA

Authors	Title
Borchers AT, Keen CL, Gershwin, ME	Microgravity and immune responsiveness: implications for space travel
Cassone VM, Stephan FK *Cassone is a member of the neurovestibular team, NSBRI*	Central and peripheral regulation of feeding and nutrition by the mammalian circadian clock: implications for nutrition during manned space flight
Convertino VA *Convertino is an EAC member, NSBRI*	Planning strategies for development of effective exercise and nutrition countermeasures for long duration spaceflight
Da Silva MS, Zimmerman PM, Meguid MM, Nandi J, Ohinata K, Xu Y, Chen C, Tada T, Inui A	Anorexia in space and possible etiologies: an overview
Fang YZ, Yang S, Wu G	Free radicals, antioxidants and nutrition
Ferrando AA, Paddon-Jones D, Wolfe RR *This group consists of members of the nutrition and physical fitness team, NSBRI*	Alterations in protein metabolism during space flight and inactivity
Heer M	Nutritional interventions related to bone turnover in European space missions and simulation models
Kerwin J, Seddon R *Kerwin is a member of the Board of Directors, Industry Forum and User Panel, and Seddon is an EAC member, NSBRI*	Eating in Space - from an Astronaut's perspective

Lane HW and Feeback D L *Lane is a member of the nutrition and physical fitness team, NSBRI*	Overview: history of nutrition in spaceflight
Lane HW and Feeback D L *Lane is a member of the nutrition and physical fitness team, NSBRI*	Water and energy dietary requirements and endocrinology of human spaceflight
Perchonok M and Bourland, C *Perchonok is on the nutrition and physical fitness team, NSBRI*	NASA Food Systems: past, present and future
Smith SM and Heer M *Smith is on the nutrition and physical fitness team, NSBRI*	Calcium and bone metabolism during spaceflight
Smith SM *Smith is on the nutrition and physical fitness team, NSBRI*	Red blood cell and iron metabolism during spaceflight
Smith SM, Uchakin, PN, Tobin, BW *Smith, Uchakin and Tobin are all on the nutrition and physical fitness team, NSBRI*	Spaceflight nutrition research: platforms and analogs
Soller BR, Cabrera M, Smith SM, Sutton JP *Soller is on the smart medical systems team, Cabrera is part of the integrated human function core and on the nutrition and physical fitness team, Smith is on the nutrition and physical fitness team, Sutton is Director, NSBRI*	Smart medical systems with application to nutrition and fitness in space
Sonnenfeld G *Sonnenfeld is Associate Team Leader for the immunology, infection and hematology team, NSBRI*	Immune function during space flight
Stein TP	Space flight and oxidative stress
Tobin BW, Uchakin PN, Leeper-Woodford SK *Tobin and Uchakin are on the nutrition and physical fitness team, NSBRI*	Insulin secretion and sensitivity in spaceflight: diabetogenic effects
Turner ND, Braby LA, Ford J, Lupton JR *All authors are on the nutrition and physical fitness team, Lupton is Team Leader of the nutrition and physical fitness team, NSBRI*	Opportunities for nutritional amelioration of radiation-induced cellular damage
Wade CE, Miller MM, Baer LA, Moran MM, Steele MK, Stein TP	Body mass, energy intake and water consumption of rats and humans during spaceflight
Williams DR *Williams is former Director of the Space and Life Sciences Directorate, NASA JSC*	Bioastronautics: optimizing human performance through research and medical innovations
Zerwekh JE *Zerwekh is on the bone loss team, NSBRI*	Nutrition and renal stone disease in space

Appendix II

Committee on Research and Technology Transfer (CRTT) [1]

NSBRI Senior Management

Jeffrey Sutton, M.D., Ph.D. (NSBRI), Chair
Ron White, Ph.D. (NSBRI)

Team Leaders

Harry Charles, Ph.D. (Johns Hopkins, Technology Development Team)
Richard Cohen, M.D., Ph.D. (MIT, Cardiovascular Alterations Team)
Lawrence Crum, Ph.D. (U Washington, Smart Medical Systems Team)
Jay Buckey, Jr., M.D. (Dartmouth, Technology Development Team)

NASA/JSC Medical Operations

Nitza Cintron, M.D., Ph.D.
Craig Fischer, M.D.

Industry Forum

Joseph Kerwin, M.D. (Wyle) [2]
Mark Wilson (Boeing)

User Panel

Owen Garriott, Ph.D.

Board of Directors

Susanne Churchill, Ph.D. (Harvard)

External Advisory Council

Theodore Berger, Ph.D. (USC)

Board of Scientific Counselors

Hal Broxmeyer, Ph.D. (Indiana U)

Academic-Industry Enterprises

Frank Lansburger, Ph.D. (MIT)

Venture Creation/Capital

Noubar Afeyan, Ph.D. (Flagship Ventures)

Legal/Intellectual Property

TBD

---

[1] Updated October 4, 2002
[2] Dr. Kerwin is also a member of the Board of Directors and User Panel

Appendix K

National Space Biomedical Research Institute

Core Research Program Publications and Presentations List

October 1, 2001 – September 30, 2002

National Space Biomedical Research Institute Publications

Articles

Belay, T., and G. Sonnenfeld. Differential effects of catecholamines on *in vitro* growth of pathogenic bacteria. *Life Sci* 71:447-456, 2002.

Belay, T., H. Aviles, M. Vance, K. Fountain, and G. Sonnenfeld. Effects of the hindlimb-unloading model of spaceflight conditions on resistance on mice to infection with Klebsiella pneumoniae. *J Allergy Clin Immunol* 110:262-268, 2002.

Bloomfield, S. A. Cellular and molecular mechanisms for the bone response to mechanical loading. *Int J Sport Nutr Exerc Metab Suppl* (S):128-136, December 11, 2001.

Bloomfield, S. A., H. A. Hogan, and M. D. Delp. Decreases in bone blood flow and bone material properties in aging Fischer-344 rats. *Clin Orthop* 396:428-457, March 2002.

Bloomfield, S. A., M. R. Allen, H. A. Hogan, and M. D. Delp. Site- and compartment-specific changes in bone with hindlimb unloading in mature adult rats. *Bone* 31(1):149-157, July 2002.

Brooks-Asplund, E. M., A. A. Shoukas, S. Y. Kim, S. A. Burke, and D. E. Berkowitz. Estrogen has opposing effects on vascular reactivity in obese, insulin-resistant male zucker rats. *J Appl Physiol* 92(5):2035-44, May 2002.

Chang, P. Y., N. Kanazawa, L. Lutze-Mann, and R. A. Winegar. HZE particle radiation induced tissue-specific and p53-dependent mutagenesis in transgenic animals. *Phys Med* 17, supplement 1:189-91, 2001.

Charles, Jr., H. K., T. J. Beck, H. S. Feldmesser, T. C. Magee, T. S. Spisz, and V. L. Pisacane. Precision bone and muscle loss measurements by advanced, multiple projection DEXA (AMPDXA) techniques for spaceflight applications. *Acta Astronaut* 49(3-10):447-450, August-November 2001.

Cucinotta, F. A., J. F. Dicello, H. Nikjoo, and R. Cherubini. Computational model of the modulation of gene expression following DNA damage. *Radiat Prot Dosimetry* 99(1-4):85-90, 2002.

Cucinotta, F. A., W. Schimmerling, J. W. Wilson, L. E. Peterson, G. Badhwar, P. Saganti, and J. F. Dicello. Space radiation cancer risks and uncertainties for Mars missions. *Radiat Res* 156:682-688, 2001.

Dang, L. H., C. Bettegowda, D. L. Huso, K. W. Kinzler, and B. Vogelstein. Combination bacteriolytic therapy for the treatment of experimental tumors. *Proc Natl Acad Sci* 98(26):15155-60, 2001.

Dijk, D. J., D. F. Neri, J. K. Wyatt, J. M. Ronda, E. Riel, A. Ritz-De Cecco, R. J. Hughes, A. R. Elliott, G. K. Prisk, J. B. West, and C. A. Czeisler. Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights. *Am J Physiol Regul Integr Comp Physiol* 281:R1647-1664, November 2001.

Dimitri, P. S., C. Wall III, J. G. Oas, and S. D. Rauch. Application of multivariate statistics to vestibular testing: discriminating between Meniere's disease and migraine associated dizziness. *J Vestib Res* 11(1):53-65, 2001.

Elstad, M., K. Toska, K. H. Chon, E. A. Raeder, and R. J. Cohen. Respiratory sinus arrhythmia: opposite effects on systolic and mean arterial pressure in supine humans. *J Physiol* 1:536(Pt 1):251-9, October 2001.

Glickman, G., R. Levin, and G. C. Brainard. Ocular input for human melatonin regulation: relevance to breast cancer. *Neuroendocrinology Lett* 23:17-22, July 2002.

Gomes, M. D., S. H. Lecker, R. T. Jagoe, A. Navon, and A. L. Goldberg. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. *Proc Natl Acad Sci* 98(25):14440-14445, December 2001.

Fukuhara C., J. C. Dirden, and G. Tosini. Regulation of Period 1 expression in cultured rat pineal. *NeuroSignals 11: 103-114*, 2002.

Hecht, H., J. Kavelaars, C. C. Cheung, and L. R. Young. Orientation illusions and heart-rate changes during short-radius centrifugation. *J Vestib Res* 11(2):115-127, 2001.

Heldt, T., E. B. Shim, R. D. Kamm, and R. G. Mark. Computational modeling of cardiovascular response to orthostatic stress. *J Appl Physiol* 29(3):1239-1254, March 2002.

Hirasaki, E., S. T. Moore, T. Raphan, and B. Cohen. Head and body movements in the yaw and roll planes during straight walking. *Soc Neuroscience*, November 2001.

Howard, I., and G. Hu. Visually induced reorientation illusions. *Perception* 30(5):583-600, 2001.

Judex, S., L. R. Donahue, and C. T. Rubin. Genetic predisposition to osteoporosis is paralleled by an enhanced sensitivity to signals anabolic to the skeleton. *FASEB J Express* 10.1096/fj.01-0913fje, 2002.

Kourentzi, K. D., G. E. Fox, and R. C. Willson. Microbial identification by immunohybridization assay of artificial RNA labels. *J Microbiol Methods* 49(3):301-306, May 2002.

Lednicky, J. A., S. J. Halvorson, and J. S. Butel. PCR detection and DNA sequence analysis of the regulatory region of lymphotropic papovavirus in peripheral blood mononuclear cells of an immunocompromised rhesus macaque. *J Clin Microbiol* 40(3):1056-1059, March 2002.

Lieberman, P. Human language and our reptilian brain. The subcortical bases of speech, syntax, and thought. *Perspect Biol Med* 44(1):32-51, Winter 2001.

Martin, E., Y-C Lee, and F. Murad. YC-1 activation of human soluble guanylyl cyclase has both heme-dependent and heme-independent components. *PNAS* 98(23):12938-12942, November 6, 2001.

Meerlo P., M. Koehl, K. van der Borght, and F. W. Turek. Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. *J Neuroendocrinol*, 14: 397-402, 2002.

Miller, T. A., L. A. Lesniewski, J. M. Muller-Delp, A. K. Majors, D. Scalise, and M. D. Delp. Hindlimb unloading induces a collagen isoform shift in the soleus muscle of the rat. *Am J Physiol Regul Integr Comp Physiol* 281(5):R1710-1717, November 2001.

Monahan, K. D., and C. A. Ray. Limb neurovascular control during altered otolithic input in humans. *J Physiol* 538(Pt 1):303-308, January 2002.

Monahan, K. D., M. K. Sharpe, D. Drury, A. C. Ertl, and C. A. Ray. Influence of vestibular activation on respiration in humans. *Am J Physiol Regul Integr Comp Physiol* 282(3):R689-94, March 2002.

Monahan, K. D., and C. A. Ray. Interactive effect of hypoxia and otolith organ engagement on cardiovascular regulation in humans. *J Appl Physiol* 93(2):576-580, August 2002.

Moore, S. T., E. Hirasaki, T. Raphan, and B. Cohen. The human vestibulo-ocular reflex during linear locomotion. *Ann NY Acad Sci* 942:139-147, October 2001.

Mukkamala, R., and R. J. Cohen. A forward model-based validation of cardiovascular system identification. *Am J Physiol Heart Circ Physiol* 281(6):H2714-2730, December 2001.

Murphy, J. C., G. E. Fox, and R. C. Willson. Structured RNA isolation and fractionation with compaction agents. *Anal Biochem* 295:143-148, 2001.

Naghavi, M., R. John, S. Naguib, M. S. Siadaty, R. Grasu, K. C. Kurian, W. B. van Winkle, B. Soller, S. Litovsky, M. Madjid, J. T. Willerson, and W. Casscells. pH Heterogeneity of human and rabbit atherosclerotic plaques; a new insight into detection of vulnerable plaque. *Atherosclerosis* 164, 27-35, 2002.

Nyhan, D., S. Kim, S. Dunbar, D. Li, A. Shoukas, and D. Berkowitz. Impaired pulmonary artery contractile responses in a rat model of microgravity: role of nitric oxide. *J Appl Physiol* 92(1):33-40, January 2002.

Oman C. M., W. Shebilske, J. Richards, T. Tubre, A. Beall, and A. Natapoff. Three dimensional spatial memory and learning in real and virtual environments. *J Spatial Cognition and Computation* 2(4): 1-20, 2002.

O'Sullivan, C. E., R. S. Peng, K. S. Cole, R. C. Montelaro, T. Sturegeon, H. B. Jenson, and P. D. Ling. Epstein-Barr virus and human immunodeficiency virus serological responses and viral burdens in HIV-infected patients treated with HAART. *J Med Virol* 67:320-326, 2002.

Ray, C. A., and K. D. Monahan. The vestibulosympathetic reflex in humans: neural interactions between cardiovascular reflexes. *Clin Exp Pharmacol Physiol* 29(1-2):98-102, January-February 2002.

Rogers, N. L., and D. F. Dinges. Shiftwork, circadian disruption and consequences. *The Economics of Neuroscience* 3(9):1-7, 2001.

Rogers, N. L., M. P. Szuba, J. P. Staab, D. L. Evans, and D. F. Dinges. Neuroimmunologic aspects of sleep and sleep loss. *Semin Clin Neuropsychiatry* 6(4):295-307, October 2001.

Rubin, C. T., G. Xu, and S. Judex. The anabolic activity of bone tissue, suppressed by disuse, is normalized by brief exposure to extremely low magnitude mechanical stimuli. *FASEB J* 15:2225-2229, 2001.

Shearer, W. T., D. J. Lugg, H. M. Rosenblatt, P. M. Nickolls, R. M. Sharp, J. M. Reuben, and H. D. Ochs. Antibody responses to phiX-174 in human subjects exposed to the Antarctic winter-over model of spaceflight. *J Allergy Clin Immunol* 107:160-164, 2001.

Shearer, W. T., J. M. Reuben, J. M. Mullington, N. J. Price, B-N Lee, E. O. Smith, H. P. A. Van Dongen, M. P. Szuba, and D. F. Dinges. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 107:165-170, 2001.

Shearer, W. T. Contamination of the spacecraft environment: immunologic consequences. *Gravit Space Biol Bull* 14:7-14, 2001.

Shearer, W. T., B. N. Lee, S. G. Cron, H. M. Rosenblatt, E. O. Smith, D. J. Lugg, P. M. Nickolls, R. M. Sharp, K. Rollings, and J. M. Reuben. Suppression of human anti-inflammatory plasma cytokines IL-10 and IL1-RA with elevation of proinflammatory cytokine IFN-γ during the isolation of the Antarctic winter. *J Allergy Clin Immunol*, (109):854-857, May 2002.

Strangman, G., D. A. Boas, and J. P. Sutton. Noninvasive brain imaging using near infrared light. *Biol Psychiatry* 52:679-693, 2002.

Strangman, G., J. C. Culver, J. H. Thompson, and D. A. Boas. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *NeuroImage* 17:719-731, 2002.

Tosini G., and C. Fukuhara. The mammalian retina as a clock. *Cell and Tissue Res.* 309:119-126, 2002.

Vilchez, R. A., J. A. Lednicky, S. J. Halvorson, Z. S. White, C. A. Kozinetz, and J. S. Butel. Detection of polyomavirus SV40 tumor antigen DNA in AIDS-related systemic non-Hodgkin's lymphoma. *J Acquir Immune Defic Syndr* 29(2):109-116, February 1, 2002.

Vilchez, R. A., C. R. Madden, C. A. Kozinetz, S. J. Halvorson, Z. S. White, J. L. Jorgensen, C. J. Finch, and J. S. Butel. Association between simian virus 40 and non-Hodgkin lymphoma. *Lancet* 359(9309):817-823, March 9, 2002.

Wang, Y., D. L. Huso, H. Cahill, D. Ryugo, and J. Nathans. Progressive cerebellar, auditory, and esophageal dysfunction caused by targeted disruption of the frizzled-4 gene. *J Neurosci* 21(13):4761-71, 2001.

Wilkerson, M. K., P. N. Colleran, and M. D. Delp. Acute and chronic head-down tail suspension diminishes cerebral perfusion in rats. *Am J Physiol Heart Circ Physiol* 282 (1):H328-334, January 2002.

Wright, Jr., K. P., R. J. Hughes, R. E. Kronauer, D. J. Dijk, and C. A. Czeisler. Intrinsic near-24-hour pacemaker period determines limits of circadian entrainment to a weak synchronizer in humans. *Proc Natl Acad Sci* 98(24):14027-14032, November 20, 2001.

Yoo, J. Y., D. L. Huso, D. Nathans, and S. Desiderio. Specific ablation of Stat3beta distorts the pattern of Stat3-responsive gene expression and impairs recovery from endotoxic shock. *Cell* 108(3):331-44, 2002.

Young, L. R., H. Hecht, L. E. Lyne, K. H. Sienko, C. C. Cheung, and J. Kavelaars. Artificial gravity: head movements during short-radius centrifugation. *Acta Astronaut* 49(3-10):215-226, August-November 2001.

Zee, D. S., M. F. Walker, and S. Ramat. The cerebellar contribution to eye movements based upon lesions: binocular, three-axis control and the translational vestibulo-ocular reflex. *Ann NY Acad Sci* 956:178-179, April 2002.

Zhang, Z., R. C. Willson, and G. E. Fox. Identification of characteristic oligonucleotides in the 16S ribosomal RNA sequence dataset. *Bioinformatics* 18(2):244-250, February 2002.

Zhou, W., P. Weldon, B. Tang, and W. M. King. Rapid adaptation of translational vestibulo-ocular reflex: independence of retinal slip. *Ann NY Acad Sci* 956:558-560, April 2002.

Zhou, W., P. Weldon, B. Tang, and W. M. King. Rapid adaptation of translational vestibulo-ocular reflex: time course, consolidation and specificity. *Ann NY Acad Sci* 956:555-557, April 2002.

Articles (Submitted, In Press, or In Preparation)

Adams, G. R., V. J. Caiozzo, F. Haddad, and K. M. Baldwin. Cellular and molecular responses to increased skeletal muscle loading after irradiation. *Am J Physiol Cell Physiol*, 2002, in press.

Allen, M. R., and S. A. Bloomfield. Hindlimb unloading has a greater effect on cortical compared to cancellous bone in mature female rats. *J Appl Physiol*, 2002, in press.

Allen M. R., J. L. Stafinsky, C. Nolan, H. A. Hogan, S. A. Bloomfield, and C. L. Smith. Raloxifene attenuates bone loss in mechanically unloaded, ovariectomized female rats HLS rats, in preparation.

Aviles, H., T. Belay, K. Fountain, M. Vance, and G. Sonnenfeld. Increase susceptibility to Pseudomonas aeruginosa infection under hindlimb unloading conditions, submitted.

Baldwin, K. M., and F. Haddad. Skeletal muscle plasticity: cellular and molecular responses to altered physical activity paradigms. *Am J Phys Med Rehabil*, 2002, in press.

Berkowitz, D., L. Marucci, B. Winters, E. Asplund, D. Nyhan, and A. Shoukas. Impaired vascular reactivity in a rat model of microgravity. *J Appl Physiol*, in review.

Brooks-Asplund, E. and A. Shoukas. Baroreceptor contribution to the cardiovascular reflex responses of phenylephrine and sodium nitroprusside in the conscious rat. *Am J Physiol*, in review.

Brooks-Asplund, E. M., D. E. Berkowitz, S. L. Dunbar. and A. A. Shoukas. Hindlimb unweighting attenuates cardiac output and stroke volume responses to upright tilt in male rodents. *Am J Physiol*, in review.

Carter, J. R., C. A. Ray, and W. H. Cooke. Vestibulosympathetic reflex during mental stress. *J Appl Physiol*, in press.

Carter, J. R., C. L. Sauder, and C. A. Ray. Effect of morphine on sympathetic nerve activity in humans. *J Appl Physiol*, in press.

Cassone, V. M., and F. K. Stephan. Central and peripheral regulation of feeding and nutrition by the mammalian circadian clock: implications for nutrition during manned space flight. *Nutrition*, in press.

Dai, M., T. Raphan, and B. Cohen. Adaptation to roll-tilts during constant rotation, in preparation.

Davidson, A. J., A. S. Poole, S. Yamazaki, and M. Menaker. Food-anticipatory activity and circadian rhythms of Per1-luciferase activity in the rat digestive system, in preparation.

Davies, P. F. Multiple signaling pathways in flow mediated endothelial mechanotransduction: PYK-ing the right location. *Arter Thromb Vasc Biol*, 2002, in press.

DeWalt, B., J. C. Murphy, G. E. Fox, and R. C. Willson. Compaction agent clarification of microbial lysates. *Protein Expr Purif*, 2002, in press.

Dicello, J. F. How do we get from cell and animal data to risks for humans from space radiations? *J Radiat Res*, 2002, in press.

Dinges, D. F., H. P. A. Van Dongen, et al. Cumulative sleep loss in space flight: neurobehavioral consequences and countermeasures. *Acta Astronaut*, 2001, submitted.

Dornhoffer, J. L., N. Mamiya, P. Bray, R. D. Skinner, and E. Garcia-Rill. Effects of rotaton on sleep state-dependent midlatency auditory evoked P50 potential in human. *Exp Brain Res*, 2002, submitted.

Eatman, D., R. A. Listhrop, A. S. Beasley, R. R. Socci, I. Abukhalaf, and M. A. Bayorh. Influences of prostanoids and nitric oxide on post-suspension hypotension in female sprague-dawley rats. *Prostaglandins Leukot Essent Fatty Acids*, in press.

Ferrando, A. A., D. Paddon-Jones, and R. R. Wolfe. Alterations in protein metabolism during space flight and inactivity. *Nutrition*, 2002, in press.

Fukuhara, C., J. C. Dirden, and G. Tosini. Regulation of period 1 expression in the rat pineal. *J Appl Physiol*, 2001, submitted.

Gazendam, J. A. C., N. S. Freedman, H. P. A. Van Dongen, D. F. Dinges, A. I. Pack, and R. J. Schwab. Light-dark patterns in the intensive care unit. *Aviation, Space, and Environmental Medicine*, in press.

Glickman, G., J. Hanifin, M. D. Rollag, J. Wang, H. Cooper, and G. C. Brainard. Inferior retinal light exposure is more effective than superior retinal exposure in suppressing melatonin in humans. *J Biol Rhythms*, 2002, in press.

Hatakana, T., K. P. McKeown, and A. A. Shoukas. Effects of pulsatile flow on extravascular fluid uptake during cardiopulmonary bypass. *J Thorac Cardiovasc Surg*, in review.

Hegemann, S., V. Patel, M. Shelhamer, P. D. Kramer, and D. S. Zee. Adaptation of the phase of the human linear vestibulo-ocular reflex (LVOR) and effects on the oculomotor neural integrator. *J Vestib Res*, in press.

Hochstadt, J., H. Nakano, P. Lieberman, and J. Friedman. The roles of verbal working memory and sequencing in sentence comprehension deficits in Parkinson's disease, submitted.

Hong, M. Y., R. S. Chapkin, R. Barhoumi, R. C. Burghardt, N. D. Turner, C. E. Henderson, L. M. Sanders, Y. Y. Fan, L. A. Davidson, M. E. Murphy, C. M. Spinka, R. J. Carroll, and J. R. Lupton. Fish oil increases mitochondrial phospholipid unsaturation, upregulating reactive oxygen species and apoptosis in rat colonocytes. *Carcinogenesis*, 2002, submitted.

Imai, T., S. T. Moore, T. Raphan, and B. Cohen. Interaction of the body, head and eyes during walking and turning. *Exp Brain Res*, 2001, submitted.

Jagoe, R. T., S. H. Lecker, M. Gomes, and A. L. Goldberg. Patterns of gene expression in atrophying skeletal muscles: response to food deprivation. *FASEB J*, 2002, in press.

Jung, A. S., D. E. Berkowitz, E. M. Brooks-Asplund, and A. A. Shoukas. Attenuated baroreflex responses in a mouse model of microgravity. *Am J Physiol,* in final review.

Kim, S. Y., D. E. Berkowitz, R. Jhaveri, A. Shoukas, and D. Nyhan. Differential influence of pulmonary vasoconstrictors on milrinone induced vasorelaxation, in preparation.

Kourentzi, K. D., G. E. Fox, and R. C. Willson. Rapid identification of microorganisms using 5S rRNA specific molecular beacons. *Curr Microbiol,* 2001, in press.

Kraft, N. O., et al. Physiological changes, sleep, and morning mood in an isolated environment. *Aviat Space Environ Med,* 2002, in press.

Kraft, N. O., T. J. Lyons, et al. Catecholamine and psychological stress during long-duration confinement. *Aviat Space Environ Med,* 2002, in press.

Lafon, C., O. A. Sapozhnikov, V. A. Khokhlova, P. J. Kaczkowski, M. R. Bailey, and L. A. Crum. Use of a bovine eye lens for real-time observation of HIFU-induced lesion evolution. *Ultrasound Med Biol,* submitted.

Lednicky, J. A., R. A. Vilchez, W. A. Keitel, F. Visnegarwala, Z. S. White, C. Kozinetz, D. E. Lewis, and J. S. Butel. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy, submitted.

Li, Y-P, S. M. Lecker, Y. Chen, A. L. Goldberg, and M. B. Reid. TNF-α stimulates ubiquitin conjugation in skeletal muscle by upregulating UbcH2/$E2_{20k}$, an NF-κB-dependent process. *FASEB Journal,* in review.

Lupton, J. R. and N. D. Turner. Nutrition in space. *Nutrition,* in press.

Mann, J., R. Ricart-Arbona, A. Christian, D. Simonson, J. F. Dicello, and D. Huso. Epithelial-mesenchymal transition in Tamoxifen resistant tumors. *Vet Pathol,* 2002, submitted.

Monahan, K. D., and C. A. Ray. Vestibulosympathetic reflex during orthostatic challenge in aging humans. *Am J Physiol Regul Integr Comp Physiol,* in press.

Mukkamala, R., D. A. Sherman, R. J. Cohen, and R. G. Mark. A nonlinear, computational model of the pulsatile heart and circulation, submitted.

Mukkamala, R., K. Toska, and R. J. Cohen. Noninvasive identification of the total peripheral resistance baroreflex, submitted.

Murphy, J. C., D. L. Jewell, K. I. White, G. E. Fox, and R. C. Willson. PCR product purification using immobilized metal affinity chromatography spin columns. *BioTechniques,* 2002, in press.

Murphy, J. C., G. E. Fox, and R. C. Willson. Compaction agents enhance anion-exchange adsorption of nucleic acids. *J Chromatogr,* 2002, in press.

Narayanan, R., C. L. Smith, and N. L. Weigel. Vector-averaged gravity-induced changes in cell signaling and vitamin D receptor activity in MG-63 cells are reversed by a 1,25-(OH)2D3 analog, EB1089. *Bone*, 2002, in press.

Narayanan R., M. R. Allen, J. Stafinsky, D. Gaddy-Jurten, S. A. Bloomfield, C. L. Smith, and N. L. Weigel. Differential responses of hindlimb unloaded rats to 1,25 D and its analog, EB1089, in preparation.

Newman, D. J., R. Wu, D. Krebs, and D. K. Jackson. Electromyographic analysis of human false platform jumping. *J Appl Physiol*, in revision.

Nyhan, D., J. Hare, and D. Berkowtiz. Modulating effects of L-arginine and age-related vascular dysfunction, in preparation.

O'Sullivan, C., R. S. Peng, H. Jenson, and P. D. Ling. Epstein-Barr virus genome loads in the peripheral blood and antibody titers to EBV antigens in AIDS patients before and after HAART therapy, submitted.

Papadopoulos, A., and M. D. Delp. Effects of hindlimb unweighting on the mechanical and structure properties of the rat abdominal aorta. *J Appl Physiol*, 2002, in press.

Polacek, D. C., A. Passerini, E. Manduchi, G. Grant, C. Shi, and P. F. Davies. Determination of fidelity of differential transcription profiling on microarrays after linear amplification of small quantities of cellular mRNA, in preparation.

Raphan, T., T. Imai, S. T. Moore, and B. Cohen. Vestibular compensation and orientation during locomotion. *Ann NY Acad Sci*, 2001, in press.

Richards, J. T., J. B. Clark, C. M. Oman, and T. H. Marshburn. Neurovestibular effects of long-duration spaceflight: a summary of Mir Phase 1 experiences. *J Vestib Res*, 2001, submitted.

Richards, J. T., C. M. Oman, W. L. Shebilske, A. C. Beall, A. Liu, and A. Natapoff. Training, transfer and retention of three-dimensional spatial memory in virtual environments. *J Vestib Res*, 2002, submitted.

Rogers, N. L., J. McMahon, K. Lushington, and D. Dawson. Thermoregulatory changes around the time of sleep onset. *Physiol Behav*, 2001, submitted.

Sha, D., D. Kennedy, and J. Sutton. Neurocomputing for automated analysis of digital brain images. *Artificial Intelligence in Medicine*, in press.

Shearer, W. T. Recognition of clinical immunology as a distinct medical subspecialty: importance for the practice of allergy. *J Allergy Clin Immunol*, in press.

Shi, Y. F., S. Devadas, K. M. Greeneltch, D. L. Yin, R. A. Mufson, and J. N. Zhou. Stressed to death: implication of lymphocyte apoptosis for psychoneuroimmunology. *Brain Behav Immun*, 2002, in press.

Soller, B. R., P. O. Idwasi, J. Balaguer, S. Levin, S. A. Simsir, T. J. Vander Salm, H. Collette, and S. O. Heard. Noninvasive, NIRS-measured muscle pH and PO2 indicate tissue perfusion for cardiac surgical patients on cardiopulmonary bypass. *Crit Care Med,* submitted.

Soller, B. R., J. Favreau, and P. Idwasi. Investigation of electrolyte concentration in diluted whole blood using spectroscopic and chemometric methods. *Appl Spectrosc*, in press.

Soller, B. R., M. E. Cabrera, S. M. Smith, and J. P. Sutton. Smart medical systems with application to nutrition and fitness in space. *Nutrition,* in press.

Sonnenfeld, G. The immune system in space and microgravity. *Medicine & Science in Sports & Exercise*, *MSSE*, 2002, in press.

Sonnenfeld, G., and W. T. Shearer. Immune function during space flight. *Nutrition*, 2002, in press.

Sonnenfeld, G. Animal models for the study of the effects of spaceflight on the immune system. *Adv Space Res*, in press.

Strangman, G., F. Halbritter, P. Groblewski, W. C. West, T. Gaudette, and D. A. Boas. A high-speed, continuous-wave near-infrared spectroscopy (NIRS) system for non-invasive recording of brain activity. *J Biomed Opt*, submitted.

Starikov, D., C. Boney, N. Medelci, J. W. Um, M. Larios-Sanz, G. E. Fox, and A. Bensaoula. Experimental simulation of integrated optoelectronic sensors based on III nitrides. *J Vac Sci Technol,* 2002, in press.

Sutton, J. P., and I. Jamieson. Reconfigurable networking for coordinated multi-agent sensing and communications. *Information Sciences*, in press.

Takagi, H. Abe, S. Hasegawa, T. Usui, H. Hasebe, A. Miki, and D. S. Zee. Context-specific adaptation of pursuit initiation in humans. *Invest Ophthalmol Vis Sci*, in press.

Tobin, B. W., P. N. Uchakin, S. K. Leeper-Woodford. Insulin secretion and sensitivity in spaceflight: diabetogenic effects. *Nutrition*, in press.

Tosini G., and C. Fukuhara. Photic and circadian regulation of melatonin synthesis in the retina. *J Neuroendocrinol*, 2002, submitted.

Turner, N. D., L. A. Braby, J. R. Ford, and J. R. Lupton. Opportunities for nutritional amelioration of radiation-induced cellular damage. *Nutrition*, in press.

Young, L. R., K. H. Sienko, L. E. Lyne, H. Hecht, and A. Natapoff. Adaptation of the vestibulo-ocular reflex, subjective tilt, and motion sickness to head movements during short-radius centrifugation. *Exp Brain Res*, 2001, submitted.

Zhang, X. R., L. Zhang, L. Li, L. M. Glimcher, A. D. Keegan, Y. F. Shi. Reciprocal expression of TRAIL and CD95L in Th1 and Th2 cells: role of apoptosis in T helper subset differentiation. *Cell Death Differ*, 2002, in press.

Zhong, Q., K. H. Ding, R. Bollag, and C. M. Isales. Glucose-dependent insulinotropic peptide-induced elevations in transforming growth factor modulate proliferation in osteoblastic-like cells. *J Bone Miner Res*, 2001, submitted.

Zerwekh, J. E. Nutrition and renal stone disease in space. *Nutrition*, October 2002, in press.

Books and Book Chapters

Bloomfield, D. M. and R. J. Cohen. Repolarisation alternans. In Malik, M., Ed., *Risk of Arrhythmia and Sudden Death*, London: BMJ Books, 2001:256-265.

Boas, D. A., M. A. Franceschini, A. K. Dunn, and G. Strangman. Non-invasive imaging of cerebral activation with diffuse optical tomography. In Frostig, R. D., Ed., Title to be determined, CRC Press, in press.

Brady, J. V., D. H. Powell, and S. M. Mirin. Behavioral health and performance. In: Ball, J. R. and Evans, C. H. (eds.), *Safe Passage: Astronaut Care for Exploration Missions*. Washington, D.C.: National Academy Press, 2001: 137-170.

Brainard, G. C., and J. P. Hanifin. Action spectrum for melatonin suppression: evidence for a novel circadian photoreceptor in the human eye. In: Holick, M., Ed., *Biologic Effects of Light 2001*, Boston, Massachusetts: Kluwer Academic Publishers, 2002:463-474.

Chugh, D. K., and D. F. Dinges. Mechanisms of sleepiness. In Pack, A. I., Ed., *Pathogenesis, Diagnosis, and Treatment of Sleep Apnea*, New York: Marcel Decker, Inc., in press.

Dicello, J. F., and F. A. Cucinotta. Space radiation. In *Encyclopedia of Space Science and Technology*, New York: John Wiley and Sons, Inc., 2002, in press.

Judex, S., and C. T. Rubin. Mechanical influences on bone mass and morphology – investigating how exercise may regulate adaptation in the skeleton. In Orwoll, E. S. and Bliziotes, M. (eds.), *Osteoporosis: Scientific Principles and Clinical Practice*, New Jersey: Humana Press Inc., in press.

Kloss, J. D., M. P. Szuba, and D. F. Dinges. Sleep loss and sleepiness: Physiological and neurobehavioral effects. In *Neuropsychopharmacology: The Fifth Generation of Progress*, Baltimore, Maryland: Lippincott, Williams, and Wilkins, in press.

Larios-Sanz, M., K. D. Kourentzi, J. C. Murphy, K. I. Maillard, D. L. Pearson, R. C. Willson, and G. E. Fox. Monitoring microbial populations in space environments. In *Dianostico Molecular*, Mexico City, Mexico: JGH Editores SA de CV, 2001, in press.

Moore, S. T., E. Hirasaki, T. Imai, T. Raphan, and B. Cohen. Rotation axes during active head and trunk movements. In Duysens, J., Smits-Engelsman, B. C. M., and Kingma, H. (eds.), *Control of Posture and Gait, Proc. of Symposium of the International Society for Postural and Gait Research*, ISPG 2001, 211-214.

Oman, C. Human visual orientation, Chapter 5.2. In Harris, L. R. and Jenkin, M. L. (eds.), *Levels of Perception*, Elsevier, in press.

Raphan, T., T. Imai, S. T. Moore, and B. Cohen. Vestibular based compensatory and orienting behavior during walking and turning. In Duysens, J., Smits-Engelsman, B. C. M., and Kingma, H. (eds.), *Control of Posture and Gait, Proc. of Symposium of the International Society for Postural and Gait Research*, ISPG 2001, 234-237.

Rubin, C. T., S. Judex, K. J. McLeod, and Y. X. Qin. Inhibition of osteopenia by biophysical intervention. In Marcus, R., Feldman, D., and Kelsey, J. (eds.), *Osteoporosis, 2nd edition*, San Diego, California: Academic Press, 2001.

Shearer, W. T., and G. Sonnenfeld. Alterations of immune responses in space travel. In Hans M. Ed. *Encyclopedia of Space Science and Technology*. New York: John Wiley & Sons, 2002, in press.

Shebilske, W. L., B. P. Goettl, and D. Garland. Situation awareness, computer-automation, and training. In Endsley, M. R. and Garland, D. (eds.), *Situation awareness analysis measurement*. Mahwah, New Jersey: Lawrence Erlbaum, in press.

Young, L. R. Artificial gravity. In *Encyclopedia of Space Science and Technology*, New York: John Wiley and Sons, Inc., December 2001, in press.

Young, L. R. Spatial orientation. In Tsang, P. S. and Vidulich, M. A. (eds.), *Principles and Practice of Aviation Psychology*, Chapter 3, New Jersey: Lawrence Erlbaum Associates, Inc., in press.

Young, L. R., V. Henn, and H. Scherberger. Fundamentals of the theory of movement perception. Translation of Mach, E. (1875) *Grundlinien der Lehre von den Bewegungsempfindungen*, Leipzig: Wilhelm Engelmann. New York: Kluwer Academic/Plenum Publishers, in press.

Zordan, M., R. Costa, C. Fukuhara, and G. Tosini. The molecular biology of the mammalian circadian clock. In P. H. Redfern, Ed., *Biological clocks: Pharmaceutical and Therapeutic Implications*, London: Pharmaceutical Press, in press.

Patents Pending, Patent Applications in Preparation or Invention Disclosures

Charles, Jr., H. K., T. J. Beck, H. S. Feldmesser, T. C. Magee, J. A. Weiner, D. M. Lee, and C. E. Bennett. Method and apparatus for multiple projection dual energy x-ray absorptiometry scanning. JHU/APL File No. 1449-NSBRI, 2001, patent application.

Charles, Jr., H. K., T. J. Beck, H. S. Feldmesser, and T. C. Magee. Techniques for deriving tissue structure from multiple projection, dual energy x-ray absorptiometry. JHU/APL File No. 1784-NSBRI, 2001, patent application.

Charles, Jr., H. K., and T. J. Beck. Highly efficient and compact x-ray source employing a thin transmission target with spray cooling suitable for use in dual energy x-ray absorptiometry (DXA) and other x-ray systems. 2001, invention disclosure.

Murphy, J. C., and R. C. Willson. Methods and compositions for biotechnical separations using selective precipitation by compaction agents, patent pending.

Murphy, J. C., and R. C. Willson. Methods and compositions for nucleic acid separations using immobilized metal affinity agents, patent application in preparation.

Abstracts, Proceedings, Reports and Presentations

Allen, M. R., J. L. Stafinsky, C. Nolan, S. A. Bloomfield, and C. L. Smith. Raloxifene attenuates bone loss in mechanically unloaded, ovariectomized female rats. American Society for Bone and Mineral Research, 23rd Annual Meeting, Pheonix, AZ. Abstract #SU440, October 12-16, 2001.

Bailey, M. R., L. N. Couret, O. A. Sapozhnikov, V. A. Khokhlova, G. ter Haar, S. Vaezy, X. Shi, R. Martin, and L. A. Crum. Overpressure and the role of bubbles in focused ultrasound lesion shape. *Proceedings of the 1st International* Workshop on the Application of High Intensity Focused Ultrasound (HIFU) in Medicine, Chongquing, China, 2001.

Bailey, M. R., S. Vaezy, J. C. Yuen, A. Anand, N. A. Miller, P. J. Kaczkowski, and L. A. Crum. Bubbles and acoustic image-guided high intensity focused ultrasound. *J Acoust Soc Amer*, 110: 2643, 2001.

Bassett, J. P. and J. S. Taube. Lesion of the dorsal tegmental nucleus of the rat disrupt head direction cell activity in the anterior thalamus. *Soc Neurosci Abstr* 27, 2001, in press.

Belay, T., M. Vance, K. Fountain, and G. Sonnenfeld. Hindlimb suspension decrease resistance of mice infected with Klebsiella pneumoniae (abstract). *Gravit Space Biol Bull* 15:58, 2002.

Bloomfield, S. A., M. R. Allen, C. Nolan, and C. L. Smith. Attenuation of disuse bone loss by estrogen and raloxifene in mature male rats. 24th Annual Meeting of the American Society for Bone and Mineral Research, San Antonio, TX. September 20-24, 2002.

Brainard, G. C., J. P. Hanifin, M. D. Rollag, J. M. Greeson, B. Byrne, G. Glickman, and E. Gerner. Action spectrum for melatonin regulation in humans. *Photodermatology, Photoimmunology and Photomedicine*, 17:139, 2001.

Brainard, G. C., G. Glickman, J. P. Hanifin, B. Byrne, J. M. Greeson, J. Gardner, E. Gerner, and M. Rollag. Sensitivity to 420 nm light in the human melatonin suppression action spectrum: relevance to circadian phototransduction. 8th Meeting of the Society for Research on Biological

Rhythms, Jacksonville, FL, May 22-26, 2002.

Brainard, G. C. Human melatonin action spectrum: relevance to circadian phototransduction. 30th Annual Meeting American Society for Photobiology, Quebec City, Canada, July 13, 2002.

Brainard, G., M. Rollag, J. Hanifin, and G. Glickman. Retinal adaptation modulates human circadian photoreception. European Pineal and Biological Rhythms Society, Aberdeen, Scotland, July 18, 2002.

Brown, E. L., L. K. Barger, C. D. May, and M. E. Jewett. A transformation function can equate readings of wrist-worn light measuring devices to those of hand-held light monitors. *Sleep* 24:A102, 2001.

Calton, J. L., and J. S. Taube. Head direction cell activity following bilateral lesions of posterior parietal cortex. *Soc Neurosci Abstr* 27, 2001, in press.

Cano, T., J. C. Murphy, G. E. Fox, and R. C. Willson. Conformational control as a tool in plasmid purification. Oral presentation during the 224th National Meeting, American Chemical Society, Boston, MA, August 18-22, 2002. Abstract #534956, published in proceedings.

Davidson, A. J., S. Yamazaki, and M. Menaker. Liver *mPer1-luc* entrainment by macronutrient injections. Eighth Meeting Society for Research on Biological Rhythms, May 2002. Abstract published in proceedings.

Dean II, D. A. and M. E. Jewett. Circadian Performance Simulation Software (CPSS) provides a tool for validation of circadian and neurobehavioral mathematical models. *Sleep* 24:A103, 2001.

Dinges, D. F., G. Maislin, and H. Van Dongen. Chronic sleep restriction: relation of sleep structure to daytime sleepiness and performance. *Sleep* 24:A28-A29, 2001.

Dinges, D. F., H. P. A. Van Dongen, G. Maislin, and N. L. Rogers. Cumulative sleep loss in space flight: consequences and countermeasures. Proceedings of the 52nd International Astronautical Congress, Toulouse, France, October 1-5, 2001.

Fischer, U. Culture and crew communication. Symposium on Culture, Teams and CRM. Old Dominion University, Norfolk, VA., March 2002.

Frohardt, R. J., J. L. Marcroft, and J. S. Taube. Lesions of the anterior thalamus impair path integration performance on a food-carrying task. *Soc Neurosci Abstr* 27, 2001, in press.

Gardner, J., G. Glickman, J. Hanifin, B. Byrne, S. Jasser, M. Rollag, and G. C. Brainard. Monochromatic 460 nm vs. 555 nm light in the suppression of human melatonin: a within-subjects study design. Sigma Xi Student Research Day, Philadelphia, PA, April 9, 2002.

Glickman, G., J. P. Hanifin, R. L. Fucci, M. D. Rollag, E. Gerner, B. Byrne, and G. C. Brainard. Effect of pupil constriction on monochromatic light induced melatonin suppression in humans. 30th Annual Meeting American Society for Photobiology, Quebec City, Canada, July 13, 2002.

Goldenstein, S., C. Vogler, and D. Metaxas. Directed acyclic graph representation of deformable models. *IEEE Workshop on Motion and Video Computing*, 2002, in press.

Goldenstein, S., C. Vogler, and D. Metaxas. Statistical integration of DAG deformable models. *IEEE Transactions on Pattern Analysis and Machine Perception*, submitted.

Gonzalez, M., and G. Aston-Jones. Role of the noradrenergic Locus Coeruleus (LC) system in sleep and waking: circadian factors. *Soc Neurosci Abstr*, 2002, in press.

Gronfier, C., R. E. Kronauer, K. P. Wright Jr., and C. A. Czeisler. Growth hormone secretion during entrained and non-entrained conditions in humans. *Sleep* 24:A89-90, 2001. Presented during the 15th Annual Meeting of the Associated Professional Sleep Societies, Chicago, IL, June 5-10, 2001.

Heldt, T., E. B. Shim, R. D. Kamm, and R. G. Mark. Computational model of cardiovascular function for analysis of orthostatic intolerance. *Proceedings of the 2001 Bioengineering Conference,* ASME, BED-Vol. 50:895-896.

Henderson, C. E., L. M. Sanders, M. Y. Hong, S. S. Taddeo, C. M. Spinka, N. D. Turner, R. J. Carroll, R. S. Chapkin, and J. R. Lupton. Colonocyte DNA damage differs with diet but not age. *FASEB J*, 16:A998, 2002.

Ho, A. H., C. Gronfier, and C. A. Czeisler. Effects of prolonged sleep deprivation on cortisol secretion in Humans. *Sleep* 24:A251-A252, 2001.

Hogan, H. A., M. R. Allen, W. E. Rogers, N. L. Weigel, and S. A. Bloomfield. 1,25(OH)2D3 and EB1089 produce higher femoral cancellous bone density after 28-d hindlimb unloading while only 1,25(OH)2D3 enhances material properties. American Society for Bone and Mineral Research, 23rd Annual Meeting, Pheonix, AZ. Abstract #M207, October 12-16, 2001.

Hong, M. Y., L. K. Bancroft, N. D. Turner, R. S. Chapkin, C. M. Spinka, R. J. Carroll, and J. R. Lupton. Dietary fish oil, compared to corn oil, decreased oxidative DNA damage at the base and middle region of the colonic crypt in dextran sodium sulfate (DSS)-treated rats. *FASEB J*, 16:A224, 2002.

Horowitz, S., and L. P. Morin. Angular and linear stimulation: differential induction of FOS in the hamster vestibular and circadian systems. *Soc Neurosci Abstracts* 672:18, 2002.

Hull, J. T., K. P. Wright Jr., and C. A. Czeisler. Circadian and sleep-wake dependant control of urine volume output on a 28-h forced desynchrony. *Sleep* 24:A90, 2001.

Jasser, S., J. Hanifin, J. Greeson, G. Glickman, B. Byrne, M. Rollag, and G. C. Brainard. Effects of gender on human plasma melatonin levels. Sigma Xi Student Research Day, Philadelphia, PA, April 9, 2002.

Jasser, S., J. Gardner, J. Hanifin, G. Glickman, B. Byrne, M. Rollag, and G. C. Brainard. 460 nm vs. 555 nm monochromatic light in the suppression of melatonin in healthy humans: a within-subjects design. 30th Annual Meeting American Society for Photobiology, Quebec City, Canada, July 13, 2002.

Jewett, M. E., K. P. Wright Jr., J. F. Duffy, D. M. Rodriguez, and C. A. Czeisler. Practice effects observed over a month-long 28-hour forced desynchrony protocol in a cognitive throughput task are well described by a saturating exponential function. *Sleep* 24:A4, 2001.

Judex, S., F. Lombardo, L. R. Donahue, M. Hadjiargyrou, and C. Rubin. Changes in transcriptional activity induced by altered mechanical demand of the skeleton. *Annals of Biomedical Engineering* 29(S1):S37, 2001.

Judex, S., G. Xu, L. R. Donahue, M. Hadjiargyrou, and C. Rubin. Changes in trabecular bone formation induced by mechanical stimulation and disuse are accompanied by differential gene expression in a mouse model. *Transactions of the Orthopaedic Research Society 47*, San Francisco, CA, 2001:533.

Judex, S., J. Zhi, G. Xu, M. Hadjiargyrou, J. Rubin, and C. Rubin. Osteoclast differentiation factor mRNA expression and bone formation rates related to disuse and mechanical stimulation are inversely proportional. *Transactions of the Orthopaedic Research Society 47*, San Francisco, CA, 2001:39.

Judex, S., M. Hadjiargyrou, L. R. Donahue, and C. Rubin. Trabecular bone from two strains of mice is differentially mechanosensitive at the tissue and molecular level. *J Bone Miner Res* 16(S1):S151, 2001.

Jung, A., R. Harrison, D. Nyhan, S. Cottechia, A. A. Shoukas, J. Hare, and D. E. Berkowitz. Attenuated arterial pressure and contractility responses in alpha 1 B-adrenergic receptor KO mice. Abstract #111203, 74th Scientific Session, American Heart Association, Anaheim, CA, November 2001.

Kamm, R. D., E. B. Shim, A. Shirai, M. Mathe, T. Heldt, H. Younis, M. Kaazemour-Mofrat, and W. Hwang. Multi-scale simulation in biological systems. *Proceedings of The First International Symposium on Advanced Fluid Information*, 2001.

Karmali, F., R. A. Clendaniel, and M. Shelhamer. Context-specific adaptation of saccade gain does not require opposing gain changes in order to be effective. *Society for Neuroscience Abstr* 71.23, 2001.

Khokhlova, V. A., N. Miller, R. Ollos, R. W. Martin, M. R. Bailey, Y. Mohammadian, and M. Naghavi. Visualization of temperature rise induced by high intensity ultrasound in tissue. *Proc of 17th International Congress on Acoustics* CD-ROM, Rome, Italy, 2001.

Kim, S., D. Nyhan, J. Harc, A. Shoukas, and D. E. Berkowitz. Endothelial dependent and independent vascular adaptive changes to zero gravity: lessons from a rodent model. 74th Scientific Session, American Heart Association, Anaheim, CA, November 2001.

Kraft, N. O. International decision making. Symposium on Culture, Teams and CRM. Old Dominion University, Norfolk, VA. March 2002.

Kraft, N. O., J. Orasanu, U. Fischer, and L. McDonnell. Culture and decision making. International Congress of Aviation and Space Medicine, Sidney, Australia, September 2002.

Larios-Sanz, M., K. Kourentzi, D. Warmflash, R. C. Willson, D. L. Pierson, and G. E. Fox. Microbial contaminants in crew habitat modules during exploration class human space missions: monitoring potential pathogens. Panel presentation during the 73rd Annual Meeting, Aerospace Medical Association, Montreal, Canada, May 5-10, 2002.

Ling, P., J. A. Lednicky, W. Keitel, Z. S. White, F. Visnegarwala, R. A. Vilchez, and J. S. Butel. The shedding of JCV and EBV in HIV-infected patients receiving HAART. Ninth Conference on Retroviruses and Opportunistic Infections, Seattle, WA, February 2002.

Lupton, J. R., N. D. Turner, N. Popovic, R. S. Chapkin, L. A. Braby, and J. H. Ford. Nutritional countermeasures to radiation exposure. Paper presented at the Kongress Medizin und Mobilitat, Furstenfeldbruck, Germany, September 2002.

Maislin, G., N. L. Rogers, J. M. Mullington, M. P. Szuba, H. P. A. Van Dongen, and D. F. Dinges. Response surface modeling of the effects of chronic sleep restriction with and without diurnal naps. *Sleep* 24:A242-A243, 2001.

Mallis, M. M., D. F. Neri, R. Oyung, L. Colletti, T. Nguyen, and D. F. Dinges. Factors associated with behavioral alertness in pilots flying simulated night flights. *Sleep* 24:A123-A124, 2001.

Maurer, R. H., D. R. Roth, and J. D. Kinnison. Neutron energy spectroscopy on the International Space Station. 2001 ISS Utilization Conference, Cape Canaveral, FL, October 15-17, 2001.

McConnell, K. J., G. Maislin, N. L. Rogers, N. J. Price, J. M. Mullington, M. P. Szuba, C. G. Brodyan, L. Cerceo, H. P. A. Van Dongen, and D. F. Dinges. Sleep efficiency during chronic nocturnal sleep restriction with and without diurnal naps. *Sleep* 24:A431, 2001.

Menaker, M. Non-visual responses of vertebrates to visible light: the evolution of a neglected sensory modality. Abstract, keynote lecture, 30th Annual Meeting, American Society for Photobiology, July 2002.

Menaker, M., S. Yamazaki, and A. Davidson. What holds the mammalian circadian system together? Abstract 9th European Pineal & Biological Rhythms Society Meeting, July 2002.

Muir, G. M. and J. S. Taube. Who's reading the cognitive map? Head direction cell activity and behavior in a spatial navigation task. *Soc Neurosci Abstr* 27, 2001, in press.

Mukkamala, R., R. G. Mark, and R. J. Cohen. A noninvasive method for characterizing ventricular diastolic filling dynamics. Accepted in *Proceedings of the IEEE-EMBS Conference*, 2001.

Narayanan R., M. R. Allen, J. L. Stafinsky, S. A. Bloomfield, C. L. Smith, and N. L. Weigel. Effects of 1, 25(OH)2D3 and EB1089 on bone cells and bones of hindlimb unloaded adult male rats. 23rd Annual Meeting of the American Society for Bone and Mineral Research, Pheonix, AZ. Abstract #SU521, October 12-16, 2001.

Oman, C. Neurovestibular adaptation to weightlessness. Invited seminar at the Uniformed Services University of the Health Sciences, Bethesda, MD, October 2001.

Orthmann, J. L., N. L. Rogers, N. J. Price, J. M. Mullington, M. P. Szuba, H. P. A. Van Dongen, and D. F. Dinges. Changes in plasma growth hormone levels following chronic sleep restriction. *Sleep* 24:A248-A249, 2001.

Orasanu, J. Invited panel: Culture and team decision making at the Symposium on Culture, Teams, and CRM. Old Dominion University, Norfolk, VA, March 25, 2002.

Orasanu, J., U. Fischer, and J. Davison. Managing and communicating risk on the flight deck. Team Interaction in High-Risk Environments Conference. Berlin, Germany, May 15, 2002.

Popovic, N., N. D. Turner, L. A. Braby, R. S. Chapkin, and J. R. Lupton. Combined effect of radiation and a chemical carcinogen on the formation of aberrant crypt foci in rat colon. *FASEB J*, 16:A889, 2002.

Popovic, N., N. D. Turner, L. A. Braby, J. H. Ford, R. S. Chapkin, and J. R. Lupton. Nutritional countermeasures to radiation exposure. Annual RHIC/AGS User's Meeting, Brookhaven National Laboratory, Upton, NY, September 2002.

Qin, Y. X., W. Lin, and C. Rubin. Interdependent relationship between trabecular bone quality and ultrasound attenuation and velocity using scanning confocal acoustic diagnostic system. 23rd Annual Meeting of the American Society for Bone and Mineral Research, Phoenix, Arizona, October 12-16, 2001.

Ritz-De Cecco, A., M. E. Jewett, J. F. Duffy, T. L. Shanahan, and C. A. Czeisler. Assessment of phase shift of melatonin rhythm to a single bright light stimulus is confounded by masking effects of scheduled sleep:wake and/or dim light:dark cycles. *Sleep* 24:A85, 2001.

Sanders, L. M., C. E. Henderson, M. Y. Hong, R. Barhoumi, R. C. Burghardt, C. M. Spinka, N. Wang, R. J. Carroll, N. D. Turner, R. S. Chapkin, and J. R. Lupton. Dietary fish oil and pectin protect against oxidative DNA damage in rat intestinal epithelial cells due to heightened apoptosis induced by reactive oxygen species. *FASEB J*, 16:A371, 2002.

Shah, A. D., H. A. P. Van Dongen, G. Maislin, C. G. Brodnyan, and D. F. Dinges. Dynamics of slow-wave activity during chronically restricted sleep. *Sleep* 24:A247-A248, 2001.

Shelhamer, M., R. A. Clendaniel, and G. C. Y. Peng. Relative effectiveness of sensory and motor cues in context-specific adaptation of saccade gain. *Society for Neuroscience Abstracts* 71.22, 2001.

Shearer, W. T. Compromise of the human immune system in interplanetary space travel. XV Mexican Congress of Clinical Immunology, Ixtapa-Zihuatanejo, Mexico, May 1, 2002.

Shearer, W. T. Challenges to the human immune system during space travel. University of North Carolina – Chapel Hill 2002 Cellular and Molecular Biology Program Symposium: Space: Challenges for Human Physiology, Chapel Hill, NC, May 3, 2002.

Shearer, W. T. Risk factors for human immunology in space. National Space Biomedical Research Institute Summer Teachers Program, Houston, TX, June 7, 2002.

Smith, C. L., N. L. Weigel, and S. A. Bloomfield. Receptor countermeasures to bone loss in microgravity. American Society for Bone and Mineral Research, Phoenix, Arizona, October 12-16, 2001.

Soller, B. R., P. Idwasi, H. Collette, T. J. Vander Salm, and S. O. Heard. Noninvasively measured muscle pH indicates tissue perfusion for cardiac surgical patients. *Crit Care Med* 29:A114, 2001.

Soller, B. R. Assessing the microcirculation by near infrared spectroscopy. Cardiovascular Monitoring, Society of Critical Care Medicine Meeting, January 2002.

Soller, B. R. Noninvasive assessment of peripheral perfusion using NIR spectroscopy (early results). Diabetes Technology Meeting, November 2001.

Soller, B. R. Noninvasively measured muscle pH indicates tissue perfusion for cardiac surgical patients. Society of Critical Care Medicine Meeting, January 2002.

Soller, B. R., T. Khan, and N. Cingo. Fiber optic sensing of tissue pH to assess low blood flow states. Proceedings of the First IEEE International Conference on Sensors, 32-1.

Sonnenfeld, G. Space flight, immune responses and resistance to infection. Invited Seminar, Medical Division, Brookhaven National Laboratory, Upton, New York, 2001.

Sonnenfeld, G. Stress, space flight, and resistance to infection. Amino Up Chemical Company Seminar, Sapporo, Japan, 2002.

Sonnenfeld, G., H. Aviles, T. Belay, M. Vance, and K. Fountain. Stress, suspension, and resistance to infection. 8th European Symposium on Life Sciences Research in Space and 23rd Annual International Gravitational Physiology Meeting, Stockholm, Sweden, 2002.

Sonnenfeld, G. Space flight and immune responses of Rhesus monkeys. Karolinska Institute Symposium on Space Research in Non-Human Primates, Stockholm, Sweden, 2002.

Sonnenfeld, G. Space flight, the immune system, and resistance to infection. Invited Symposium on the Role of Infection in Chronic Disease, German Clinical Research Group and German Research Centre for Biotechnology, Braunschweig, Germany, 2002.

Strangman, G., T. Gaudette, and D. A. Boas. Synergy from simultaneously acquired fMRI and near-infrared optical spectroscopy data. *Proc Intl Soc Mag Reson Med* 9, 2001.

Starikov, D., C. Boney, N. Medelci, J. W. Um, A. Bensaoula, M. Larios-Sanz, and G. E. Fox. Development of integrated multifunctional optical sensors based on III nitrides. Oral presentation, Session PH-ThA4, Photonic Materials: Applications and Processing. American Vacuum Society 48th International Symposium, San Francisco, CA, October 28-November 2, 2001.

Sutton, J., and I. Jamieson. Reconfigurable network of neural networks for autonomous sensing and analysis. *Proceedings of the Fifth International Conference on Cognitive and Neural Systems*, 2001:64.

Sutton, J. Micro/nano technologies and the future of medicine. *Proceedings of NanoSpace 2001*, in press.

Warmflash, D., M. Larios-Sanz, G. E. Fox, R. C. Willson, and D. S. McKay. Technologies for microbial detection to support both vehicle/habitat medical monitoring and planetary astrobiology during human surface exploration of Mars. Panel presentation during the 73rd Annual Meeting, Aerospace Medical Association, Montreal, Canada, May 5-10, 2002.

Warmflash, D., M. Larios-Sanz, R. C. Willson, G. E. Fox, and D. S. McKay. Progress in the use of rapid molecular techniques to detect life forms in soil: implications for interplanetary astrobiology missions. 33rd Lunar & Planetary Science Conference, Houston, TX, March 11-15, 2002.

Wright, Jr., K. P., J. T. Hull, and C. A. Czeisler. Relationship between cognitive performance and core body temperature during a 28-hour forced desynchrony protocol. *Sleep*; 2001, 24:A3.

Young, L. R., and H. Hecht. Neurovestibular aspects of artificial gravity. Submitted to the 73rd AsMA Annual Scientific Meeting, May 2002.

Zhong, Q., K. Ding, A. L. Mulloy, R. J. Bollag, and C. M. Isales. Glucose-dependent insulinotropic peptide stimulates proliferation and TGF-beta synthesis in osteoblastic-like cells. American Society for Bone and Mineral Research, Phoenix, AZ, October 12-16, 2001.

Zhou, W., P. Weldon, B. Tang, and W. M. King. Retinal slip not required for rapid adaptation of the translational vestibulo-ocular reflex. *Society for Neuroscience Abstracts* 403.19, 2001.

Appendix L

National Space Biomedical Research Institute

Joint MIHCS/NSBRI Multispecialty Medical Operational Support Team (MOST) for Development and Testing of a Space-Adapted Human Patient Simulator (HPS)

Project 03-1

Presented to:
Space and Life Sciences Directorate
NASA Johnson Space Center

By:
The National Space Biomedical Research Institute
Houston, Texas

October 8, 2002

National Space Biomedical Research Institute

Joint MIHCS/NSBRI Multispecialty Medical Operational Support Team (MOST) for Development and Testing of a Space-Adapted Human Patient Simulator (HPS)

1.0 Purpose

This proposal is being submitted by the NSBRI to NASA in response to a new initiative to link NSBRI research and expertise with NASA Space Medicine personnel and resources at Johnson Space Center (JSC). The goal of the initiative is to address near- and intermediate-term operational needs, requirements, and challenges with the objective of improving the delivery of quality clinical care in-flight.

The project will combine new high-fidelity patient simulators with clinical practices and bioinstrumentation validated in medical settings, state-of-the-art information sciences and telecommunications (e.g. telemedicine), promising medical coaching and mentoring techniques, and appropriate emerging technology to develop and certify an integrated space medical system.

The objectives of the current project are:

1. To establish a multidisciplinary working team, known as the Medical Operational Support Team (MOST), comprised jointly from experts from the NSBRI and Medical Informatics and Health Care Systems (MIHCS) Office from JSC Space Medicine.
2. To assist in the development of a space-adapted human physiological model, as well as the creation of at least five clinical scenarios relevant to the space flight environment
3. To develop at least five diagnostic and/or treatment algorithms for the on-orbit care of the clinical scenarios
4. To assist in the development of training curricula for the in-flight care plans
5. To assist in the development of functional requirements for medical devices

2.0 Background and Scope

The JSC Space and Life Sciences Directorate is responsible for ensuring the health and well being of the space flight crews involved in manned missions. Towards this end, it is important to utilize enabling technologies to develop, test, and implement medical procedures, evaluate clinical equipment, assess physiological adaptation to microgravity, and improve crew and flight surgeon training to diagnose and manage in-flight medical contingencies.

Recognizing the usefulness of HPS systems for training medical skills terrestrially, JSC acquired a HPS from Medical Education Technologies, Inc (METI) for use in enhancing skill sets, knowledge, and judgment relevant for space medicine. The MIHCS administrator for the HPS project is James Logan, MD. Dr. Logan's team is engaged in work to ensure that simulations performed on the JSC HPS interface with NASA medical operations.

An opportunity exists to advance the use of HPS technology at JSC by involving individuals with extensive experience in terrestrial HPS development and applications. The outcome of an expanded effort would be to develop and test, through hardware and software modifications, patient validation of selected scenarios, and interfacing with data management, the most sophisticated physical model of a space adapted human.

To this end, JSC has approached the NSBRI to identify and support a leading HPS expert to coordinate the MOST and to engage with JSC personnel that addresses the high priority medical operational needs as set forth by NASA.

3.0 Deliverables

1. Establish MOST.
2. Develop, evaluate, and validate a minimum of five evidence-based treatment guidelines for the clinical scenarios. Deliverables will be in the form of an evidence-based treatment protocol, the final format will be a demonstration on video as well as a written report.
3. Summary analyses of the consumables utilized, discrepancies with the ISS Crew Health Care System (CheCS), and discrepancies with the current training flow will be specifically identified.
4. Evaluate current ISS CHeCS resources in the context of in-flight medical contingencies and assist MIHCS in the identification and evaluation of emerging medical devices. Each MOST/NSBRI member will evaluate a minimum of one medical resource over the two-year project. Deliverables will be in the form of a White Paper for each diagnostic or therapeutic resource evaluated. Reports may be co-authored with MIHCS personnel and will contain functional requirements (with the corresponding rationale(s) for each), a summary of the applicable medical conditions for which the resource would be useful, literature survey (if applicable), market survey (if applicable), evaluation procedure(s), relevant data, resource strengths and weaknesses, and final recommendations.
5. Adapt the clinical scenarios for training purposes, suitable for on-orbit CMO's (both physician-astronauts and non-physicians), ground-based flight surgeons, biomedical engineers, mission control teams, and international partners. Deliverables will be in the form of a JSK-based (Judgment, Skill Sets, Knowledge) annotated "script", making use of both the HPS scenario and the appropriate treatment pathway. A report will be written describing recommended requirements for medical certification and re-certification criteria for ground-

based and in-flight care providers. An evidence-based rationale will be associated with each requirement.

6. Assist in the establishment of the high fidelity medical simulation environment. Deliverables will include participation in at least three simulations over the course of the two year project.
7. Provide as needed essential expertise and ongoing guidance to the Bioastronautics program as specialty clinical subject matter experts (SMEs).
8. A quarterly progress report will be provided by the MOST PI.

4.0 Current Project Plan

This project will be conducted over a two-year period and is divided into three phases. The preponderance of work will be performed on-site at JSC.

Phase 1 – MOST Formation (months 0-2)

The first phase will be to establish a multidisciplinary working team, known as the MOST, comprised of physicians who will assist to define, develop, and evaluate a concept of operations (CONOPS) for medical care aboard the ISS, as well as to verify an associated enterprise-wide system design for remote care aboard anticipated space vehicles in the 2002-2012 timeframe.

An integrated team will be established under the direction of Harold Doerr, MD, who will act as the principal investigator (PI). Dr. Doerr will coordinate his activities with Dr. Logan and Craig Fischer, MD, head of Space Medicine at JSC, and with Jeffrey Sutton, MD, PhD, Director of the NSBRI. Dr. Doerr is Director of the Houston Center for Advanced Patient Simulation and is an Assistant Professor of Anesthesiology at Baylor College of Medicine.

In addition to Dr. Doerr, MOST/NSBRI physicians will include two practicing clinicians in the following fields: emergency medicine and internal medicine/family medicine. David Persse, MD, is the medical director of the Emergency Medical Services for the City of Houston and Assistant Professor of Emergency Medicine at Baylor College of Medicine. A clinical research assistant and clinical protocol developer will also be funded through the project; their tasks will include literature search and review, minor information technology support, editing of reports, guideline review and development, and assistance in the creation of presentations and other documents. MOST/JSC personnel will include Dr. Norman McSwain, Dr. Douglas Hamilton, Dr. Victor Hurst, and Dr. Kira Bacal.

MOST/JSC personnel will provide to MOST/NSBRI physicians training in the unique operational environment of space medicine (spacecraft and ground segments), so that they may become familiar with its capabilities and constraints.

Active MOST/NSBRI physicians will also serve as SMEs in the event of an in-flight contingency.

Dr. Doerr and the MOST will work with JSC Space Medicine to determine the operational needs and requirements relevant for HPS development. They will also work with Dr. Sutton to engage NSBRI experts and other resources that will bridge the NSBRI and Space Medicine communities to advance the HPS project. When appropriate, MOST will host short, focused meetings, at which national experts are invited to discuss clinical issues identified by MOST project personnel.

Phase 2 – Development of Space-Adapted HPS and Evaluation of Clinical Protocols (months 2-20)

MOST members will assist MIHCS in the continuing development of space-adapted normal physiological models. During this period, MOST members will also assist MIHCS in the development of at least five specific clinical scenarios for use with the HPS; these scenarios will be based upon anticipated in-flight medical contingencies as listed in the MIHCS Patient Condition Database. Best case, typical case, and worst-case clinical trajectories will be identified using the terrestrial case literature. Potential scenarios might include: crush trauma, inhalational burn, anaphylaxis, severe decompression sickness (DCS), myocardial infarction, eye injury, impacted renal stone, severe abdominal pain, hypovolemic shock, respiratory distress, or head injury. Deliverables will be in the form of a HPS scenario "script", along with applicable documentation.

When the space-adapted HPS models and clinical scenarios are ready, MOST members will assist in developing, evaluating, documenting, and baselining specific, evidence-based diagnostic and treatment algorithms developed by MIHCS, other SME's, and relevant Working Groups (chartered by the Space & Life Sciences Directorate) for anticipated in-flight medical contingencies. Practice guidelines will be correlated with in-flight medical resources ISS CHeCS via the existing MIHCS Patient Condition Database. The *chain of care* from space to earth and associated concept(s) of operations will also be examined in detail. The HPS and its clinical scenarios will be used as a test bed for the efficacy of these algorithms when used by the non-physician space care provider

Through the development of these clinical algorithms, MOST members will identify the skill sets and training curriculum for physician and in-flight care providers based on the JSK Model. The effort will utilize the HPS to examine in-flight advanced life support capabilities as well as to develop certification standards for ground-based (flight surgeon, biomedical engineer) and in-flight care providers (physician and non-physician) and guidelines for skill maintenance.

Phase 3 – Establishment of Functional Requirements for Medical Devices (months 10-24)

In concert with the scenario development, MOST members will also assist MIHCS personnel in the establishment of functional requirements for all medical devices and resources needed to support advanced medical care in space. These requirements will be used to identify and evaluate candidate medical systems, which can subsequently be tested during scenarios on the HPS.

5.0 Budget

The budget is divided into two parts – a Baylor College of Medicine portion and a NASA JSC portion.

In year 1, NSBRI costs include: support for the PI, a full time technician, NSBRI expert participation, purchase of portable equipment for MOST members and modest infrastructure support. A fringe benefit rate of 22% is applied. An off-campus BCM indirect cost rate of 28% is assessed. The total NSBRI costs are $289,550.

In year 1, NASA JSC costs include equipment (portable advanced computer and display system), compressed gas and subcontract support from Wyle Life Sciences totaling $46,300. An indirect cost rate of 10% is applied to non-equipment costs.

Baylor Activities	Year 1	Year 2	Total
Personnel	$153,720	$153,720	$307,440
Consultants	$37,500	$37,500	$75,000
Equipment	$11,700	$0	$11,700
Supplies	$1,000	$1,000	$2,000
Travel	$23,850	$23,850	$47,700
Other	$1,000	$1,000	$2,000
SUBTOTAL	$228,770	$217,070	$445,840
Indirect	$60,780	$60,780	$121,560
TOTAL Baylor	**$289,550**	**$277,850**	**$567,400**

NASA Activities	Year 1	Year 2	Total
Subcontracts	$30,000	$30,000	$60,000
Equipment	$10,000	$0	$10,000
Supplies	$3,000	$3,000	$6,000
SUBTOTAL	$43,000	$33,000	$76,000
Indirect	$3,300	$3,300	$6,600
TOTAL NASA	**$46,300**	**$36,300**	**$82,600**
TOTAL MOST	**$335,850**	**$314,150**	**$650,000**

Appendix M

NIDCD-NSBRI JOINT PROGRAM FOR THE SUPPORT OF VESTIBULAR RESEARCH

MANAGEMENT OF ADAPTATION TO ALTERED SENSORIMOTOR STATES

PI: Helen Cohen, Ed.D., Baylor College of Medicine:
Co-I: Jacob Bloomberg, Ph.D., NASA JSC

DECODING OF GRAVICEPTOR CUES, INCLUDING ADAPTIVE CHANGES

PI: Daniel Merfeld, Ph.D., Harvard University
Co-Is: Conrad Wall, Ph.D.
Lionel Zupan, Ph.D.
Robert Peterka, Ph.D., Oregon Health Sciences U.
Mark Shelhamer, D.Sc., Johns Hopkins Univ.

VESTIBULAR AND VISUAL CONTROL OF EYE MOVEMENT

PI: Jennifer Raymond, Ph.D., Stanford University

SIGNAL PROCESSING AND ADAPTATION IN CENTRAL OTOLITH PATHWAYS

PI: W. Michael King, Ph.D., Univ. of Mississippi Medical Center
Co-I: Wu Zhou, Ph.D.

PLASTICITY IN THE VESTIBULOOCULAR REFLEXES AND PERCEPTION

PI: Scott Seidman, Ph.D., University of Rochester
Co-I: Gary Paige, M.D., Ph.D.

NEURAL MECHANISMS OF VESTIBULAR ADAPTATION

PI: Dora Angelaki, Ph.D., Wash. Univ. School of Medicine
Co-I: J. David Dickman, Ph.D.

Appendix N

October 31, 2001
NRA 01-OBPR-07
OMB Approval No. 2700-0087

National Aeronautics and Space Administration
Office of Biological and Physical Research
Washington, DC 20546-0001

NASA Research Announcement Soliciting Research Proposals

Multiple Opportunities for Ground-Based Research in Space Life Sciences

1. Biomedical Research & Countermeasures Program & Advanced Human Support Technology Program (Space Human Factors Engineering Element)

2. National Space Biomedical Research Institute

3. Countermeasure Evaluation and Validation Project

A Research Announcement for the
NASA Office of Biological and Physical Research

Notices of Intent Due: November 30, 2001
Proposals Due: January 31, 2002

TABLE OF CONTENTS

NASA Research Announcement
Summary and Supplemental Information

Multiple Opportunities for Ground-Based Research in Space Life Sciences
NRA 01-OBPR-07

1. **Biomedical Research & Countermeasures Program and Advanced Human Support Technology Program**
   (Space Human Factors Engineering element)
2. **National Space Biomedical Research Institute**
3. **Countermeasure Evaluation and Validation Project**

This National Aeronautics and Space Administration (NASA) Research Announcement (NRA) solicits proposals for ground-based research in Space Life Sciences through three distinct opportunities. Applicants must: 1) determine which opportunity is best suited for their research project, 2) clearly identify which one of the three opportunities they are applying to (**do not submit the same research proposal to more than one opportunity**), and 3) follow the specific application procedures for the selected opportunity by referring to the appropriate Appendix. The following guidance should be used in determining the appropriate opportunity:

1. **Investigators submitting individual, independent projects** to the Biomedical Research & Countermeasures (BR&C) Program or the Space Human Factors Engineering (SHFE) element of the Advanced Human Support Technology (AHST) Program should refer to **Appendix B**;

2. Investigators who wish to become **members of an existing team of NASA's National Space Biomedical Research Institute (NSBRI)** should refer to **Appendix C**; and

3. Investigators who wish to propose testing a **proven biomedical countermeasure for use on the International Space Station using a bed rest microgravity model** through the NASA Johnson Space Center (JSC) Countermeasure Evaluation and Validation Program (CEVP) should refer to **Appendix D**.

Applicants are encouraged to refer to Figure 1 on page A-4 of this NRA to help determine what Countermeasure Readiness Level (CRL) their project addresses.

NASA investigators use the space environment to increase knowledge of biological and medical processes, to provide the biomedical foundation in support of the International Space Station and exploration beyond low Earth orbit, and to enrich life on Earth through the transfer of new space technology, medicine, and fundamental knowledge. This research supports NASA's mission through the Office of Biological and Physical Research (OBPR). All respondents to this NRA are strongly encouraged to promote general scientific literacy and public understanding of life sciences, the space environment, and the OBPR programs through formal and informal education opportunities. Where appropriate, supported investigators will be required to produce, in collaboration with NASA, a plan for communicating their work to the public.

In this NRA

- Appendix A provides an introduction and overview to the goals, objectives and implementation strategies of the OBPR.
- Appendices B, C, and D contain descriptions of the three opportunities, instructions for submitting a notice of intent (NOI) to submit a proposal, and instructions for proposal submission.
- Appendix E contains the "Instructions for Responding to NASA Research NRAs for Solicited Research Proposals."

Proposals submitted in response to this NRA must address the research emphases described in this announcement. Those that do not will be returned. **This NRA does not solicit flight research**. Other NRAs calling for focused research or utilization of unique resources may be issued throughout the year.

Proposals selected by NASA will be funded as grants incrementally for activities lasting up to four years, pending satisfactory progress. Proposals selected by the NSBRI will be funded as subawards by the NSBRI for activities lasting up to four years. The funding duration will depend on proposal requirements, review panel recommendations, and continuing progress of the activity. All proposals will be evaluated for overall scientific and technical merit by independent peer review panels. Relevance to NASA's programmatic needs and goals will be evaluated by NASA. Relevance to NSBRI's programmatic needs and goals will be evaluated separately by the NSBRI. Final selection will be coordinated between the Bioastronautics Research Division at NASA Headquarters and the NSBRI to ensure programmatic balance and elimination of duplicate efforts. Funds are not currently available for awards under this NRA. The government's obligation to make award(s) is contingent upon the availability of appropriated funds from which payment can be made and the receipt of proposals that the government determines are acceptable for award under this NRA. The total annual cost for ground research cannot exceed \$400,000. Costs in excess of this limit will require strong and extensive justification. NASA and the NSBRI do not provide separate funding for direct and indirect costs; thus, the amount of the award requested is the total of all costs submitted in the proposed budget. It is planned for selections to be announced by June 30, 2002, and awarded shortly thereafter.

Inclusion of Women and Minorities in Research Involving Human Subjects – NASA and the NSBRI have adopted the NIH policy regarding this matter. Women and members of minority groups and their subpopulations must be included in NASA-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

Participation in this NRA is open to all categories of United States (U.S.) organizations, industry, educational institutions, other nonprofit organizations, NASA laboratories, and other agencies of the U.S. government. In order to be reviewed, individual ground-based proposals responding according to the instructions in Appendix B must be from U.S. entities or from non-U.S. entities that involve substantive co-investigator collaboration from an U.S. entity. NASA will not fund non-U.S. entities. The NSBRI accepts and reviews proposals from foreign applicants, but potential foreign applicants should note that, normally, the country of origin, not the NSBRI, must fund projects from non-U.S. organizations. CEVP proposals submitted from international member states of the International Space Life Sciences Working Group will be reviewed, but the proposal must be approved for funding by the space agency of the member country.

A notice of intent (NOI) to propose is requested by November 30, 2001. Proposals must be submitted by January 31, 2002, 5:00 PM Eastern Time. (see Appendices B, C, and D of this NRA for specific instructions for these activities.

The following items apply only to this NRA:

Solicitation NRA Identifier:	NRA 01-OBPR-07
Number of Copies Required:	Original + 20 copies for the non-NSBRI submissions; Electronic proposals for the NSBRI submissions
Notices of Intent Due:	November 30, 2001
Proposals Due:	January 31, 2002
Selection Announcement:	June 30, 2002
Funding Begins:	Approximately 30-90 days following notification of selection
Selecting Officials:	For Individual BR&C, AHST, and CEVP proposals: Director, Bioastronautics Research Division, Office of Biological and Physical Research, NASA Headquarters For NSBRI proposals: Director, National Space Biomedical Research Institute

Additional information about the BR&C, AHST, and CEVP Programs is available from

David L. Tomko, Ph.D.
NASA Headquarters, Code UB
Washington, DC 20546-0001
Telephone: 202-358-2211
Fax: 202-358-4168
Email: dtomko@hq.nasa.gov

Information about the NSBRI is available from

Ronald J. White, Ph.D.
National Space Biomedical Research Institute
One Baylor Plaza, NA-425
Houston, TX 77030-3498

Telephone: 713-798-7412
Fax: 713-798-7413
Email: rwhite@bcm.tmc.edu

Grants Office points of contact will be identified in selection letters. The NRA will be updated and issued annually and is NASA's primary means of obtaining research proposals from the life sciences community. This NRA is restricted to the programs named above and described in detail in the Appendices. Potential investigators should read with care the program descriptions that are of interest, and focus their proposals on the specific research emphases defined in this NRA.

Your interest and cooperation in participating in this effort is appreciated.

Original Signed by

Kathie L. Olsen, Ph.D.
Acting Associate Administrator
Office for Biological and Physical Research

Background Information

Multiple Opportunities for Ground-Based Research in Space Life Sciences

I. Introduction

This NASA Research Announcement (NRA) is a consolidated NASA solicitation for research proposals in support of the NASA Office of Biological and Physical Research (OBPR) goals and objectives. Research is solicited for conduct by the Biomedical Research & Countermeasures (BR&C) Program, the Space Human Factors Engineering (SHFE) element of the Advanced Human Support Technology (AHST) Program, the National Space Biomedical Research Institute (NSBRI), and the Countermeasure Evaluation and Validation (CEVP) Project at the NASA Johnson Space Center.

The major goals of NASA's Office of Biological and Physical Research are to

- enable exploration by conducting research to enable safe and productive human habitation of space;
- use the space environment as a laboratory to test the fundamental principles of physics, chemistry, and biology;
- enable and promote commercial research in space; and
- use space research opportunities to improve academic achievement and the quality of life.

The BR&C Program is responsible for research to develop practical health-related methods for the prevention, diagnosis, treatment, and/or rehabilitation of space crews who live and work in microgravity.

The SHFE element within the AHST Program has the mission of creating and maintaining a safe and productive environment for humans in space. With space missions absorbing new technologies at an ever-increasing rate, it is imperative that planners insure that these advances will enhance crew performance without increasing stress or risk. The SHFE element is an interdisciplinary effort covering all aspects and facets of the general discipline of human factors engineering and sharing selected aspects of the behavior and performance discipline of the BR&C Program. The SHFE element encompasses a broad range of activities from basic research to development of state-of-the-art tools for measuring human performance, to applying those tools to solve operational human/system interface issues in human space flight programs. Development of new technologies and conceptual designs for flight crew accommodations needed for human missions beyond low earth orbit is also considered the responsibility of the SHFE element.

The NSBRI is a NASA-initiated and -funded private, non-profit research consortium charged by NASA with developing biomedical countermeasures for potential health problems that could occur in astronauts either during long-duration space flight or on their return to Earth. The NSBRI's current program consists of nearly 90 research and technology projects in twelve research areas.

The goal of the CEVP is to systematically and scientifically evaluate and validate terrestrial proven biomedical candidate countermeasures for space flight use that have reached a high degree of maturity. Candidate countermeasures will first be evaluated experimentally using ground-based analogs of space flight. A candidate countermeasure's targeted effects will be assessed, its side effects defined, and its interactions with other countermeasures identified. After evaluation, a candidate countermeasure may be validated in systematic experiments during actual space flight to assess those same factors. The CEVP functions using a team approach, in which the investigator becomes a member of a team that integrates space medicine and space research expertise resident inside and outside of the Agency. This team is coordinated by the NASA Johnson Space Center (JSC). The CEVP is the final step in a process in which ideas and concepts emerging from basic research are developed into operational countermeasures that are turned over by researchers to be implemented as part of NASA's mission operations.

The BR&C Program, the NSBRI, the SHFE element of the AHST Program, and the CEVP share scientific and educational goals to fund research that will result in the delivery of health-related countermeasures for astronauts. NASA is committed to maintaining a strong, openly competitive, peer-reviewed research program. Opportunities for investigators that are covered by this NRA include individual investigator awards (directly through BR&C & AHST Programs), participation in focussed discipline team research (NSBRI), and systematic experiments to evaluate and validate potential countermeasures (CEVP). Investigators should apply through whichever of these mechanisms is most suitable to enable them to conduct research in support of NASA's OBPR Programs. ***It is critical for investigators to read carefully <u>all</u> of the instructions in this NRA. All proposals will undergo peer-review using the same processes and procedures, but procedures and forms for proposal submission differ for the different programs and elements, and the eventual funding of selected proposals will differ for the different types of awards.*** Programmatic balance is maintained by the selecting official(s) for the program.

The research programs described in this NRA support the utilization of specialized NASA ground-based facilities and the development of special technologies required in the pursuit of its research goals. Investigators can access NASA specialized ground-based facilities for their research. Please refer to the *Space Life Sciences Ground Facilities Information Package* for instructions on how to incorporate the use of these facilities into a proposal:
http://research.hq.nasa.gov/code_u_nra/current/NRA-01-OBPR-07/index.html

This and the following Appendices define the research program and elements encompassed by this NRA, describe the specific areas of ground-based research that proposals should address, and describe the specific emphases that are acceptable for submission in response to this NRA. **This NRA does not request proposals for flight research**. It is important that the prospective investigator read the relevant section(s) carefully, as many of the programmatic emphases are different from those appearing in previous NRAs. In addition, each Appendix includes guidelines, requirements, and instructions for preparing and submitting proposals, and defines the administrative policies governing the programs and applicants to the particular component described in this NRA.

II. Critical Path Roadmap

In order to identify and make publicly known the biomedical risks of space flight and the research questions that must be answered to reduce those risks, NASA has developed the Critical Path Roadmap (CPR). The CPR is an interdisciplinary tool to assess, understand, mitigate, and manage the risks associated with long-term exposure to the space environment. It assumes an overarching strategy that integrates requirements, risks, risk factors, critical questions, tasks, deliverables, and risk mitigation with the intent of directing biomedical research in support of human space flight, especially human missions of exploration. **Each investigator must examine and understand the CPR, and specify in their proposal which critical questions their proposed research will answer.**

The CPR is based in part on recommendations from internal NASA experts, NSBRI scientists, advisory committees, task forces, and published reports such as the National Research Council (NRC) Space Studies Board's "A Strategy for Research in Space Biology and Medicine in the New Century," the Aerospace Medical Advisory Committee, the NASA Task Force on Countermeasures, the International Space Life Sciences Working Groups publications on Radiation, Bone, Muscle, Cardiovascular, Human Factors, and Neuroscience Workshops; and the NASA Medical Policy Board Document.

The ultimate goal of the CPR is to protect the health and safety of space flight crews by allowing NASA and the community of scientists to better define and focus the research that is required for development and validation of operational health care "deliverables" for the prevention, treatment and rehabilitation of space flight changes and of appropriate habitation and medical care systems.

The current CPR is a product that has identified 55 risks and 250 critical questions. A more extensive overview as well as a list of all the risks and critical questions for the CPR should be reviewed by potential investigators on the Web site http://criticalpath.jsc.nasa.gov/.

III. Countermeasure Readiness Levels (CRL)

NASA's Biomedical Research and Countermeasures (BR&C) Program has developed a scale to allow NASA to define, assess, and quantify the level of "countermeasure readiness." The use of this scale allows NASA to determine how each funded research project fits into the countermeasure development "flow" and to monitor progress in countermeasure development. This section describes this scale and how it is used. **Each investigator must examine and understand the CRL scale and specify in the proposal the CRL that will result from the funding and conduct of their proposed research.** Figure 1 illustrates the CRL scale, which describes the level of scientific maturity of BR&C research from the fundamental studies that suggest potential countermeasures to studies that allow the systematic evaluation and validation of countermeasures ready for operational implementation.

Figure 1. Countermeasure Readiness Levels

BASIC RESEARCH

1. Phenomenon observed and reported. Problem defined.
2. Hypothesis formed, preliminary studies to define parameters. Demonstrate feasibility.

RESEARCH TO PROVE FEASIBILITY

3. Validated hypothesis. Understanding of scientific processes underlying problem.
4. Fomulation of countermeasures concept based on understanding of phenomenon.
5. Proof of concept testing and initial demonstration of feasibility and efficacy

COUNTERMEASURE DEVELOPMENT

6. Laboratory/clinical testing of potential countermeasure in human subjects to demonstrate efficacy of concept
7. Evaluation with human subjects in controlled laboratory conditions simulating operational space flight environment

COUNTERMEASURE EVALUATION & VALIDATION

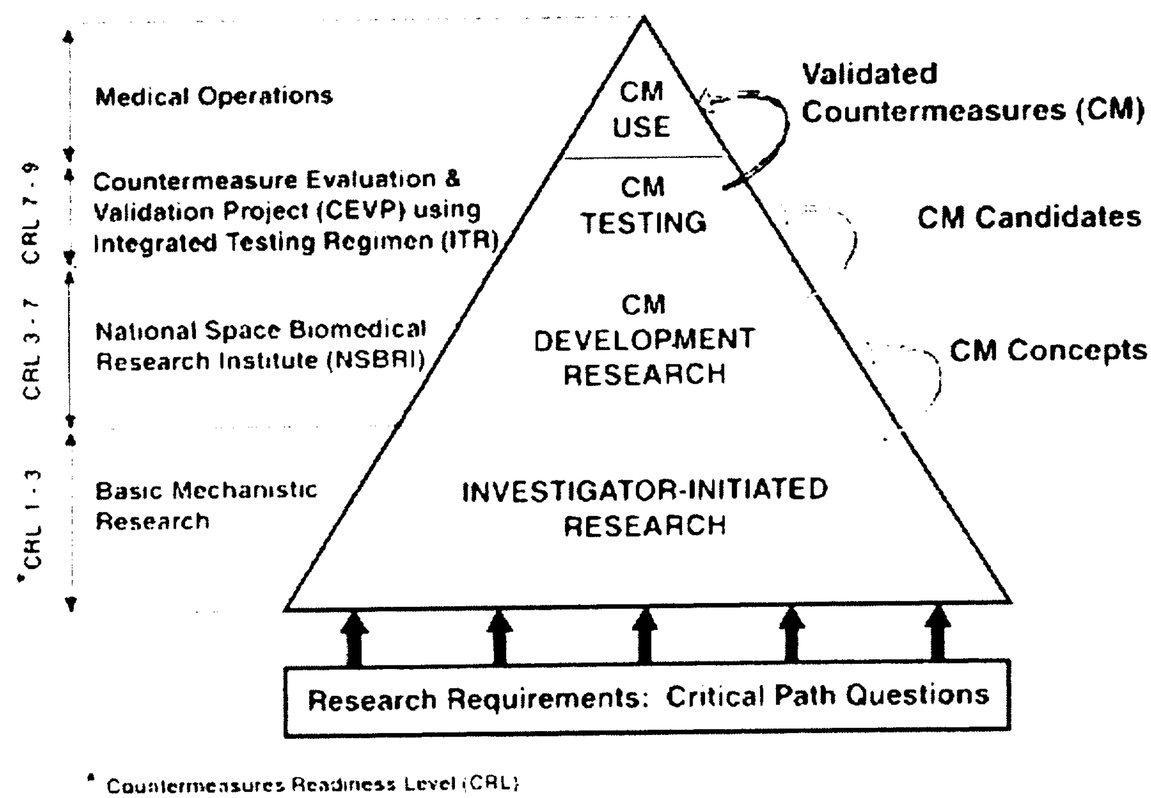
8. Validation with human subjects in actual operational space flight to demonstrate efficacy and operational feasibility

COUNTERMEASURE OPERATIONS

9. Countermeasure fully flight tested and ready for operational implementation

Countermeasure development usually progresses through systematic research. Research flows through various levels of countermeasure readiness. Figure 2 represents this general progression. The boundaries between the types of activities are approximate. The CEVP is focused on CRL levels of 7 and 8 only. CEVP research will systematically evaluate and validate potential countermeasures that have completed laboratory testing, bridging the gap between research and space flight operations. A potential countermeasure ready for validation in flight is one that has a thorough, successful history of ground-based, clinical and/or flight analog testing.

Figure 2. Countermeasure Development Process



IV. Review and Selection Process

This appendix supersedes, modifies, or extends the requirements enumerated in Appendix E. All proposals must comply with the general requirements of the Announcement as described in both Appendices A and E. Appendices B-D contain specific requirements and explanations for each opportunity above and beyond NASA-specified requirements. Appendix E outlines the NASA-specified requirements for proposal submission and should be used for clarification and reference. Upon receipt, proposals will be reviewed for compliance with the requirements of this Announcement. This includes

1. Submission of complete proposals specified in this Announcement. Proposals must be responsive to the areas of program element emphasis described in this Announcement and include a project description that is not more than 20 pages in length.
2. Submission, as specified in the detailed instructions to investigators, of appropriate Institutional Review Board (IRB) or Animal Care and Use Committee (ACUC) certification for all proposals using human or animal test subjects.
3. Submission of a budget within the guidelines specified in this Announcement and for a funding period not exceeding three years in duration.
4. Proposals that are revised versions of proposals previously submitted to NASA must be clearly designated as such on the proposal cover page, and must contain an explanation of how the revised proposal has addressed criticisms from previous NASA review. This explanation should be presented in a separate section of **no more that two pages at the beginning of the project description**, and is in addition to the 20 pages allowed for the project description. Related changes to the research plan should be highlighted in the body of the project description.
5. Submission of all other appropriate forms as required by this NASA Research Announcement (refer to appropriate Appendix).

Note: Non-compliant proposals may be withdrawn from the review process and returned to the investigator without further review.

Compliant proposals submitted in response to this Announcement will undergo an intrinsic scientific or technical merit review. Only those proposals most highly rated in the merit review process will undergo the additional reviews for program relevance and cost.

Scientific or Technical Merit Review

A merit review of proposals submitted to this NRA will be conducted by panels of scientific or technical experts. A single set of discipline-specific panels, administered by NASA Peer Review Services, will evaluate all proposals submitted to this NRA. The number and diversity of experts required will be determined by the response to this NRA, and by the variety of disciplines represented in the proposals relevant to the research emphases described in Section I of this Appendix. Merit review panels will ***score proposals from 0-100***.

The score assigned by each panel ***will not be affected by the proposed cost of the work nor will it reflect the programmatic relevance of the proposed work to NASA***. However, the panels will be encouraged to include comments concerning the proposal's budget and relevance to NASA in the critique of each proposal, after it has been scored.

All of the following will be used in determining the merit score:

- **Significance:** Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or technology be advanced? What will be the effect of these studies on the concepts, methods, or products that drive this field? What is the likelihood that the proposed research will lead to new countermeasures or tests of the utility of countermeasures? Is there a significant societal or economic impact?

- **Approach:** Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Is the proposed approach likely to yield the desired results? Does the applicant acknowledge potential problem areas and consider alternative tactics? Are there strong interdisciplinary components?

- **Innovation:** Does the project employ novel concepts, approaches, or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

- **Investigator:** Are the scientists in the project, including collaborators, suitably trained for the proposed work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)? Is the evidence of the investigator's productivity satisfactory?

- **Environment:** Does the scientific environment in which the work will be performed contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

Evaluation of Programmatic Relevance and Cost

A **second review** will evaluate the programmatic relevance and cost of all proposed work. Evaluation of the cost of a proposed effort includes consideration of the realism and reasonableness of the proposed cost and the relationship of the proposed cost to available funds. Is the proposal responsive to the needs of NASA or the NSBRI, ***as expressed in this NRA***? Programmatic relevance will include an evaluation of how the proposed work may help achieve an appropriate balance of scientific and technical tasks required by critical research issues faced. Evaluation of programmatic relevance will vary according to the specific element of this NRA. For example, CEVP proposals will be evaluated for operational relevance and feasibility of implementation.

Development of a Selection Recommendation

A selection recommendation will be developed based on the results of the two levels of review described above. The most important element in the evaluation process is the merit review, which carries the highest weight in final evaluation and selection. The other factors are approximately equal in weight to each other. The development of selection recommendations is the responsibility of NASA for the individual proposals submitted to the Biomedical Research and Countermeasures (BR&C) Program and Advanced Human Support Technologies (AHST) elements of this NRA and for CEVP proposals. The development of selection recommendations is the responsibility of the NSBRI for proposals submitted to the NSBRI elements of this NRA. Selections for funding of individual BR&C, AHST and CEVP proposals will be made by the Director of the Bioastronautics Research Division, Office of Biological and Physical Research (OBPR), and selection of NSBRI proposals will be made by the NSBRI management with the approval of the NSBRI Board of Directors. Final selection will be coordinated between the Bioastronautics Research Division at NASA Headquarters and the NSBRI to ensure programmatic balance and elimination of duplicate efforts.

NASA and the NSBRI reserve the right to select and make an award covering only a portion of an investigator's investigation, in which case the investigator will be given the opportunity to accept or decline such partial acceptance. In cases in which two or more proposals address similar problems and/or adopt similar approaches, NASA or the NSBRI may desire joint participation on the part of two or more investigators in a single project. Any negotiations prior to final decisions will occur only after the peer review of proposals has been completed. The selection review may also recommend changes in which program should fund a specific proposal (e.g., a proposal not selected for participation in an existing NSBRI team may be recommended for selection by the Bioastronautics Research Division or an individual proposal not selected as an individual proposal and not from a current NSBRI principal investigator may be recommended as an NSBRI team proposal.) In either case, acceptance of such a recommendation shall be at the discretion of the Principal Investigator. If a proposal submitted to OBPR is found to be more appropriate to satisfy the NSBRI requirements, the Principal Investigator will be expected to become a full member of the appropriate NSBRI team.

V. Program Reporting

It is expected that results from funded research will be submitted to peer-reviewed journals as the work is completed. Published papers must acknowledge NASA or NSBRI support. In addition, investigators whose proposals are selected must also provide annual reports on progress in achieving the goals of the research project.

Final Report. A final report is required that shall include a summary of completed research and a record of all scientific communications and peer-reviewed publications to date. This report must be submitted to the NASA Technical Monitor or to the NSBRI within 60 days after the end of the grant period.

VI. Support of Education and Outreach

NASA envisions that the selected proposals will be structured and operated in a manner that supports the country's educational initiatives and goals (including historically black colleges and universities and other minority universities), and in particular the need to promote scientific and technical education at all levels. NASA envisions that the selected proposals will support the goals for public awareness and outreach to the general public (see Appendix B). The selected investigators are invited to participate in NASA-funded educational programs.

OBPR Policy for Education (K-12) and Public Outreach

The proposal represents an opportunity for NASA to enhance and broaden the public's understanding and appreciation of the value of Biomedical Research and Countermeasures in the context of NASA's mission. Therefore, all investigators are strongly encouraged to promote general scientific literacy and public understanding of Biomedical Research and Countermeasures research through formal and/or informal education opportunities. If appropriate, proposals should include a clear and concise description of the education and outreach activities proposed. Examples include such items as involvement of students in the research activities, technology transfer plans, public information programs that will inform the general public of the benefits being gained from the research, and/or plans for incorporation of scientific results obtained into educational curricula consistent with educational standards.

Where appropriate, the supported institution will be required to produce, in collaboration with NASA, a plan for communicating to the public the value and importance of their work.

VII. Bibliography

1. **Life Sciences Program Tasks and Bibliography (Task Books)** for FY1995-2000 are available at http://peer1.nasaprs.com/peer_review/taskbook/taskbook.html/

2. **NSBRI Program Overview.** This document is available at http://www.nsbri.org/

3. **Space Life Sciences Ground Facilities Information Package.** This document is available at http://research.hq.nasa.gov/code_u/nra/current/NRA-01-OBPR-07/index.html

4. Information about space life sciences research publications can be found by using the National Library of Medicine's PubMed, LOCATORplus, and Gateway search systems. Coverage of space life sciences references in these systems has been enhanced by the SPACELINE Project through the support of NASA's Office of Biological and Physical Research. In addition, a space "limit" has been added to PubMed that permits limiting searches to a subset of space life sciences-related references only. Additional information may be obtained from the SPACELINE Project (phone: 301-295-2482; email: spaceline@usuhs.mil).
SPACELINE Project web address: http://spaceline.usuhs.mil
National Library of Medicine web address: http://www.nlm.nih.gov

5. **The Space Life Sciences Data Archive (LSDA)** is an online database containing descriptions and results of completed NASA-sponsored flight experiments. Descriptions are included of experiments, missions, procedures, hardware, biospecimens collected, personnel, and documents. Biospecimens that are available for research purposes are described in detail. A limited number of experiments contain final reports and spreadsheet data suitable for downloading. Data from human subjects are unavailable online for reasons of privacy.
Internet address: http://lsda.jsc.nasa.gov/
LSDA Help Desk: (281) 483-7876

Email: lsda@semail.jsc.nasa.gov

6. **Center for Advanced Studies in the Space Life Sciences** contains a list of workshops and seminars sponsored by the Center. The proceedings and final reports of these workshops are also posted as they become available at http://www.mbl.edu/CASSLS/

7. **Medical Policies and Requirements Document**. National Aeronautics and Space Administration, Medical Policy Board. Richard Williams, M.D., Chairperson. NASA Headquarters. This document is available at http://peer1.nasaprs.com/peer_review/prog/mpbhand.pdf

8. **A Strategy for Research in Space Biology and Medicine in the New Century.** National Academy of Science. National Research Council Committee on Space Biology and Medicine. Mary J. Osborn, Committee Chairperson. 1998. Washington DC: National Academy Press. http://www.nas.edu/ssb/csbm1.html/

9. **The NASA Strategic Program Plan for Space Radiation Research**. http://spaceresearch.nasa.gov/programs/1998_radiation_strat_plan.pdf/

10. **Space Physiology and Medicine, 3rd ed**. A. Nicogossian, C. Huntoon, and S. Pool. (Eds.). 1994. Philadelphia, PA: Lea & Febiger.

11. **Cell & Molecular Biology Research in Space**. *The FASEB Journal*, Vol. 13, Supplement, 1999.

12. **Radiation Protection Guidance for Activities in Low-Earth Orbit.** December 31, 2000. NCRP Report 132. Bethesda, MD: National Council on Radiation Protection and Measurements.

13. **Workshop on Space Flight Validation of Radiation Risk**. January 24-26, 1996. Universities Space Research Association, 3600 Bay Area Boulevard, Houston, TX, 77058.

14. **Shielding Strategies for Human Space Exploration**. J. W. Wilson, J. Miller, A. Konradi and F. A. Cucinotta, Editors. NASA CP-3360, December 1997, pp. 456. Also available from the NASA Langley Technical Reports Server, http://techreports.larc.nasa.gov/ltrs/ltrs.html/

15. **Acceptability of Risk >From Radiation - Application to Human Space Flight**. April 30, 1997. Symposium Proceedings No. 3. Bethesda, MD: National Council on Radiation Protection and Measurements.

16. **Modeling Human Risk: Cell & Molecular Biology in Context**. June 1997. Ernest Orlando Lawrence Berkeley National Laboratory Report, LBNL-40278. Berkeley, CA.

17. **Radiation Hazards to Crews of Interplanetary Missions: Biological Issues and Research Strategies**. 1996. Washington, DC. Task Group on the Biological Effects of Space

Radiation. Space Studies Board Commission on Physical Sciences, Mathematics and Applications, National Research Council. National Academy Press.

18. **Task Force on Countermeasures.** This report incorporates the output of the Countermeasures Task Force, the Vestibular Countermeasures Task Group, and the Behavior and Performance Working Group into a unified document. This document is available at http://peer1.nasaprs.com/peer_review/prog/countermeasures/countermeasures.html/

19. **International Workshop on Cardiovascular Research in Space**. *Medicine and Science in Sports and Exercise*, Volume 28, Number 10 Supplement, 1996.

20. **Muscle Research in Space: International Workshop**. *International Journal of Sports Medicine*, Volume 18, Supplement 4, S257-S331, 1997.

21. **Space Neuroscience Research**. *Brain Research Reviews*, Volume 28, Numbers 1/2, Special Issue, 1998.

22. **International Workshop on Bone Research in Space**. *Bone, Official Journal of the International Bone and Mineral Society*, Volume 22, Number 5 (Supplement), 1999.

23. **Space Human Factors Project Plan (2000) and the Space Human Factors Project Implementation Plan, FY00-FY01 (2000).** http://peer1.nasaprs.com/peer_review/prog/prog.html

24. **Small Clinical Trials: Issues and Challenges.** Institute of Medicine, National Academy Press, Washington, DC. http://www.nap.edu/books/0309073332/html/

25. **Sex and Gender: Exploring the Biological Contributions to Human Health**. *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. 59 Fed. Reg. 14508 (1994).*

APPENDIX B
NRA 01-OBPR-07

Multiple Opportunities for Ground-Based Research in Space Life Sciences Technical Description

Opportunity to Submit Individual Investigations for the Biomedical Research and Countermeasures or Advanced Human Support Technology Programs

NOTE: This appendix should only be used for scientists interested in conducting an individual, independent research project.

I. Introduction

The Biomedical Research and Countermeasures (BR&C) Program directly supports NASA's missions in the Office of Biological and Physical Research and the Human Exploration and Development of Space Enterprises. It also responds directly to the requirements, approved by the Office of the Chief Health and Medical Officer, which deal with the health and safety of human space travel (see *Medical Policies and Requirements Document*, Bibliographic Reference #7 of Appendix A).

The goals of this program are to

- develop an understanding of the physiological mechanisms that are responsible for space flight-related biomedical and behavioral changes in humans in support of countermeasure development;
- develop countermeasures that allow humans to live and work in microgravity for long durations, minimize the risks in readapting to gravity, and optimize crew safety, well-being, and performance; and
- identify, characterize, and mitigate (preventing and reducing) health, environmental, and other operational human medical risks associated with space exploration.

II. Biomedical Research and Countermeasures (BR&C) Program Emphases

Elements and Emphases for FY 2002

The emphasis of the current ground-based component of this program is to develop insights into physiologic changes that are likely to occur as a consequence of extended periods of flight. The BR&C Program supports basic, applied and clinical research. Researchers may use hypogravity simulation models (e.g., bed rest, unilateral lower limb suspension, tail suspension, etc.) or hypergravity produced by centrifugation for their research studies. Experiments may use human subjects, animal models, or other appropriate models in the development of countermeasures. The program is composed of five research elements, each focused on the development and ultimate use of countermeasures to the deleterious effects of space flight: 1) Physiology, 2) Behavior and Performance, 3) Environmental Health, 4) Clinical Research in Support of Space Missions, and 5) Radiation Health.

Mechanistic research is solicited that supports the development of ground-based biomedical countermeasures to the effects of space flight. A countermeasure to help astronauts is any means or procedural strategy that prevents or reduces the negative effects of space or aids in the recovery upon return to Earth. It should be noted that the astronaut corps is diverse, comprised of men and women 30-60 years of age and of various ethnic backgrounds. Countermeasures should be robust enough to be efficacious across this population and be tailored for individual specificity. **This program encourages integrated approaches that study interactions that occur between different physiological systems in the design and application of potential countermeasures.** Identifying the effects of experimental interventions on non-target systems as well as the targeted system is deemed to be of particular importance. Research is also sought to support the solution to operational and clinical problems. This section describes the elements and research emphases within the BR&C Program. **High priority in FY 2002 will be given in particular to proposals for research in the areas of Radiation Health and Clinical Studies.**

It is expected that the average total annual (direct+indirect) cost of selected proposals will be between $200,000 and $250,000. In general, the total annual cost of a single proposal may not exceed $400,000.

1. Physiology

Proposals are requested for ground-based studies that will lead to a better understanding of the effects of space flight and exposure to microgravity on physiological function. Space physiology has included 1) fluid volume and cardiopulmonary, including cardiovascular alterations; 2) musculoskeletal, including bone loss and muscle alterations and atrophy; 3) neuroscience, including vestibular function, circadian rhythms, sensorimotor function, and endocrine control; 4) immunology, infection, and hematology; 5) food, nutrition, and metabolism, and 6) integrative physiology; as well as 7) advanced technology development within the above elements. Research proposals in other areas of physiology are also solicited (e.g., renal, endocrine physiology, etc.). Studies that use integrated approaches are particularly encouraged. Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at: http://criticalpath.jsc.nasa.gov.

Contact: Bruce Hather, Ph.D./Bioastronautics Research Division
Telephone: 202-358-1796
Email: bhather@hq.nasa.gov

2. Behavior and Performance

The Behavior and Performance element of the program addresses issues of 1) perception and cognition, 2) human physical performance, 3) personal, interpersonal, and group dynamics (coping, response to stress, etc.); 4) habitability, and 5) sleep and circadian rhythms. Physiological studies should be directed toward understanding the effects of responses to space flight on behavior and performance measures.

This element supports experiments designed to understand the mechanisms by which microgravity, confinement, cumulative sleep loss, mission design and events, spacecraft environment, and noise and light affect the behavior and performance of flight crews and ground-support crews. It also addresses psychosocial, gender, and cross-cultural aspects of human missions in space. Studies of relationships between individuals and individuals in groups are also addressed. Existing databases and ground simulations in extreme and isolated analogs and test beds may be used to extrapolate to responses that might be expected in long-duration space flight. Behavior and performance research priorities for ground-based studies include

a. Psychological Research

Research is solicited on: the development and validation of predictive tools for the assessment of psychological well-being, cognitive processing, mood, and emotion; especially as those are affected by multicultural and gender variables in long-duration space missions.

b. Psychiatric Issues

Research is required to detect and treat behavioral disorders that might occur in locations remote from usual health care facilities, e.g., during long-duration space flight.

Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at: http://criticalpath.jsc.nasa.gov. For a broad, detailed listing of NASA Life Sciences Behavior and Performance research priorities, the Countermeasures Task Force Report on Behavior and Performance can be obtained online at
http://research.hq.nasa.gov/code_u/code_u.cfm

Contact: David L. Tomko, Ph.D./Bioastronautics Research Division
Telephone: 2 02-358-2211
Email: dtomko@hq.nasa.gov

3. Environmental Health Research

Research within the Environmental Health element includes three interrelated disciplines, each dealing with a specific aspect of the spacecraft environment – Barophysiology, Microbiology, and Toxicology. The Environmental Health element has established the following goals: (1) to understand the effects of the spacecraft environments on humans and other organisms; and (2) to develop standards and countermeasures, where necessary, to optimize crew health, safety, and productivity.

For FY 2002, proposals are particularly sought for ground studies to determine the effects of potential toxins found on the International Space Station on human health. Since the work and living environment of the space flight crew is one and the same, the individual may be exposed to these potential toxins for extended times as compared to limited work hours here on Earth. Additionally, proposed studies that evaluate the added risk of several potential toxins with space radiation are encouraged. Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at: http://criticalpath.jsc.nasa.gov.

Contact: Bette Siegel, Ph.D./Bioastronautics Research Division
Telephone: 202-358-2245
Email: bsiegel@hq.nasa.gov .

4. Clinical Research in Support of Space Missions (Medicine in Extreme Environments)

The Clinical Research in Support of Space Missions element of the program will focus on the development of medical knowledge and technologies required to maintain human health and performance in space and on return to Earth. Medical knowledge must be expanded so that the practice of Space Medicine in the microgravity environment can be evidence based. Medical and surgical procedures and treatment and imaging systems are required to diagnose and treat illnesses and injuries that may occur in space. The Clinical Research in Support of Space Missions element of the program will support research required to improve, or answer specific questions about in-flight diagnosis, therapy, and postflight rehabilitation.

a. Diagnosis

Ground-based research analogs for space flight research are required to complete the understanding of the patho-physiology, diagnosis and therapeutic modalities required for implementation of an evidence-based practice of Space Medicine. Proposals for the development of non-invasive diagnostic tests and autonomous and semi-autonomous patient monitoring systems are requested. Research is also sought for the development of medical information systems that support the onboard medical provider.

b. Therapy

High priority will be given to research proposals to study the mechanisms of changes that could occur during space flight in the therapeutic effectiveness and adverse drug interactions of medications for common illnesses. Proposals are sought for research to enhance surgical capabilities in space. High priority will be given to proposals that investigate the application of fiber optic-based and minimally invasive surgical techniques.

Proposals are sought in medical education focused on the development and maintenance of medical capabilities for both physicians and non-physician crew medical officers. Priority will be given to those research proposals that develop and test new training paradigms. Proposals are a priority that address the development of space flight treatment capabilities for acute medical and surgical emergencies such as wounds, lacerations, and burns; toxic exposures; decompression illness; dental, ophthalmologic, urologic, gastrointestinal, and gynecologic emergencies.

c. Rehabilitation

Proposals are sought for research to develop effective rehabilitation techniques for deconditioned space travelers on their return to Earth. Priority will be given to proposals addressing rehabilitation after long-duration space flight.

d. Pharmaceuticals and Blood Replacement Solutions

Proposals are sought for ground-based research to enhance the "shelf-life" and effectiveness of pharmaceuticals, intravenous fluids, and blood replacement substances, which are stored for extended periods of time and would be required for clinical care of patients in extreme environments (e.g., radiation resistant, storage at ambient temperature, small volume, etc.).

Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at http://criticalpath.jsc.nasa.gov.

Contact: Victor S. Schneider, M.D./Bioastronautics Research Division
Telephone: 202-358-2204
Email: vschneider@hq.nasa.gov

5. Radiation Health

The Radiation Health element of the program supports research in the areas of 1) radiation physics, 2) biological effects of shielding materials, 3) genetic biological predisposition, and 4) bioengineering and radiation protection. For FY 2002, the primary area of emphasis for the Space Radiation Health element is the *reduction of radiation risk* based on development of mechanistic insights into the biological effects of radiation. Purely phenomenological approaches, e.g., testing of pharmacological substances with presumed radioprotective effects without developing new knowledge, are not acceptable. Instead, proposals are required to be hypothesis-driven and are expected to obtain their data in ground-based experimental radiobiology studies with proton and high-energy heavy ion beams in the energy range corresponding to space radiation.

Scientists working in rapidly developing areas of life sciences not necessarily associated with the study of radiation are particularly encouraged to consider the contributions that their field of study can make to Radiation Health, and to propose investigations relevant to the Space Radiation Health element. Proposals are required to provide evidence for expertise in radiation, either by reference to the Principal Investigator's work or by the inclusion of active collaborators expert in radiation research.

High-priority research proposals will

1. Determine carcinogenic risks following irradiation by protons and HZE particles.
2. Determine how cell killing, induction of chromosomal aberrations, or carcinogenesis vary as a function of the thickness and composition of radiation shielding.

3. Increase the confidence of extrapolation to humans from knowledge of radiation-induced genetic alterations or carcinogenesis in rodents.
4. Determine if exposure to heavy ions at levels occurring in deep space pose a risk to the integrity and function of the central nervous system.
5. Lead to significant advances in our understanding of cancer risk, consequences of CNS damage, and acute and early damage due to solar particle events.
6. Link biological mechanisms to significant improvements in accuracy of prediction of radiation risk for humans in space (especially carcinogenesis).

Additionally, studies are requested that lead to significant advances in our understanding of genetic mechanisms of radiation damage and repair in cells and tissues, especially those aspects that are complementary to research in genomic instability, which have been jointly funded with the National Cancer Institute. Proposals addressing genetic sensitivity to space radiation and genetic intervention to alter such sensitivity are encouraged. **Proposals are requested that test methods to protect from or counteract the effects of high energy radiation damage while increasing new knowledge regarding the mechanisms of organismal protection from radiation or in their recovery from radiation damage.**

Proposals are of interest that are based on basic mechanisms of molecular biology that are likely to result in development of biological countermeasures in humans that could lead to prevention or intervention (including genetic or pharmacological agents) against effects of radiation damage in space.

NASA has signed agreements with Loma Linda University Medical Center related to the use of proton beams and with Brookhaven National Laboratory (Brookhaven) for the use of heavy ion beams at the Alternating Gradient Synchrotron (further details are provided in Section 5.0 of *Space Life Sciences Ground Facilities Information Package*). A new facility at Brookhaven, the Booster Applications Facility (BAF), is under construction. It is expected to become operational in 2003 and will deliver beams of protons and heavy ions ranging up to gold, at energies between tens and thousands of MeV/nucleon. The BAF includes irradiation stations, beam controls and laboratory facilities required for most radiobiological investigations. **NASA negotiates beam delivery directly with these institutions, and investigators proposing to use these irradiation facilities should not include the cost of beam time in their budgets. However, investigators should include the cost of carrying out the experiments, including travel to these facilities.**

Experimental studies not directly using protons or heavy ions in the relevant energy range or not directly relevant to the interpretation of experiments already conducted with such radiation will not be funded. The Brookhaven BAF will become operational in 2003. Research proposals are encouraged that use the BAF to answer the focused questions above. Proposals should take into account the impact of gender, age, nutrition, stress, genetic predisposition, or sensitivity to other factors of importance in managing space radiation risks.

Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at http://criticalpath.jsc.nasa.gov.

Contact: Walter Schimmerling, Ph.D./Bioastronautics Research Division
Telephone: 202-358-22005
Email: wschimm@hq.nasa.gov

III. Advanced Human Support Technology Program (Space Human Factors Engineering Element)

Emphases for FY 2002

The Space Human Factors Engineering (SHFE) element solicits research proposals in the areas of 1) habitability and work environment, 2) training, 3) mission support, 4) crew performance and workforce characteristics, 5) data analysis and design, and 6) workload and task characteristics. The investigator should highlight, where possible, how the results of the proposed research can be used (at the earliest possible time) to support operations on the ISS or in training in preparation for space flight. Proposals for research in other areas relevant to the SHFE element may be submitted in response to this NRA but will likely receive lower priority for funding.

The research focus for each of the areas of emphasis (not in priority order) follows:

Habitability and Work Environment

Methods for objectively or quantitatively measuring habitability features are needed. This NRA solicits studies to develop tools for predicting the effects of combinations of habitability-related issues (e.g., noise, visual environment, privacy) on crew performance and safety.

Training

This NRA solicits studies that focus on deciding when training is needed (i.e., just in time training), and how to determine if training prior to a planned or unplanned task is absolutely essential or just helpful. Proposals are sought that would study the effectiveness of embedded training in actual operational equipment; supporting analyses of risk/error and training benefit should be compared to traditional methods. Studies to assess team training, and strategies to measure learning both for the group and the individual, are also solicited.

Mission Support

Proposals to determine the appropriate composition of automated tasks overseen by the workforce (flight and ground support crews), and research to determine the effect of "online" documentation of procedures, are solicited. Proposals are also solicited to determine how best to communicate mission performance data to crews, involve crews during the planning of off-nominal situations or when new information requires changes in operations, and how to develop strategies and/or technologies which aid and measure the crews ability to functionally make these changes.

Crew Performance (and Workforce Characteristics)

Proposals are solicited that lead to technologies or processes that monitor human/machine performance (within adjustable limits) and allows appropriate and timely feedback to the monitoring crew for task replanning.

Data Analysis and Design

Proposals for improved methods and tools for data collection, analysis and organization are solicited. Typical challenges in this area include effective use of mission equipment and crew; efficient transmission, archiving, and distribution of data; and rapid access to mission data for real-time replanning. Proposed research should include human factors issues in design of human interfaces and in understanding of human use of scientific and engineering data.

Workload and Task Characteristics

Proposals for non-intrusive methods of workload assessment including the effects of levels of workload on performance are solicited. Proposals are also solicited for development of models that predict the effects of various schedules and workloads on human performance, with emphasis on measuring the effects of how task allocation between humans and automated systems affect both crew and system performance.

Further information on the SHFE element of the Advanced Human Support Technology Program (reference 23) can be found at http://peer1.nasaprs.com/peer_review/prog/prog.html

Additional information about the Advanced Human Support Technology Program is available from

Charles J. Barnes, Ph.D.
NASA Headquarters, Code UB
Washington, DC 20546
Telephone: 202-358-2365
Fax: 202-358-4168
Email: cbarnes@hq.nasa.gov

Contact: Mr. Thomas Rathjen/NASA Johnson Space Center
Telephone: 281-483-3651
Email: trathjen@ems.jsc.nasa.gov

IV. Application Procedures for Individual Investigators Proposing to the Biomedical Research and Countermeasures or Advanced Human Support Technology Program

Instructions for Notice of Intent and Proposal Submission

Proposals for individual investigator grants must comply with the general requirements of this research opportunity as described in this appendix (Appendix B). Appendix E outlines general NASA-specified requirements for proposal submission and should be used for clarification and reference. This appendix supersedes, modifies, or extends the requirements enumerated in Appendix E.

SYS-EYFUS Registration for All Applicants

SYS-EYFUS is an electronic system used by NASA Headquarters to manage research solicitation activity, plan for the receipt of research proposals, track the receipt and peer evaluation of these proposals, and manage funded research (grants, cooperative agreements, etc.) sponsored by NASA's Office of Equal Opportunity (Code E), Office of Earth Science (Code Y), Office of Human Resources & Education Division (Code F), Office of Biological and Physical Research (Code U), Office of Space Science (Code S), and the Office of Space Flight (Code M). SYS-EYFUS also supports the funding and administration of awards pursuant to selection of these research opportunities.

All investigators planning to submit a proposal to this solicitation are requested to register online with SYS-EYFUS. Comprehensive help, instructions, and contact information are provided online. SYS-EYFUS can be accessed at the following address:

http://proposals.hq.nasa.gov/

If you have previously registered with SYS-EYFUS, you are requested to verify and update your user information. If you have forgotten your user ID or password, select the "Forgot Your Password" option and type in your first and last name to search our database. The system will send an automatic email message with your username and password to the email address listed in our database.

Instructions for Preparing a Notice of Intent

All investigators planning to submit a proposal in response to this solicitation are requested to submit a **non-binding** notice of intent (NOI) to propose by November 30, 2001, via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

Submission of a notice of intent is strongly encouraged, but not mandatory.

- Login to SYS-EYFUS and select "New Notice of Intent."
- The Division Specific Opportunities screen will appear. In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Notice of Intent submission Form. All fields are required.
  a. For the proposal type field on this form, new/no prior support means that the investigator has not received NASA funding from 1999 through 2001, new/prior support means that

the investigator has received NASA funding between 1999 and 2001, and revised means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002.

- Click on "Submit NOI Page."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name, and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the NOI. After you are done, click on "Continue." IMPORTANT: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Members Page, your NOI will be displayed. Click on "Resubmit NOI Page" to complete your NOI submission.
- You may edit and resubmit your NOI at any time before the submission deadline of November 30, 2001. Once you submit an NOI, it cannot be deleted. For title, team member, or any other changes, please edit your existing NOI and resubmit changes to avoid duplicate records.

Instructions for the Preparation of Proposals

An original signed proposal, plus twenty (20) complete copies of the proposal, should be mailed to the address indicated and in the manner described of this document.

All proposals submitted to the Bioastronautics' Biomedical Research and Countermeasures Program must include the completed cover page form as described in this Appendix. The name of the Principal Investigator should appear in the upper right hand corner of each page of the proposal, except on the cover page form where special places are provided for this information. Note that the proposal must specify the period of performance for the work described; periods of performance may be for any duration up to three (3) years but should be suitable for the project proposed.

The proposal must include the following material, in this order:

(1) Proposal Cover Page: Solicited Proposal Application, including certification of compliance with U.S. code (if applicable). One signed original required.

Please see "How to Submit Proposal Cover Page Information" below for instructions on how to complete the proposal cover page information.

(2) Transmittal Letter or Prefatory Material, if any (see Appendix E for details)

(3) Proposal Title Page, with Notice on Restriction on Use and Disclosure of Proposal Information, if any (see Appendix E for details)

(4) Project Description. The length of the Project Description section of the proposal cannot exceed 20 pages using regular (12 point) type. Referenced figures must be included in the 20 pages of the Project Description. The Bibliography section is not considered part of the 20-page project description. Proposals that exceed the 20-page limit for the project description (22-page limit for revised proposals; see below) will not be reviewed. The proposal should contain sufficient detail to enable reviewers to make informed judgments about the overall merit of the proposed research and about the probability that the investigators will be able to accomplish their stated objectives with current resources and the resources requested. In addition, the proposal should clearly indicate the relationship between the proposed work and the research emphases defined in this Announcement. Reviewers are not required to consider information presented as appendices or to view and/or consider Web links in their evaluation of the proposal.

New applications, where the investigator has received NASA funding in related fields from 1999 through 2001, must present results and evidence of progress of the associated NASA-supported research as part of the project description.

Revised applications (revisions of 1999, 2000, or 2001 submissions) must be so designated on the proposal cover page and explained in the project description. This explanation should be presented in a separate section of **no more than two pages** at the beginning of the project description, and is in addition to the 20 pages allowed for the project description. Related changes to the research plan should be highlighted in the body of the project description. Changes within the proposal may be highlighted by appropriate bracketing, indenting, or changing of typography. Clearly present any work done since the prior version was submitted. **Revised applications that do not address the criticisms in the previous review will be considered nonresponsive and will be returned without review.**

(5) Management Approach

Each proposal must specify a single Principal Investigator who is responsible for carrying out the proposed project and coordinating the work of other personnel involved in the project. In proposals that designate several senior professionals as key participants in the research project, the management approach section should define the roles and responsibilities of each participant and note the proportion of each individual's time to be devoted to the proposed research activity. The proposal must clearly and unambiguously state whether these key personnel have reviewed the proposal and endorsed their participation.

(6) Personnel/Biographical Sketches

The biographical sketch for each investigator should not exceed two pages. If the list of qualifications and publications exceeds two pages, select the most pertinent information (see Appendix E for details).

(7) Other Support (see Appendix E for details)

(8) Facilities and Equipment (see Appendix E for details)

(9) Special Matters (specific information on animal or human subjects protocol approval required, if applicable)

The Special Matters section must contain a statement from the investigator's institution that states that the proposed work will meet all Federal and local human subject requirements and animal care and use requirements, if applicable. Note that no animal subjects may be utilized unless specific information justifying and describing their use is included in the proposal. Policies regarding the protection of human research subjects in NASA-sponsored research are detailed in NASA Management Instruction (NMI) 7100.8B (Protection of Human Research Subjects), and animal care and use requirements are detailed in the NASA Code of Federal Regulations (CFR) 1232 (Care and Use of Animals in the Conduct of NASA Activities), both of which are available from the Office of Biological and Physical Research, Code UB, NASA Headquarters, Washington, DC, 20546. Assurance of compliance with human subject or animal care provisions is required on Form A, to be submitted with each proposal. In addition, a letter signed by the chairperson of the Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC), or both, as appropriate, regarding approval of the experimental protocol, should be included with each copy of the proposal. If IRB or IACUC review is unavoidably delayed beyond the submission of the application, enter "Pending" on Line 9b or 10a of Form A, and be advised that the certification must be received within 60 days after the due date for which the application is submitted. If certification is not received within 60 days after the application due date, the application will be considered incomplete and will not be reviewed. NASA shall require current IRB or IACUC certification prior to each year's award. All U.S., non-NASA proposals providing IACUC approval must also contain the institution's Public Health Assurance number.

(10) Detailed Budget

NASA is expected to be operating on the basis of full cost accounting as soon as possible, including all Civil Service salaries with overhead. In the interim period, proposals should use the accounting method authorized at their institutions at the time proposals are due and for the entire proposed period of performance. Funds to support the Resident Research Assistant (RRA) Postdoctoral Program costs (e.g., stipend, travel, computer time, supplies, etc.) are to be budgeted within the NASA intramural Principal Investigator budget.

The budget must include travel funds for the Principal Investigator to attend a biannual BR&C Principal Investigator meeting. If other travel is planned, the proposal budget should include appropriate travel funds for visits to NASA field centers (as appropriate) and presentation of findings at professional society meetings.

(11) Supporting Budgetary Information

In this solicitation, the terms "cost" and "budget" are used synonymously. Sufficient proposal cost detail and supporting information are required; funding amounts proposed with no explanation (e.g., Equipment: $1,000, or Labor: $6,000) may cause delays in evaluation and award. Generally, costs will be evaluated for realism, reasonableness, allowability, and allocation. The budgetary forms define the desired detail, but each category should be explained in this section. Offerors should exercise prudent judgment in determining what to include in the proposal, as the amount of detail necessarily varies with the complexity of the proposal.

The following examples indicate the suggested method of preparing a cost breakdown:

Direct Labor
Labor costs should be segregated by titles or disciplines with estimated hours and rates for each. Estimates should include a basis of estimate, such as currently paid rates or outstanding offers to prospective employees. This format allows the Government to assess cost reasonableness by various means including comparison to similar skills at other organizations.

Other Direct Costs
Please detail, explain, and substantiate other significant cost categories as described below:
Subcontracts: Describe the work to be contracted, estimated amount, recipient (if known), and the reason for subcontracting.
Consultants: Identify consultants to be used, why they are necessary, the time they will spend on the project, and the rates of pay (not to exceed the equivalent of the daily rate for Level IV of the Executive Schedule, exclusive of expenses and indirect costs).
Equipment: List separately. Explain the need for items costing more than $5,000. Describe basis for estimated cost. General purpose equipment is not allowable as a direct cost unless specifically approved by the NASA Grant Officer. Any equipment purchase requested as a direct charge must include the equipment description, how it will be used in the conduct of the basic research proposed, and why it cannot be purchased with indirect funds.
Supplies: Provide general categories of needed supplies, the method of acquisition, and estimated cost.
Travel: Describe the purpose of the proposed travel in relation to the grant and provide the basis of estimate, including information on destination and number of travelers where known.
Other: Enter the total of direct costs not covered previously. Attach an itemized list explaining the need for each item and the basis for the estimate.

Indirect Costs
Indirect costs should be explained to an extent that will allow the Government to understand the basis for the estimate. Examples of prior year historical rates, current variances from those rates, or an explanation of other basis of estimates should be included. Where costs are based on allocation percentages or dollar rates, an explanation of rate and application base relationships should be given. For example, the base to which the General and Administrative (G&A) rate is applied could be explained as application base equals total costs before G&A less subcontracts.

All awards made as a result of this NRA will be funded as grants. However, while proposals submitted by "for profit" organizations are allowed, they cannot include a "fee."

(12) Appendices, if any (reviewers are not required to consider information presented in appendices)

How to Submit Proposal Cover Page Information

All investigators planning to submit a proposal in response to this solicitation must electronically submit proposal cover page information online and provide a hard copy of the cover page attached to each proposal copy by January 31, 2002. The proposal cover page can be submitted and printed via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

- Login to SYS-EYFUS.
- To submit a New Proposal Cover Page, click the "New Proposal Cover Page" option from the SYS-EYFUS Options screen, and the New Proposals Cover Page screen will appear.
- If you previously submitted an NOI in response to this solicitation, choose to carry over the existing NOI. This option will populate the cover page fields with the NOI information. Edit the information as necessary, click "Continue" and proceed to the instructions for the Proposal Cover Sheet Submission Form below.
- If you did not previously submit an NOI, click on New Proposal Cover Page option, and the Division Specific Opportunities screen will appear.
- In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Proposal Cover Page Submission Form. Fill in all the fields. All fields are required.
  For the proposal type field on this form, new/no prior support means that the investigator has not received NASA funding from 1999 through 2001, new/prior support means that the investigator has received NASA funding between 1999 and 2001, and revised means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002. Click on "Continue."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the proposal. After you are done, click on "Continue." **IMPORTANT**: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Member Page, the Proposal Options Page appears.
- Please fill out the budget form by clicking on the "Budget" button, filling in project costs, and clicking "Continue." This will bring you to the Proposal Budget Review Page. Click "Continue" if the information is correct.
- After verifying your budget information, you will be returned to the Proposal Options Page. Click the "Show/Print" button.
- At the page entitled Proposal Information Item List click "Continue" to preview your Proposal Cover Page. Print the cover page from your Internet browser once you have reviewed the information. The cover page must be signed by both the Principal Investigator

and the authorizing official and attached to the font of your proposal before submission of hard copies to NASA.

- You may edit and resubmit your proposal cover page at any time before the submission deadline of January 31, 2002. Please note that once you submit a proposal cover page, it cannot be deleted. For title, team member, budget or any other changes, please edit your existing proposal cover page and resubmit changes to avoid duplicate records.
- One (1) signed original and twenty (20) copies of the proposal must be received by 5:00 PM on January 31, 2002, at the following address:

  NASA Peer Review Services
  Subject: 01-OBPR-07
  500 E Street SW, Suite 200
  Washington, DC 20024

V. Review and Selection Process

Investigators should refer to Appendix A, Section IV, for a description of the Review and Selection Process.

VI. Eligibility

All categories of U.S. institutions are eligible to submit proposals in response to this NRA. Principal Investigators may collaborate with universities, Federal Government laboratories, the private sector, and state and local government laboratories. In all such arrangements, the applying entity is expected to be responsible for administering the project according to the management approach presented in the proposal.

The applying entity must have in place a documented base of ongoing high quality research in science and technology or in those areas of science and engineering clearly relevant to the specific programmatic objectives and research emphases indicated in this NRA. Present or prior support by NASA of research or training in any institution or for any investigator is not a prerequisite to submission of a proposal or a competing factor in the selection process.

All types of institutions are eligible to submit proposals in response to this NRA, but only the U.S. investigators and U.S. institutions that collaborate in a selected proposal qualify for funding of their portion of any collaborative research. Proposals without substantive collaboration from a U.S. entity will not be reviewed except in the case of CEVP proposals submitted by investigators from the International Life Sciences Working Group Space Agencies members. CEVP proposals approved for funding by the international member states will be reviewed.

VII. Foreign Proposals

Only ground-based proposals submitted in response to this NRA from U.S. entities, or from non-U.S. entities that involve substantive co-investigator collaboration from a U.S. entity, will be reviewed. U.S. co-investigators who are collaborating on such proposals with non-U.S. entities must ensure that their scientific role is clearly delineated in the proposal, that their expertise is shown to make a substantial contribution, and that their funding requirements are included in the proposal. Proposals from non-U.S. entities with significant co-investigator collaboration from a U.S. entity, must be endorsed by the respective government agency or funding/sponsoring institution in that country from which the non-U.S. participant is proposing. Such endorsement should indicate that the proposal merits careful consideration by NASA, and if the proposal is selected, sufficient funds will be made available to undertake the activity as proposed. This Letter of Endorsement from the sponsoring non-U.S. government agency or funding/sponsoring institution should be forwarded along with the proposal.

All proposals from non-U.S. entities which involve substantive co-investigator collaboration from a U.S. entity must be typewritten in English and comply with all other submission requirements stated in this NRA. These proposals will undergo the same evaluation and selection process as those originating in the U.S. All proposals must be received before the established closing date. Sponsoring foreign government agencies or funding institutions for proposals from non-U.S. entities meeting the above guidelines may, in exceptional situations, forward a proposal without endorsement to the above address if endorsement is not possible before the announced closing date. In such cases, the NASA sponsoring office should be advised when a decision on endorsement can be expected.

Successful and unsuccessful non-U.S. investigators will be contacted directly by the NASA sponsoring office. Copies of these letters will be sent to the sponsoring government agency or funding institution. Should a non-U.S. proposal with significant U.S. participation be selected, NASA's Office of External Relations will arrange with the foreign sponsoring agency or funding institution for the proposed participation on a non-exchange-of-funds basis, in which NASA and the non-U.S. sponsoring agency or funding institution will each bear the cost of discharging their respective responsibilities.

Depending on the nature and extent of the proposed cooperation, this arrangement may entail

1. a letter of notification by NASA;
2. an exchange of letters between NASA and the sponsoring foreign governmental agency; or
3. a formal Agency-to-Agency Memorandum of Understanding (MOU).

Export Control Guidelines Applicable to Foreign Proposals and Proposals Including Foreign Participation.

Proposals including foreign participation must include a section discussing compliance with U.S. export laws and regulations, e.g., 22 CFR Parts 120-130 and 15 CFR Parts 730-774, as applicable to the circumstances surrounding the particular foreign participation. The discussion must describe in detail the proposed foreign participation and is to include, but not be limited to, whether or not the foreign participation may require the prospective investigator to obtain the prior approval of the Department of State or the Department of Commerce via a technical assistance agreement or an export license, or whether a license exemption/exception may apply. If prior approvals via licenses are necessary, discuss whether the license has been applied for or if not, the projected timing of the application and any implications for the schedule. Information regarding U.S. export regulations is available at http://www.pmdtc.org and http://www.bxa.doc.gov. Investigators are advised that under U.S. law and regulations, spacecraft and their specifically designed, modified, or configured systems, components, and parts are generally considered "Defense Articles" on the United States Munitions List and subject to the provisions of the International Traffic in Arms Regulations (ITAR), 22 CFR Parts 120-130.

APPENDIX C
NRA 01-OBPR-07

Multiple Opportunities for Ground-Based Research in Space Life Sciences Technical Description

Opportunity to Participate on a National Space Biomedical Research Institute Team

NOTE: Only investigators who are applying to join one of the pre-existing NSBRI research teams should use this appendix for the preparation of their application.

I. Introduction

The National Space Biomedical Research Institute (NSBRI), a private, non-profit organization, invites research proposal applications to join an existing ground-based research team in one of the twelve active research areas:

1. *Bone Loss* – Addressing bone loss and weakening during space flight with the inherent fracture risks
2. *Cardiovascular Alterations* – Addressing the inflight occurrence of cardiac dysrhythmia and postflight impairment of the cardiovascular response to orthostatic and exercise stress
3. *Human Performance Factors, Sleep and Chronobiology* – Investigating maintenance of high cognitive performance and vigilance despite environmental stress and sleep disturbances
4. *Immunology, Infection and Hematology* – Addressing immune system impairment and altered susceptibility to infection, increased allergic response, decreased blood volume and postflight anemia
5. *Integrated Human Function* – Developing an overall understanding of the human body's response to space flight
6. *Muscle Alterations and Atrophy* – Focusing on the loss of skeletal muscle mass, strength, and endurance that accompanies space flight
7. *Neurobehavioral and Psychosocial Factors* – Investigating methods and tools that can be utilized to enable crews to cope with stress, isolation and compatibility
8. *Neurovestibular Adaptation* – Addressing the problems of space motion sickness and disorientation during flight and the postflight problems of balance and gaze disorders
9. *Nutrition, Physical Fitness and Rehabilitation* – Developing methods to maintain health and fitness before, during, and after space flights
10. *Radiation Effects* – Addressing the problem of increased cancer risk caused by the natural space radiation environment;
11. *Smart Medical Systems* – Developing new methods of medical monitoring, diagnosis, and therapy for use on space missions
12. *Technology Development* – Developing instrumentation and other technological products that will enhance the research of the other teams and benefit people on Earth.

Each of the twelve research teams consists of a set of individual, coordinated, and complementary projects focused on a common theme. Team management and coordination is the responsibility of a program director called a **Team Leader**. The current Team Leaders for these twelve teams are listed in Section III of this Appendix.

Applications will be accepted from all categories of organizations, public and private, and for-profit and non-profit, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. The mechanism of support shall be an NSBRI subagreement with funds provided by the National Aeronautics and Space Administration (NASA) through a cooperative agreement (Cooperative Agreement NCC 9-58 with NASA's Lyndon B. Johnson Space Center). Annual renewal awards are subject to an independent, external review. Potential foreign applicants should note that, normally, the country of origin, not the NSBRI, must fund applications from non-U.S. organizations. Potential foreign applicants should coordinate their application with both the NSBRI and the appropriate funding agency in their own country.

II. Background

The NSBRI is responsible for the development of countermeasures against the deleterious effects of long-duration space flight and applied space biomedical research directed toward this specific goal. Its mission is to lead a world-class, national effort in integrated, critical path space biomedical research that supports NASA's Human Exploration and Development of Space (HEDS) Strategic Plan by focusing on the enabling of long-term human presence in, development of, and exploration of space. This is accomplished by

- designing, testing and validating effective countermeasures to address the biological and environmental impediments to long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that ultimately determine these impediments, where such activity fosters the development of novel countermeasures;
- establishing biomedical support technologies to maximize human performance in space, reduce biomedical hazards to an acceptable level and deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the general benefit of mankind, including the treatment of patients suffering from gravity- and radiation-related conditions on Earth; and
- ensuring open involvement of the scientific community, industry and the public at large in the Institute's activities and fostering a robust collaboration with NASA, particularly through NASA's Lyndon B. Johnson Space Center.

Institute Infrastructure

The NSBRI is governed by a consortium of twelve institutions -- Baylor College of Medicine, Brookhaven National Laboratory, Harvard Medical School, The Johns Hopkins University School of Medicine and the Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School of Medicine, Mount Sinai School of Medicine, Rice University, Texas A&M University, the University of Arkansas for Medical Sciences, the University of Pennsylvania Health System, and the University of Washington. The Institute's headquarters are located in Houston at Baylor College of Medicine.

Consortium membership is not a requirement for research program participation. At present, non-consortium institutions and laboratories lead nearly one-half of the projects funded by the Institute. The management plan for the Institute is based on the model used by the National Institutes of Health. An independent Board of Scientific Counselors is responsible for assuring excellence in the Institute's intramural program through independent external peer review, and an External Advisory Council is responsible for advising Institute management concerning programmatic effectiveness. The NSBRI also has a User Panel of former and current astronauts and flight surgeons responsible for assuring that the research program is focused squarely on astronaut health and safety. An Industry Forum of representatives of space and biomedically-related industries assists the Institute in developing industry participation in NSBRI and in timely technology transfer. In addition to its research program, the NSBRI has developed a vital education and outreach program that takes advantage of the Institute's core research activities.

III. Specific Research Focus and Opportunity

Proposals submitted to the NSBRI in response to this NRA MUST address one of the twelve research areas discussed below. Proposals that impact more than one area should be directed to only one primary research area, although a secondary research area may be designated if the proposal has significant overlap with that area. The following subsections are meant to guide the investigator to the key problems and issues that are central to each research area. Innovative approaches to solve these problems are encouraged. Note that proposals will be evaluated for their responsiveness to the critical needs expressed in the subsections. Generally, proposals that are not responsive to these needs will not be funded.

General Information

To carry out the NSBRI's primary mission, that of designing, testing and validating effective countermeasures to address the biological and environmental impediments to human space flight (both within and beyond low-Earth orbit), the NSBRI focuses its research program on the primary needs of low-Earth orbit long-duration space flight and on the major challenges of exploration-class missions. These missions pose the greatest challenge to future space travelers, and meeting their challenge with appropriate countermeasures lies at the core of the NSBRI's responsibility. For planning purposes, a typical Mars-type exploration mission might involve trips of six months to one year each way, with a stay on Mars of one to two years. A typical long-duration space flight within low-Earth orbit might involve missions of six months or longer. In either case, effective adaptation, supported by appropriate countermeasures, is critical to a successful mission and to the long-term health maintenance of the astronauts. Potential physiological changes that may occur during prolonged space flight include, among others, significant loss of muscle and bone mass, decreased dietary intake of nutrients, profound metabolic and endocrine alterations, important changes in cardiovascular function and deleterious effects on sensorimotor performance. By addressing long-term missions of this type, increased safety, health and performance will be realized for shorter-duration space flights.

Countermeasure Readiness Levels. Since the NSBRI's primary mission concerns countermeasures, it is important to understand some of the steps involved in effective countermeasure development. These steps are called countermeasure readiness levels and are measured on a scale of 1 to 9, with the higher numbers referring to higher levels of readiness. (Investigators should read Appendix A, Section III, for a full discussion of CRLs.) As Figures 1 and 2 in Appendix A show, countermeasure development begins with basic research (levels 1 to

3), moves through countermeasure feasibility and development studies (levels 3 to 7) and ends with countermeasure ground evaluation, flight validation and operational implementation (levels 7 to 9). It is expected that the NSBRI's research program will contain studies that, for the most part, range from CRL 3 through 7.

1. NSBRI Bone Loss Team

Team Leader: Jay R. Shapiro, M.D.
Professor, Department of Medicine
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road, Rm. A3068
Bethesda, MD 20814-4799
Telephone: 301-295-3600
Fax: 301-295-3557
Email: jshapiro@usuhs.mil

Weightlessness during space flight initiates a series of physiologic responses that lead to dramatic alterations in the musculoskeletal system. These include muscle atrophy that decreases muscle strain on bone, alterations in blood flow and fluid balance that alter fluid shear at the tissue level, and alterations in hormonal mechanisms controlling bone remodeling. It is well recognized that net bone loss is almost universally found in animals and humans after exposure to microgravity. Bone loss is associated with an increased risk of fracture. Less is known about the effects of weightlessness on soft connective tissues, ligaments and tendons, cartilage and the integrity of intervertebral discs. Delayed recovery of bone strength following return to Earth's gravity may perpetuate increased fracture risk and lead to skeletal fragility.

In space flight-tested rodents, bone loss occurs primarily as a consequence of depressed bone formation. In humans, increased bone resorption is primarily responsible for net bone loss. Although the magnitude of bone loss varies widely between individuals, observations of changes in bone mineral density in Mir astronauts/cosmonauts indicate that approximately 6 to 12% of bone mass may be lost during a six-month flight. Although it is recognized that muscle loss precedes loss of bone, the sequential relationships between muscle and bone loss remain poorly defined.

The research agenda for the bone loss team is set by the Critical Path Roadmap Bone Loss risks (see Appendix A, Section II) associated with long-duration space flight: acceleration of age-related osteoporosis; fracture and impaired fracture healing; injury to soft connective tissue, joint cartilage and intervertebral disc rupture with or without neurological complications; and renal stone formation. An additional important topic involves the recognized prolonged delay in the return of bone mineral density to normal following space flight, with the attendant increase in fracture risk during that period.

The current NSBRI research program includes nine projects of basic and clinical studies that share the objective of leading to countermeasure development. Details concerning the current intramural projects are provided on the Web site http://www.nsbri.org/Research/Bone.html. Two projects focus on basic mechanisms related to nutrient intake and bone mass, specifically on glucose-dependent insulinotropic peptide (GIP) and on leptin. A third project focuses on changes in estrogen and vitamin D receptor function in simulated microgravity. Other projects are concerned with fracture healing in simulated weightlessness and the effect of ultrasound on the rate of healing, muscle-bone relationships during recovery from skeletal unloading, the efficacy of a biomechanical countermeasure to inhibit bone loss, the effects of bisphosphonate treatment on osteocyte integrity during simulated weightlessness, the study of a spinal-cord injured patient model of microgravity, and the prevention of microgravity-induced renal stone risk.

Focused Research Questions

The objective of this research solicitation is to obtain investigations that are complementary to the current research program. Thus, proposals are being sought that address three important issues: fracture and impaired fracture healing, bone mass and strength, and injury to soft connective tissue, joint cartilage, and intervertebral disc rupture with or without neurological complications. Competitive proposals should seek countermeasures that will promote normal fracture healing, restore bone lost during flight with the appropriate quantity and quality of bone, or protect soft connective tissues from injury and restore tissue integrity following prolonged space flight.

Fracture Risk/Fracture Healing. At this time, no firm data exist about the occurrence of major extremity/vertebral fractures or microfractures during, or following, extended space flight. Information is available about rates of bone loss experienced by Mir cosmonauts and astronauts. The relationship of this data to estimated fracture risk during extended space flight has not been determined. How can available data on bone loss during extended space flight be used to develop a practical estimate of fracture risk? How does weightlessness impair normal fracture healing? Are there agents that will impair or promote fracture healing during and after exposure to microgravity (e.g., cytokines/hormones acting at the tissue level, pharmacologic agents used during flight that could impair fracture healing, pharmacological agents that could promote healing, biomechanical agents that could promote fracture healing)?

Bone Mass vs. Strength and Muscle/Bone Relationship. Persistent deficits in the mechanical strength of bone may persist long after return to Earth's gravity and may lead to skeletal fragility in old age. What is the relationship between bone mass and bone strength (quantity vs. quality of bone) following real or simulated space flight? What analytical methods are available to define muscle/bone relationships? Can one develop a human model to simulate the muscle/bone relationships that exist following space flight?

Soft Connective Tissue Injury. What is the nature and incidence of soft connective tissue injury and pain during and after prolonged weightlessness or bed rest? What is the injury to cartilage, intervertebral discs, and ligaments and tendons? Are there site-specific patterns of injury to soft connective tissues? What are the gene expression patterns related to soft connective tissue injury? What is the histomorphology of the tissue response? What are the modulators of soft connective tissue injury (cytokines, growth factors and hormones)? What are the reparative processes in cartilage, intervertebral discs and tendons following injury? What are the most effective countermeasures to prevent this type of injury during or after space flight?

2. NSBRI Cardiovascular Alterations Team

Team Leader: Richard J. Cohen, M.D., Ph.D.
Whitaker Professor of Biomedical Engineering
Harvard-MIT Division of Health Sciences and Technology
Massachusetts Institute of Technology
45 Carleton Street, Rm. E25-335A
Cambridge, MA 02139-4301
Telephone: 617-253-7430
Fax: 617-253-3019
Email: rjcohen@mit.edu

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to microgravity and other factors. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. The extent of cardiovascular adaptation appears to increase with duration of space flight. The extent and implications of these adaptations for long-duration (months to years) space flight remain largely unknown. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume and a modest decrease in arterial pressure. During space flight, the cardiovascular system is not subjected to the stresses associated with changes in posture in a gravitational field. In addition to microgravity, space flight is associated with other physiologic stressors such as sleep disruption, confinement and other environmental alterations that may also adversely affect cardiovascular structure and function.

Long-duration space flight leads to the development of orthostatic intolerance upon reentry, may cause a reduction in cardiac mass, and might alter susceptibility to heart rhythm disturbances. In addition, long-duration space flight affects cardiovascular response to exercise and may in principle lead to the manifestation of previously asymptomatic cardiovascular diseases.

The objectives of the NSBRI Cardiovascular Alterations Team are to

- characterize and quantify the adverse effects of space flight on cardiovascular structure and function;
- determine the mechanisms of these adverse effects;
- develop effective countermeasures to these adverse effects; and
- develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on Earth.

These research objectives are driven by the Critical Path Roadmap Cardiovascular risks (see Appendix A, Section II) associated with long-duration space flight: impaired cardiovascular response to orthostatic stress, occurrence of serious cardiac dysrhythmias, diminished cardiac function, manifestation of previously asymptomatic cardiovascular disease, and impaired cardiovascular response to exercise stress.

The current research program involves nine ground-based projects and two potential space-flight studies. Details concerning the current intramural projects for this team are provided on the Web site http://www.nsbri.org/Research/Cardio.html. Many of the projects impinge on more than one critical risk. The strategy of the cardiovascular team is to have a dynamic interplay between projects focused on studies in animals, humans and computer simulations. Part of the strategy is to develop new technologies to be used in the studies which also have applications for astronaut monitoring and therapy and spin-off applications on Earth. The primary focus of the team has been on the problem of postflight orthostatic hypotension. In addition, several of the projects deal with the issue of cardiac arrhythmias in space and with the risk of diminished cardiac function.

Focused Research Questions

The objective of this research solicitation is to add investigations that are complementary to the current research program and fill in the gaps in that program. Thus, proposals are being sought that specifically address the following risks:

Diminished Cardiac Function. Proposals are solicited that address the relationship between cardiac atrophy and central or peripheral cardiovascular function (e.g., changes in cardiac systolic and diastolic function that could lead to orthostatic hypotension). These studies may include animal or human studies. Proposals that specifically identify and test countermeasures are preferred.

Manifestation of Previously Asymptomatic Cardiovascular Disease. Proposals that address this critical risk may focus on methods to identify individuals for the presence of *silent* cardiovascular disease that may manifest itself during space flight. Proposals may also address whether and by what specific mechanisms space flight may accelerate such cardiovascular disease processes.

3. NSBRI Human Performance Factors, Sleep, and Chronobiology Team

Team Leader: Charles A. Czeisler, M.D., Ph.D.
Professor of Medicine, Harvard Medical School
Chief, Division of Sleep Medicine, Brigham and Women's Hospital
221 Longwood Avenue, Room 438A
Boston, MA 02115
Telephone: 617-732-4013
Fax: 617-732-4015
Email: caczeisler@rics.bwh.harvard.edu

The success of human space missions depends on each astronaut remaining alert and vigilant while operating sophisticated equipment and following complex procedures. During long-duration space flight, the space environment affects a number of physiological systems critically involved in human performance, and it is vital to mission success to understand the biological limits of human performance under space flight conditions. This team is focused on these issues and, in particular, is concerned with the following aspects of the space environment: weightlessness (microgravity), altered light-dark cycles, altered or reduced sleep/rest opportunities, high levels of automation, and habitation in a remote, inaccessible location. The primary thrust of the team's research program involves altered circadian organization, sleep disruption and cumulative sleep loss, and the associated neurobehavioral decrements occurring during long-duration space flight.

The goals of the Human Performance Factors, Sleep, and Chronobiology Team are to:

- characterize and quantify the adverse effects of long-duration space flight on sleep and circadian rhythmicity;
- characterize and quantify the effect of sleep loss and/or circadian dysfunction on physical and neurobehavioral performance;
- understand the basic mechanisms underlying the deterioration of sleep, circadian organization and human neurobehavioral function during space flight;
- develop high-fidelity mathematical models of performance based on circadian organization and sleep-wake history;
- develop effective countermeasures to optimize sleep and facilitate circadian adaptation in space and thereby maintain optimal neurobehavioral performance; and
- develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight, with possible spin-off applications on Earth.

These research objectives are driven by the Critical Path Roadmap risk (see Appendix A, Section II) related to human performance failure because of sleep and circadian rhythm problems.

The current research program involves nine ground-based research projects. Details concerning this program are provided on the Web site http://www.nsbri.org/Research/Sleep.html. Although the focus of the team is on a single risk, many of the projects impinge on more than one critical risk. The team strategy is to develop a synergistic interaction between research projects at the molecular, cellular, organismic and human levels; and to integrate predictive biomathematical modeling of the sleep and circadian systems into the fabric of the program.

Focused Research Questions

The objective of this research solicitation is to obtain investigations that are complementary to the current research program and fill in gaps in that program. Thus, proposals are being sought that specifically address the following research topics:

Physical Effects. Proposals are sought to determine how the factors associated with space flight, including stress, diminished sleep opportunities, and circadian disruption, affect sleep- and/or circadian-mediated neuroendocrine, metabolic, neurologic or autonomic functions, particularly how those factors increase the biomedical risks of space flight during extended-duration missions. How do individual characteristics alter the responses to these factors?

Novel Countermeasure Development. Proposals are sought to determine how recent advances in the neurobiology of sleep and/or circadian rhythms (e.g., orexin/hypocretin system, circadian photoreception, output pathways for regulation of sleep or circadian rhythms) can be used to develop countermeasures to facilitate adaptation to the space environment and thereby maintain optimal neurobehavioral performance during an exploration-class space mission.

4. NSBRI Immunology, Infection, and Hematology Team

Team Leader: William T. Shearer, M.D., Ph.D.
Professor of Pediatrics and Microbiology & Immunology
Baylor College of Medicine
6621 Fannin, MC 1-3291
Houston, TX 77030-2399
Telephone: 832-824-1274
Fax: 832-825-7131
Email: wshearer@bcm.tmc.edu

For 40 years, biomedical researchers have been attempting to gather definitive information on the possible development of a secondary immunodeficiency due to conditions of space travel. Although definitive information is yet to be obtained, past and present research demonstrates that the conditions that humans face in long-term space flight have an impact upon the immune system. For example, radiation of the type found during a space flight is known to induce changes in host resistance so that, in time and without proper shielding and other precautions, infections and malignant cells gain the advantage and conquer the host. Other important conditions that pose risks for astronauts are weightlessness, confinement in a restricted space, stress, isolation, microbial contamination, and sleep deprivation. Clinical observations with patients undergoing immune suppression and model studies with humans and animals document the importance of a sufficient level of immune function to protect against the consequences of early cell death, reactivation of latent viral infections, and development of malignancies. The science of space immunology, therefore, is founded upon well-received principles and assumptions that prescribe a need for well-planned and executed experiments capable of predicting the risks to the human immune system in long-term space travel and for an active countermeasure development program designed to reduce the risks to the immune system to an acceptable level.

Because stress is almost a constant condition of space flight, investigators have sought to establish a model where the same type of stress could be experienced by a large number of subjects at the same time. Models studied to date have included medical students taking examinations, subjects during heavy exercise, humans exposed to high altitudes, isolation, and sleep deprivation, and the head-down bed rest model that simulates several conditions of space travel. Some of these model studies suggest that serious consequences could result from possible immune system aberration during long-term space travel.

Space-based countermeasure development in this area is still at the research level. Because of the four-decade-long experience with humans who have congenital immunodeficiencies and the nearly 20-year history of coping with the best understood secondary immunodeficiency, AIDS, considerable progress has been made in restoring immunity and preventing it from being damaged. Restoration of humoral immunity can be accomplished with immunoglobulin treatments, and bone marrow stem cells can replace defective or damaged stem cells and their immune system descendants. Vaccines have for decades prevented human infection, and simple measures such as adequate nutrition and proper sleep have enabled humans to avoid serious complications of intercurrent infections. Application of these measures to restore immunity or even prevent immune damage in space is a high priority of the Institute's research program.

The Critical Path Roadmap risks (see Appendix A, Section II) in this area are increased risk of infection due to impaired immune response, altered environmental exposure, and persistent viruses or the reactivation of viruses; increased risk of carcinogenesis due to increased radiation-induced or cell-mediated oncogene expression, decreased immune system surveillance, and reactivated viruses; altered hemodynamics and cardiovascular dynamics caused by altered blood components; altered wound healing caused by altered immune cell function or altered local tissue transport properties; altered host-microbial interactions resulting from changes in microflora, alterations in host susceptibility, or genetic changes or mutations of microorganisms; and increased risk of allergies and hypersensitivity reactions.

The current research program in this area consists of six projects described on the Web site http://www.nsbri.org/Research/Immune.html. These projects use various model systems, including irradiated and hind-limb suspended animals, to examine latent virus activation, stem-cell alteration, mucosal immune and HPA-axis responses and apoptosis of T cells, etc., during space flight. One project focuses on microbe contamination of a spacecraft. There is a high degree of overlap among these projects. For example, altered microbes and increased susceptibility to infection caused by space conditions are among the interests of all six projects, and neuroendocrine abnormalities are a subject of five of the projects.

Focused Research Questions

Proposals are being sought in three areas: the types of altered immune function that occur in space, the possible increased risk of allergies and hypersensitivity reactions that may occur in space; and the development of specific, targeted countermeasures that would reduce the risks associated with this research area.

Altered Immune Function. How do the various factors associated with space flight (e.g., radiation, physical and psychological stress, confinement, weightlessness, etc.) affect immune function, cancer risk, susceptibility to microbial infections, latent virus reactivation, stem cell/progenitor cell biology and function, mucosal immunity, etc.? Do alterations in the body's systems in these areas during space flight pose significant risks to crewmembers? Are there assays that reliably predict changes in these systems, and can these assays be adapted to space travel?

Allergies and Hypersensitivity Reactions. Do unique environmental factors inside the spacecraft promote the transmission and activity of microbial pathogens or cause increased risk of infection, autoimmunity, allergy or hypersensitivity reactions independent of altered immune function? How would altered immunity in space, if it occurs, affect the development of allergies, hypersensitivities and autoimmune diseases?

Countermeasure Development. Are there countermeasures that would remove the immune-specific risks associated with space flight (see the Critical Path Roadmap risks listed above) or reduce these risks to acceptable levels?

5. NSBRI Integrated Human Function Team

Team Leader: Martin J. Kushmerick, M.D., Ph.D.
Professor of Radiology, Physiology & Biophysics and Bioengineering
Department of Radiology, AA-010K HSC
University of Washington
1959 N.E. Pacific Street, Box 357115
Seattle, WA 98195-0001
Telephone: 206-543-3762
Fax: 206-221-6515
Email: kushmeri@u.washington.edu

This research area seeks to integrate knowledge from the other discipline research areas, enabling an understanding of overall human function and leading to a reliable evaluation and prediction of an astronaut's safety and functional capacity during an extended space mission. Thus, the goals of this program are to develop the general methodology necessary to integrate the variety of physiological research findings emanating from different laboratories, thereby advancing the description and understanding of human systems and their parts; to improve the ability to predict human responses to functional stresses, especially those encountered in long-duration space flight; and to assess the potential efficacy of countermeasures in reducing the risks involved in space flight. The loss of homeostasis and/or appropriate dynamic responses under stress likely involves the interaction of varied human functions and mechanisms at many levels (e.g., molecules to organ systems). Because of genetic and experiential differences among individuals, the methodology developed to enable integration needs to address generic human responses as well as individual functional characteristics. Successful projects should develop algorithms and concepts that specify how integration of the sub-components in a hierarchy of complex component interactions could be accomplished. The term "*Digital Human*" captures this vision and goal in a simple yet profound way.

There are six projects in the current program. Details concerning these projects are available on the Web site http://www.nsbri.org/Research/Integrated.html. All focus on metabolism and on cardiac and skeletal muscle at the level of molecular, cellular, and organ properties. Each demonstrates a desirable balance of experimental work and synergistic modeling in the areas of cell electrical properties, control of intracellular calcium dynamics, cross-bridge properties in different cell types; cellular energy metabolism, whole-body substrate distribution and metabolism that may be altered during space travel, and convergence of cellular to organ mechanics.

Focused Research Questions

Proposals are sought that will create analytical and predictive models and enable simulations that answer questions involving multiple human subsystems. Such models will integrate human function across multiple scales of organization and widely varying time scales, using both vertical (hierarchical) and horizontal integration involving such diverse organizational scales as molecule, cell, tissue, organ, and organism. It is anticipated that these projects will involve interplay between fundamental mechanistic and phenomenological analyses. Projects must be stronglyrelated to experimental data but may or may not involve new experimental work. In order to be considered for funding, proposals must address one of the following areas.

Neuroendocrine Model Development. This project should develop an integrative approach to modeling human neuroendocrine function, including important elements of metabolism and nutrition. The model should take into account global and intermediary metabolism, cell cycle control, pituitary-hypothalamus and peripheral interactions, common endocrine interactions with a range of body functions, and physiological and psychological stresses.

Musculoskeletal Model Development. This project should focus on developing an integrative approach to modeling the interaction between bone and muscle in humans, with a view to simulating the atrophy and bone loss that takes place during musculoskeletal unloading and the restoration that takes place during reloading. The model should represent the role of limb mechanical effects (loads and stresses) integrated with bone, muscle and tendon properties, as well as calcium metabolism, and effects of parathyroid hormone and vitamin D.

6. NSBRI Muscle Alterations and Atrophy Team

Team Leader: Kenneth M. Baldwin, Ph.D.
Professor, Department of Physiology & Biophysics
University of California, Irvine
Medical Sciences I, Rm. D340
Irvine, CA 92697-4560
Telephone: 949-824-7192
Fax: 949-824-8540
Email: kmbaldwi@uci.edu

Human and animal research clearly indicates that the skeletal muscle system is negatively impacted by prolonged exposure to the unloading involved in space flight and bed rest in humans and tail-suspension in animals. The following critical deficits have been identified as important to counteract during extended space flight: reduced muscle mass (atrophy), which is thought to be due to an imbalance in protein synthetic to protein degradation activity within targeted fibers (the mechanism for such a response is largely unknown); reduced muscle strength leading to a decrease in physical-activity performance and high power-output capacity (deficits in strength often exceed the loss in muscle mass, suggesting that complex mechanisms are responsible for the reduced performance); a slow-to-fast shift in the contractile protein phenotype (e.g., shifts to faster myosin heavy chain [MHC] and calcium-cycling proteins) inducing muscle fibers to become less economical in sustaining force output; a decreased resistance to fatigue, which could have functional implications in the performance of extravehicular activity in space and in performing emergency egress activity upon spacecraft landing; a proneness to muscle injury, which is due to the atrophy and loss of strength with increased susceptibility to accidents that could cause damage to other systems (e.g., bone fractures); changes in muscle properties that are closely linked to changes in the ability of the nervous system to accurately control movements, thereby affecting safety when performing any type of work.

The Critical Path Roadmap risks (see Appendix A, Section II) in this area are closely associated with the loss of skeletal muscle mass, strength and endurance; inability to adequately perform tasks due to motor performance, muscle endurance, and disruption in structural and functional properties of soft and hard connective tissues of the axial skeleton; inability to sustain muscle performance levels to meet the demands of performing activities of varying intensities; propensity to develop muscle injury, connective tissue dysfunction and bone fractures due to deficiencies in motor skill, muscle strength and muscle fatigue; and the impact of deficits in skeletal muscle structure and function on other systems.

The current NSBRI research program includes eight projects closely aligned with addressing issues relevant to the critical path. Details concerning the research program are provided on the Web site http://www.nsbri.org/Research/Muscle.html. Each project addresses key fundamental issues and questions directly related to human health, performance and safety during long-duration space flight. However, the program lacks a robust research effort using human subjects, does not address issues related to the effect of altered loading on muscle and sensory-motor function, and does not adequately explore non-exercise (e.g., artificial gravity) countermeasures.

Focused Research Questions

Loading/Unloading Human Skeletal Muscle. How do altered loading states and paradigms of resistance training influence molecular and cellular processes that impact protein turnover in human muscle fibers? Are there synergistic effects when various activity paradigms are carried out simultaneously with other countermeasures, such as nutritional modification and pharmacological intervention?

Muscle Loading and Sensory-Motor Function. How do altered loading states affect sensory motor processes that affect posture, balance and the performance of locomotor tasks of varying intensity and complexity?

Artificial Gravity and Muscle Function. How does artificial gravity (e.g., gravity-equivalent acceleration and variable-G forces) affect the structure and function of human skeletal muscle in normal and atrophying skeletal muscle, as well as other systems impacted by microgravity?

7. NSBRI Neurobehavioral and Psychosocial Factors Team

Team Leader:

David F. Dinges, Ph.D.
Professor of Psychology in Psychiatry and Chief, Division of Sleep and Chronobiology
Department of Psychiatry
University of Pennsylvania School of Medicine
423 Guardian Drive, 1013 Blockley Hall
Philadelphia, PA 19104-6021
Telephone: 215-898-9949
Fax: 215-573-6410
Email: dinges@mail.med.upenn.edu

The success of long-duration missions, particularly exploration missions, will depend heavily on prevention, identification, and mitigation of neurobehavioral and psychosocial risks to crew health, safety, and productivity. Astronauts aboard exploration missions will endure behavioral challenges for a much longer period of time than have ever been experienced during space flight. Stressors and risk factors on these missions include confinement for up to three years with the same small group of people; isolation from family and friends; limited communication with Earth, including as much as a 24-minute delay in bi-directional communications; and loss of privacy due to habitability constraints. There are also risks to neurobehavioral capability and emotional stability posed by prolonged weightlessness, enhanced radiation exposure, physical illness, interpersonal strife, and equipment failure in space. Language, culture, gender, and work role differences will also pose challenges to crew communication and effectiveness. Without mitigation, these stressors individually and collectively have the potential to erode cognitive performance; change neuroendocrine, cardiovascular, and immune responses; disrupt appetite, sleep, and other basic regulatory physiology; lead to neuropsychiatric impairment through anxiety and depression; and potentiate serious interpersonal problems among crewmembers.

This research area is concerned with developing novel ways to monitor individual astronaut brain functions, as well as group behaviors, and to provide preventive and operational countermeasures to enhance crew performance, motivation, and quality of life. The scope of this area fits within the Critical Path Roadmap risks for Human Performance (see Appendix A, Section II): identification of the neurobehavioral and psychosocial risks to crew health, safety, well being, performance, and productivity during long-duration space missions; evaluation of the effects of space-related stressors (i.e., habitability constraints, microgravity, radiation, work requirements, sleep deprivation, perceived risks, restricted communication with Earth and boredom) on physiological and psychological functions of individuals and crews; development of accurate, practical techniques and approaches to monitor behavior and performance capability during missions; development and validation of countermeasures to manage or mitigate space-related risks to neurobehavioral functions and to enhance health, motivation, safety, and performance during such missions; identification of strategies to maintain motivation and ensure an effective quality of life in space; and development of procedures to determine optimal leadership style, crew composition, organization, and communication with Earth.

The team's initial strategic research agenda involves eight ground-based studies that collectively address four thematic questions. Details concerning the current program are provided on the Web site http://www.nsbri.org/Research/Psycho.html. Questions addressed by the current projects include

- What are the effects of culture, personality and leadership on performance, stress and health in isolated groups?
- What are the major influences on interpersonal actions, communications and problem solving in small groups?
- How can affective, neurobehavioral and neurocognitive dysfunction be objectively detected in remote locations?
- What neurobiological processes of stress and arousal are the optimal targets for behavioral and pharmacological interventions?

Focused Research Questions

Proposals are being sought that address one of the following questions.

Neurobehavioral and Psychosocial Responses to Space Flight. What are the effects of long-term exposure to the major factors in the space environment on emotions (including emotional reactivity, stress neurobiology and responses, modulation of mood, and vulnerability to affective disorders), cognition and performance (including processes of sensation and perception, learning, vigilance, problem solving, decision making, and motor skills), and behavioral health?

Novel Countermeasure Development. How can novel neuroscience technologies (e.g., neuroimaging via fMRI, MRS, PET, NIR; transcranial magnetic stimulation) or novel behavioral methodologies (e.g., virtual reality, prolonged behavioral monitoring, and experimental manipulation of small group microsocieties in isolation and in tandem) be used to develop countermeasures for the psychosocial and neurobehavioral effects of prolonged space flight?

Performance Strategies. What are the behavioral strategies, scheduling strategies and habitat design elements that can maintain or enhance crew performance and prevent the development of hostility between crews and ground-support personnel during long-duration space flight?

8. NSBRI Neurovestibular Adaptation Team

Team Leader: Charles M. Oman, Ph.D.
Senior Research Engineer and Director, Man-Vehicle Laboratory
Department of Aeronautics and Astronautics
Center for Space Research, Massachusetts Institute of Technology
77 Massachusetts Avenue, Rm. 37-219
Cambridge, MA 02139-4301
Telephone: 617-253-7508
Fax: 617-258-8111
Email: cmo@space.mit.edu

The most overt change affecting an astronaut in space flight is the immediate response of the neurovestibular system to weightlessness (traditionally called a gravitational change). Initially, problems arise when astronauts transition to a weightless condition (from 1 G to 0 G), unfortunately at a time when physical and cognitive performance is often critical for mission success and safety. Problems appear again at the end of a mission, during and following a return to Earth (from 0 G to 1G). Postflight problems have generally been more severe after three-to-five month Mir and International Space Station (ISS) flights than on typical one-to-two week Shuttle missions, showing that, for some components of the vestibular system, adaptation to 0 G takes place over time scales of months, rather than weeks. Looking beyond ISS to interplanetary exploration missions, one can anticipate operationally significant vestibular problems when astronauts make the transition from 0 G to partial G, or from 0-G to an artificial gravity environment.

During the 1980s and '90s, space neurovestibular research largely focused on understanding the effects of otolith weightlessness on the vestibulo-ocular reflex (VOR) and on attempting to predict space sickness susceptibility. Today, the research agenda is set by the Critical Path Roadmap Neurovestibular Adaptation risks (see Appendix A, Section II) associated with long-duration space flight: disorientation and reduced performance on cognitive and physical tasks, including vehicle egress, especially during/after G-level changes (associated with acute spontaneous, and head-movement-contingent vertigo, nystagmus, oscillopsia, saccadic errors, and reduced dynamic visual acuity); impaired neuromuscular coordination strength upon return to positive G leading to increased incidence of falls and injury during emergency egress and escape (gait ataxia, postural instability); impaired cognitive and/or physical performance due to spatial disorientation; motion sickness symptoms or treatments (including short-term memory loss, reaction time changes, drowsiness, fatigue, torpor, irritability, and ketosis) as a result of changes in G level or use of artificial gravity; autonomic dysfunction (including cardiovascular, respiratory, gastrointestinal, sleep, and mood changes), which may be of vestibular origin; and permanent impairment of orientation or balance function due to microgravity or radiation (causing chronic imbalance, gait ataxia, vertigo, eye movement disorders, chronic vestibular insufficiency, and poor dynamic visual acuity). Thus, NSBRI's neurovestibular adaptation research program supports research aimed at developing scientifically-based countermeasures against the vestibular problems associated with space flight: space motion sickness, disorientation, oculomotor deficits, postflight postural instability, and gait ataxia.

The current research program involves seven ground-based projects; details concerning these projects are provided on the Web site http://www.nsbri.org/Research/Neuro.html. Six of the projects focus on the highest priority critical path risk (disorientation and reduced performance on cognitive and physical tasks) while one or two projects focus on the other risks. No project addresses the fourth risk, autonomic dysfunction, which may be of vestibular origin.

Focused Research Questions

This research solicitation seeks investigations that are complementary to the current team portfolio and that collectively address four of the five critical path risks. Thus, proposals are being sought that specifically address the following risks.

Vestibular/Autonomic/Emetic Physiology. What is the physiological basis for the "sensory conflict" theory for motion sickness? What is the locus and function of the putative "conflict" signal? What is the neural or chemical linkage between balance and emetic centers? What mechanisms establish the threshold for nausea and emesis? What neurotransmitter and receptor systems are involved? Is the physiology of space motion sickness fundamentally different from other forms of motion sickness? Can more effective anti-motion sickness drugs be developed which target emetic centers or the vestibular-emetic linkage? Drugs must be effective, easily and safely used over days to weeks with minimal side effects and must not impair neurovestibular adaptation. Can improved anti-motion drug delivery systems and dose and side effect monitoring systems be developed? What are the best ground-based techniques for evaluating 0 G pharmacokinetics and for assessing the effectiveness and side effects of drug countermeasures?

Postflight Neurovestibular Function. Does the neurovestibular response to weightlessness impair postlanding cardiovascular regulation and contribute to orthostatic intolerance? How is it mediated? Can an effective countermeasure (e.g., artificial gravity) be developed to exploit this knowledge? What are the relative contributions of neurovestibular adaptation, neuromuscular deconditioning and cardiovascular deconditioning during space flight to the postflight problems of neuromuscular coordination, ataxia and locomotion? What is the effect of possible cardiovascular, muscular and skeletal rehabilitation therapies on neurovestibular recovery? Can somatosensory information be used effectively to accelerate postflight neurovestibular readaptation?

9. NSBRI Nutrition, Physical Fitness and Rehabilitation Team

Team Leader: Joanne R. Lupton, Ph.D.
Regents Professor and William W. Allen Endowed Chair in Human Nutrition
Texas A&M University
218 Kleberg Center, MS 2471
College Station, TX 77843-2471
Telephone: 979-845-2142
Fax: 979-862-2378
Email: jlupton@tamu.edu

An individual's mutually interdependent nutritional status and level of physical fitness affect the physiological function of all of the body's systems. Optimum astronaut performance during space flight requires that these systems be maintained at an appropriate level of function, with appropriate reserves to enable astronauts to respond to the special challenges that arise during and just after a mission. The primary foci of this research area are the critical needs for adequate nutrition during a long-duration space flight simultaneous with a prescribed use of exercises to maintain appropriate fitness. Since physical activity will, in part, determine nutrient needs, and since the optimization of nutrient delivery will, in part, depend upon blood flow and muscle mass, which are both affected by physical activity, these two disciplines need to be considered together.

The critical issues for nutrition are counteracting the observed anorexia of space flight; determining nutrient needs to meet the modified requirements obtained during space flight, with stressors that include weightlessness and a different radiation environment; and developing new nutritional strategies, including the use of functional foods, supplements, and the timing of food intake relative to the specific prescribed exercise activities that will optimize human performance.

The critical issues for physical fitness include developing appropriate aerobic and resistive exercises that will prevent or reduce some of the physiological changes during space flight; determining the mode, frequency, duration, and intensity for each exercise; and defining the appropriate individual exercise prescription; determining the optimal timing of exercise components with respect to food intake and other activities; and developing the hardware to most efficiently implement the exercise countermeasures.

Although the Critical Path Roadmap (see Appendix A, Section II) contains specific risks associated with food and nutrition, the risks that may be ameliorated by nutritional and exercise-related interventions are reduced cardiovascular capacity, loss of bone mineral density, diminution of skeletal muscle function, depressed immune response, radiation-enhanced development of cancer, decrease in cognitive function, alterations in sleep patterns, and neurobehavioral and psychosocial risks.

The nutrition and physical fitness program presently consists of three nutrition countermeasure projects and one potential space-flight physical fitness project. Details concerning these projects are provided on the Web site http://www.nsbri.org/Research/Nutrition.html.

Three of the four projects involve countermeasures to the same critical problem: muscle wasting. The combination of muscular inactivity and stress during space flight results in a loss of skeletal muscle mass that leads to decreased muscle strength, which may compromise crew capabilities. A bed rest study will determine whether an amino acid supplement can ameliorate these negative effects by increasing protein synthesis. A bioreactor cell culture project, which addresses myocyte response in an *in vitro* model, will use the same amino acid supplement as the bed rest study and address mechanisms of insulin secretion. The physical fitness countermeasure should enhance the nutritional countermeasure by increasing blood flow to muscle and also by maintaining muscle strength.

Focused Research Questions

The objective of this research solicitation is to fill in gaps and strengthen the current research program. Proposals are requested that specifically address the following focused research questions.

Exercise Countermeasures. Without routine aerobic exercise during long-duration space missions, there is a decrease in intensity and endurance of aerobic capability as measured by oxygen consumption (VO_2 max) and heart rate per energy exerted (watts). Resistive exercise is required for maintenance of muscle performance as measured by strength and endurance. Muscle atrophy and loss of force and power have been documented through muscle biopsies. The primary goal of research in this area should be to study the effectiveness of exercise countermeasures to ameliorate the above undesirable effects of space flight. End points should include parameters quantifying the cardiovascular response, bone metabolism, body composition, and skeletal muscle metabolism and function. The exercise countermeasures must utilize approaches applicable or relevant to space flight, and the study design must include strict dietary control and contain measures of energy balance. It is expected that implementation of a successful proposal will require coordination with the currently funded bed rest and nutritional study.

Appetite and Thirst Controls. In spite of adequate provision of food and water, inadequate food intake is characteristic of human space flight. This reduction of food intake translates into a significant energy deficit with resultant loss of body mass and diminution of physical fitness. Suboptimal intake of essential macro and micronutrients and inadequate water intake also occurs. It is thought that alterations of central and peripheral appetite and thirst homeostasis underlie these perturbations. Proposals in this area should be aimed at understanding underlying mechanisms and designing effective nutritional countermeasures to these deficiencies in nutrient intake.

Alterations in Nutrient Partitioning and Metabolism as a Function of Weightlessness and/or Other Space Flight Stressors. For crewmembers, space flight appears to increase resting metabolic rate in the presence of chronic stress and increased protein turnover. Limited data suggest insulin insensitivity and increased fat oxidation occur. Examples of other changes occur with iron and calcium. Red cell mass is decreased by 10-15% during space flight resulting in the release of additional iron, a strong pro-oxidant, suggesting that it might be prudent to reduce dietary iron intake. These changes raise important questions in humans regarding the identification of nutritional countermeasures to combat the detrimental alterations in body composition and nutrient partitioning (e.g., bone, muscle, and adipose tissue) as well as in associated organ systems. It is likely that these effects reflect alterations in systems coordination as well as individual cell function. These manifestations may relate to direct influences of microgravity or other as yet undefined space flight stressors. Proposals focused on this area should aim at the development of countermeasures to ameliorate the above detrimental alterations in nutritional physiology and biochemistry.

Meal Allocation: Nibbling vs. Meal Eating, Supplements vs. Whole Meals, Timing of Nutrient Intake. The timing and frequency of meals with respect to activity, including sleep cycles and exercise, and to the most effective utilization of nutrients may be a key factor in maximizing astronaut health on long-duration space flights. For example, aerobic exercise has been shown to increase blood flow, which could benefit the uptake of amino acids into muscle if the amino acids were provided at the time of maximal blood flow. Similarly, after a substantial meal, there is a depression in protein synthesis. Since total body protein synthesis decreases in space flight, perhaps supplements between meals of amino acids in addition to the protein in three meals may be the most effective food pattern to enhance muscle protein synthesis and consequently maintain muscle function. For another example, extravehicular activity (EVA) often requires 7-9 hour periods of highly focused activity with no intake but water. Determination of specific nutrients (both type and amount) and timing of ingestion to maximize mental and physical performance for these tasks would enhance crew safety and performance. Proposals focused on this area should focus on meal patterns, distribution of nutrients, and the timing of meals or supplements in relationship to maximum utilization of nutrients, physical activity, and assigned tasks.

10. NSBRI Radiation Effects Team

Team Leader: John F. Dicello, Ph.D.
Professor of Oncology
The Johns Hopkins Oncology Center, Johns Hopkins University
Harry and Jeanette Weinberg Bldg., Rm. 1440
401 N. Broadway
Baltimore, MD 21231-8922
Telephone: 410-614-4194
Fax: 410-502-1419
Email: diceljo@jhmi.edu

Exposure to higher than normal radiation levels is one of the major health risks to humans on long-term space flights. This exposure results primarily from galactic cosmic rays (GCR) and solar particle events. The protons and high Z, energetic particles (HZE) involved may exert sizable biological effects even at low fluence, and there are considerable uncertainties associated with secondary particle effects (e.g., HZE fragments, neutrons, etc.). Although the health risks from exposure to radiation (x-rays, gamma rays or electrons) encountered on Earth are comparatively well-known, the health risks from space radiation are not well-known. The space-related risks are summarized in the Critical Path Roadmap for the radiation effects area (See Appendix A, Section II): cancer induction; central nervous system (CNS) damage from ionizing radiation; synergistic effects resulting from simultaneous exposure to radiation, weightlessness, and other spacecraft environmental factors (e.g., cytotoxic compounds present in the spacecraft); acute effects resulting from damage to the nervous system, intestinal tract, and blood-forming organs; and the effects of space radiation on fertility, sterility, and heredity.

The current NSBRI radiation research program involves six ground-based projects, details of which may be found on the Web site http://www.nsbri.org/Research/Radiation.html. A major component of the program is focused on one model system, the Sprague-Dawley rat, and one major endpoint, mammary tumorigenesis. The biological endpoint being addressed is cancer. In addition, two projects address CNS damage, one addresses genetic damage, and one addresses possible nutritional countermeasures to space radiation.

Focused Research Questions

Each application must provide a strategy and schedule that would describe how the results of the proposed experiments would finally yield data that could be used directly for providing a quantitative estimate of risk or for producing an effective countermeasure. It is important that this strategy be as explicit as possible and contains a schedule that would yield results within the necessary time frame. The objective of this NRA is to solicit new research investigations that augment the existing radiation team's program. In particular, proposals are being sought that specifically address the following.

Improving the Predictions of Risks to Human Health from Space Radiations. What is the proper methodology to extrapolate the biological results of experimentation to human risk? How can existing epidemiological data for humans be utilized to interpret biological data in terms of risk assessments for exposures in space? What are the methodologies required to extrapolate biological results to low-dose risk predictions? Are the risks from the various radiations in space independent? What is the dependence of the biological response on fluence and fluence rate? Are the single-particle events from the HZEs in space properly simulated with present accelerator-based exposures?

Providing Effective Countermeasures that Will Significantly Reduce these Risks. The countermeasures referenced here are biological or biochemical agents useful for modulation of significant radiation effects, which offer substantial promise as prevention or countermeasure tools to reduce or minimize human risk arising from space-radiation exposures. Proposed agents shall have demonstrated efficacy for chemoprevention of malignancies with low or no significant toxicity. Radiation countermeasure agents shall be based on scientific understanding of their likely efficacy against protons and high energy, highly charged nuclei (HZE particles). With this in mind, are there chemical or biological agents that can be implemented to mitigate radiation risks? Are there radioprotectants that mitigate acute exposures? Are there classes of minimally toxic agents that will globally reduce radiation risks?

11. NSBRI Smart Medical Systems Team

Team Leader: Jeffrey P. Sutton, M.D., Ph.D.
Director, Neural Systems Group
Massachusetts General Hospital
Harvard-MIT Division of Health Sciences and Technology
Bldg. 149, 13th Street, 9th Fl.
Charlestown, MA 02129-2000
Telephone: 617-726-4350/731-2388
Fax: 617-726-4078 FAX
Email: sutton@nmr.mgh.harvard.edu

Research in this area is focused on the ultimate development of an advanced, integrated, and autonomous system for astronaut health assessment, maintenance, and medical care. This system would include subsystems for the delivery and evaluation of medical interventions and other countermeasures that reduce the deleterious effects of space travel and enhance the overall well being of astronauts. The scope of research in this area includes new types of biometric sensors; novel medical and surgical techniques; robotic medical assistance systems; advanced drug synthesis and delivery systems; smart algorithms for medical data systems; automated decision support for training and care; and systems-engineered platforms for sensor, algorithm, and effector integration.

Although this research area is concerned with most of the risks related to the clinical capabilities component of the Critical Path Roadmap (see Appendix A, Section II), its scope is significantly wider. The current program is accessible at http://www.nsbri.org/Research/Med_Sys.html and consists of eight multi-disciplinary projects that integrate engineering, computation and biomedicine with innovation in technology and medical care. These projects address the following general topics: novel sensor systems for monitoring and diagnosis, novel three-dimensional imaging strategies, novel therapeutic modalities and intelligent systems for mentoring and training.

Focused Research Questions

There are several gaps that exist in the current program, and the objective of this solicitation is to fill some of them with projects that are complementary to the currently funded set. Specifically, projects are sought that address the following topics.

Decision Support System for Monitoring. Formalized approaches are needed to decide how changes in measured data should be integrated and brought to the attention of crew and/or ground support personnel. These approaches require domain-specific models of both short- and long-term changes in physiological status and status of the crew's environment and life support systems. Computational techniques are required to direct monitoring systems, allocate monitoring resources across systems, and determine when, to whom, and how urgently to report monitoring results. Communication latencies, dropouts and limited bandwidth introduce unavoidable disturbances. System architectures and collaborative approaches therefore need to be developed to support the requirement for shared decision-making and data management.

Decision Support Systems and Knowledge Bases for Diagnosis and Treatment. Physiological monitoring and medical care in a remote, isolated environment will depend on automated and semi-automated processes, alerts and reminders, and methods for aiding human decision makers. This, in turn, requires the ready availability of medical knowledge resources, including textbooks, atlases, guidelines, formularies, diagnostic decision aids, and other tools. Methods for organizing and retrieving knowledge relevant to a medical problem, inferring conclusions, developing and customizing diagnostic and treatment plans, and monitoring responses are needed.

Novel Therapeutic Modalities. Recognizing that facilities and specialty expertise for treating illness and injury will be limited, research is needed to identify alternative approaches that emphasize less invasive therapeutic interventions. Methods and devices that can be used by individuals with limited expertise under adverse space-flight conditions are required. The focus should be on approaches that minimize resource requirements and restore functionality, allowing mission completion.

12. NSBRI Technology Development Team

Team Leader (Acting): Jeffrey P. Sutton, M.D., Ph.D.
(See Section 11)

The goal of this research area is to develop technologies that support the ground-based or space-flight research mission of the NSBRI. Thus, this team creates systems and tools such as sensors, instruments, devices, and intelligent software that can support the other NSBRI Research Teams and the space life science research community at large. The tools and technologies developed through this program can be used for human or animal studies, countermeasure development or application, and medical care. Generally, the requirements for these tools and technologies are predicated on the carefully developed needs of the other research teams. These projects should support the investigation of the effects of space flight on human physiology and behavior; apply this information toward the development of techniques, technologies, instruments, and countermeasures that will sustain humans during future long-duration space missions; and benefit the quality of life and medical care on Earth.

The current program consists of eight multi-disciplinary projects that identify, integrate, and apply scientific and engineering technology to the research and development needs of the other NSBRI teams and the entire space flight community working on countermeasures. The currently funded projects are strongly related to the activities of nine other NSBRI research areas. Details concerning the current program are provided on the Web site http://www.nsbri.org/Research/Tech.html.

Focused Research Needs

The objective of this solicitation is to obtain technology and instrumentation development projects that are complementary to the current research program and that support the needs of the other NSBRI research areas. Emphasis in all proposals should be on computer control and automation for ease of operation and speed in conducting the activity. Similarly, all human sample collecting and monitoring should be minimally invasive or non-contact. All projects being developed for ultimate space flight must address size, weight, safety, and other dynamic conditions of space operations. This solicitation will generally focus on projects that deliver a specific product in a specified period of time, typically one to four years. Proposals will be expected to be of a maturity equivalent to that of a typical NASA Phase A (Conceptual Design) study. Proposals should address one of the following needs.

Non-Invasive Physiological Monitoring. Development of instruments or devices to monitor vital signs, core body temperature, eye motion, body fluid chemistry, etc. Sensor and sensor systems for use in long-duration space missions and comparable ground-based research should be easy to use, non-invasive (or minimally invasive), comfortable to wear, unobtrusive, and non-interfering with task performance. Particular emphasis should be placed on flexible and adaptable devices and systems that can be used for multiple purposes and that automatically collect and store data.

Automated Assay and Sample Processing Equipment. Development of automated approaches to carrying out biochemical assays (especially inflight) with minimal operator intervention. Biochemical assays of cellular function require multiple steps in which cells of interest are isolated from other cells, incubated with replacement media, exposed to particular reagents, and then analyzed. There is a generic need for a means of handling samples in which sequential incubations and washes may be performed both on Earth and in space-based environments in an automated manner.

Minimally Invasive Automated Sampling Device. Development of devices to collect blood and other bodily fluids with minimum patient disturbance and discomfort. Frequent measurement of analytes in blood and other serous fluids can indicate the need for or the effectiveness of countermeasures. Long term, a noninvasive body-worn device which can continuously collect and analyze tiny quantities of blood or body fluids would be of extreme importance. In the shorter term, an easy-to-use, non- or minimally invasive method of withdrawing or collecting such fluids without the problems and discomfort of frequent blood draws would be a major aid to space research.

IV. Application Procedures for the Opportunity to Participate on a National Space Biomedical Research Institute Team

Proposals to join an NSBRI research team must comply with the requirements of this research opportunity as described in this appendix (Appendix C). Appendix E outlines general NASA-specified requirements for proposal submission and should be used only for clarification of matters not specifically discussed here. Appendix C supersedes, modifies or extends the requirements enumerated in Appendix E.

General Instructions

Proposals to join one of the NSBRI's research teams must utilize NSBRI's Internet-based Electronic Proposal Submission System (EPSS). This system has been designed to enable one or more investigators to collaborate on the development of a proposal, to retain complete privacy throughout the proposal development process and to allow fast and accurate proposal submission. If a proposal is selected for funding, the electronic proposal information will serve as an active record file, enabling simplified investigator information changes, annual report submission and NASA Task Book submission.

This electronic submission system automatically prepares and submits a notice of intent to propose. To assure that the notice of intent is submitted by **November 30, 2001**, go to the Web site https://myportal.nsbri.org/myportal.cfm and register to obtain a personal account on the system. After entering contact information, investigators will receive a username and password for entry into EPSS and can enter the limited information required for a notice of intent. After this, the above Web address will serve as the entry point for proposal development and modification. All information entered, with the exception of the information required for the notice of intent, will remain private until electronic submission is completed.

Proposal information requested closely follows the information requested by NIH grant application form PHS 398. This information includes Basic Personal and Institutional Information, Project Description, Performance Sites, Key Personnel, Investigator Budgets with Justifications, Other Support, Biographical Sketches, Laboratory Resources, and Research Plan.

A proposal overview screen will guide applicants through the process of completing the required proposal information. EPSS offers a collaborative work environment for the Principal Investigator and Co-Investigators to view and submit various portions of the proposal. For example, the Principal Investigator can enter or upload <u>all</u> information for the proposal. Co-Investigators can view all proposal information but are permitted to enter only their <u>specific</u> personal information and their assigned project and budgetary information. All investigators can allow an administrative support person to act on their behalf, assisting them in the entry of their proposal information. EPSS will contain an Investigator Profile section, containing biographical sketches and other information, for each investigator registered in the system. This information can be used by authorized proposing investigators, eliminating the duplicate entry of such information.

Electronic applications must be submitted before 5:00 PM, EST, Thursday, January 31, 2002. After submission using EPSS, the Principal Investigator **must** mail a printed proposal cover page, with the appropriate institutional approvals, to the following address within one week of the submission deadline:

Ronald J. White, Ph.D.
Attn: NRA 01-OBPR
NSBRI
One Baylor Plaza, NA-425
Houston, TX 77030-3498
(713-798-7412)

Please direct any questions concerning this application procedure to the NSBRI by calling 713-798-7412, by faxing your questions to 713-798-7413, or by sending your inquiry to contact_us@www.nsbri.org. The technical requirements to operate EPSS are Internet Explorer 4.0+ or Netscape 4.03+ for Windows, Macintosh or Unix. EPSS is best viewed using Internet Explorer 6.0.

Eligibility - Current Principal Investigators funded by the NSBRI are NOT eligible to propose to this NRA. In addition, current Team Leaders and Associate Team Leaders are NOT eligible to serve as Co-Investigators on studies proposed by other Principal Investigators.

Notice of intent – To facilitate planning for the review process, investigators are requested to submit a notice of intent to propose by using EPSS and following the online instructions. This non-binding notification should be completed by November 30, 2001.

Budgetary Matters – Budgets are to be prepared according to the instructions provided online through EPSS. It is expected that the average annual total (direct + indirect) cost of selected proposals will be between $200,000 and $250,000. In general, the annual total cost of a single proposal may not exceed $400,000. ***Investigators should be aware that NSBRI awards require an institutional contribution to the proposed project (cost sharing) at the level of at least 10% of the total NSBRI award. This contribution is not to be identified in the submitted project budget but will be requested at the time the institutional award is made.***

Duration of Proposed Research – Proposals may be submitted for a maximum duration of one to four years funding, with an assumed start date of October 1, 2002. Some applicants may be invited to initiate their project earlier, from July to September 2002.

Special Ground Facilities – A variety of special ground research facilities, including centrifuge facilities, bed rest facilities, etc., are available for use by investigators submitting proposals in response to this NRA. Interested investigators are referred to the *Space Life Sciences Ground Facilities Information Package* for instructions on how to incorporate the use of these facilities into a proposal (see http://research.hq.nasa.gov/code_u/nra/current/NRA-01-OBPR-07/index.html/). The NSBRI will negotiate appropriate use of those facilities on behalf of selected investigators, but investigators must include the cost of using these facilities in their proposal.

Special Travel and Reporting Requirements – Principal Investigators selected in response to this NRA will be expected to attend two, two-day research team meetings each year at a location to be determined and one, annual, three- to four-day general investigator workshop/retreat in the Houston area. Budgets should reflect the costs associated with these meetings and should include a statement indicating that this travel is a special requirement. Selected investigators will become part of the NSBRI's intramural research program and will be expected to provide an annual progress report. Progress is reviewed by the NSBRI's Board of Scientific Counselors. In addition, investigators will be required to provide annual project information for inclusion in NASA's Life Sciences Program Tasks and Bibliography. The progress report and Task Book information will be collected electronically.

Data Management Plan – Most data collected through NSBRI support are required to be placed in a central Institute data archive. Investigators should plan for delivering their data to the NSBRI archive ***as it is collected*** and should include the cost of such data archiving in their submitted proposal. If selected, a data management plan, including a list of the data products and a schedule for their delivery, must be prepared and submitted to the NSBRI. No additional costs should accompany this plan.

V. Review and Selection Process

Investigators should refer to Appendix A, Section IV, for a description of the review and selection process. Elements of review and selection unique to the NSBRI are as follows:

Applications will be evaluated for scientific and technical merit and for the likelihood that the research proposed will have a significant impact on achieving the goals stated in this NRA. The initial review will be carried out by an appropriate panel of experts who will discuss and provide a written critique of each proposal. Proposals deemed to be in the competitive range for this submission will receive a second-level review by the NSBRI scientific program directors to determine relevancy of the proposed project to the research program in the research area under consideration. For studies involving human subjects, adequacy of plans to include both genders and minorities and their subgroups as appropriate for the research goals and plans for subject recruitment and retention will be taken into account. Applicants should be aware that some meritorious proposals may not be selected for funding. Selection recommendations, based on merit score, programmatic relevance, and cost, are prepared by NSBRI management, reviewed by the NSBRI External Advisory Council, and approved by the NSBRI Board of Directors. Final selection will be coordinated between the Bioastronautics Research Division at NASA headquarters and the NSBRI to insure programmatic balance and elimination of duplicate efforts.

Selection will be based on the merit score awarded by the peer review panel, on the programmatic relevance as determined by NSBRI management, and on cost. The most important element in the evaluation process is the merit review, which carries the highest weight in final evaluation and selection. The other factors are approximately equal in weight to each other. For studies involving human subjects, adequacy of plans to include both genders and minorities and their subgroups as appropriate for the research goals and plans for subject recruitment and retention will be taken into account.

Original signed by
Bobby R. Alford, M.D.
Chairman of the Board and CEO

NSBRI

Multiple Opportunities for Ground-Based Research in Space Life Sciences Technical Description

Opportunity to Participate in the Countermeasure Evaluation and Validation Project (CEVP)

I. Introduction

The CEVP provides a mechanism for proposing experiments that, in an integrated fashion, will systematically and scientifically evaluate and validate candidate countermeasures that have reached a high degree of maturity. Such candidate countermeasures will have been experimentally tested in scientific studies designed to test their effects on the target system. That is, they will have completed testing at CRL 6, usually in a ground-based analog of space flight (See Appendix A, III for a discussion of the CRL scale). In the CEVP, they will be evaluated experimentally using ground-based analogs of space flight to assess their targeted effects, their side effects, and their interactions with other countermeasures. After evaluation, a candidate countermeasure may be validated in systematic experiments during actual space flight to assess those same factors. This NRA solicits experiments to test proven countermeasures in bed rest ground studies only (a microgravity analog).

The CEVP functions using a team approach, in which the investigator becomes a member of a team led by the NASA Johnson Space Center (JSC) that integrates space medicine and space research expertise resident inside and outside the agency. The CEVP is the final step in a process in which ideas and concepts emerging from basic research are developed into operational countermeasures and turned over by researchers to be implemented as part of mission operations.

The CEVP uses a baseline standardized complement of integrated physiological and psychological tests, termed the Integrated Testing Regimen (ITR), that will be used to examine candidate CM efficacy and intersystem effects.

II. Focused Investigation Questions and Opportunities Specific to CEVP

The objective of this solicitation is to obtain ground-based, bed rest investigations on human subjects that are complementary to or that enhance the current complement of countermeasures of the CEVP. Competitive proposals submitted in response to this NRA MUST be an evaluation of experimentally proven mature countermeasures that

- **are at the levels of CRL 7 and 8 (see Appendix A, Section III)**. Proposals submitted to CEVP that do not meet the CEVP CRL requirement may be considered under one of the other research opportunities of this solicitation.

- **address two primary risk areas: 1) bone loss and/or 2) muscle loss.** The strategies employed in both these areas must balance the requirements to maintain bone and muscle integrity while minimizing operational costs, such as crew time and extensive hardware development.
- are focused on the use of currently available flight hardware.
- determine contingency capabilities and protocols designed to minimize deconditioning in the event CVIS, TVIS and/or iRED are unavailable. Some examples of current contingency devices are described in section VIII of this appendix.
- use the Integrated Testing Regimen (ITR) as the primary countermeasure evaluation tool.
- consider use of the "small n" statistical tools to minimize the number of subjects (See Reference 24 in Appendix A).

Information about the CEVP is available from

John N. Evanoff, Ph.D.
NASA Johnson Space Center
Human Adaptation & Countermeasures Office
2101 NASA Road 1, Mail Code SK2
Houston, Texas 77058-3696
Telephone: 281-244-6426
Fax: 281-483-2888
Email: jevanoff@ems.jsc.nasa.gov

Collection of Countermeasure-Unique Data

Use of unique tests, essential to the evaluation of the efficacy of a particular proposed countermeasure, may be necessary in addition to the standard ITR tests. These tests, expected to be minimal in number, will be collected on all test subjects and must be well justified by the investigator in the Research Proposal Form. Countermeasure-unique tests will be of lower priority than ITR tests for funding and scheduling. Additional ancillary tests, to be completed as part of the study, but not essential to evaluation of the candidate countermeasure, may be included in the proposal (and costed in the proposal budget). The supplementary tests will be considered as long as they do not confound the primary objective of the study.

Statistical Considerations

Bed rest studies are limited to relatively small subject numbers due to constraints on facilities and funding. Proposals must address statistical considerations and show how the experimental results are generalized. Strategies to limit the requirement for control subjects (e.g., use of "historical" controls from earlier bed rest studies) should be considered in the experimental design. These and other options and their potential benefits should be presented within the proposal.

The National Academy of Science's Institute of Medicine recently completed a review of methodologies for small number clinical trials at the request of NASA. A summary of this meeting and recommendations may be found on the Web site http://www.iom.edu/IOM/IOMHome.nsf/Pages/smalln. The full text of the Institute of Medicine report is available online at http://books.nap.edu/catalog/10078.html.

Current Protocols using Existing Hardware under Nominal Conditions

Proposals should be focused on the use of currently available flight hardware or minor derivatives of such hardware. Such research could compare the efficacy of these modified exercise prescriptions vs. the baseline with the intent of increasing efficacy or minimizing operational consequences of exercise, such as decreasing crew exercise time requirements. Studies requiring exercise in bed rest subjects should specify how the exercises are to be performed in a horizontal position, and any ancillary support equipment that will be required. Studies requiring augmented instrumentation above what is currently available in the flight hardware suite [Interim Resistive Exercise Device (iRED), Treadmill with Vibration Isolation System (TVIS), or Cycle Ergometer Vibration Isolation System (CEVIS)] should clearly specify these capabilities and define concepts and costs for implementation on the ground.

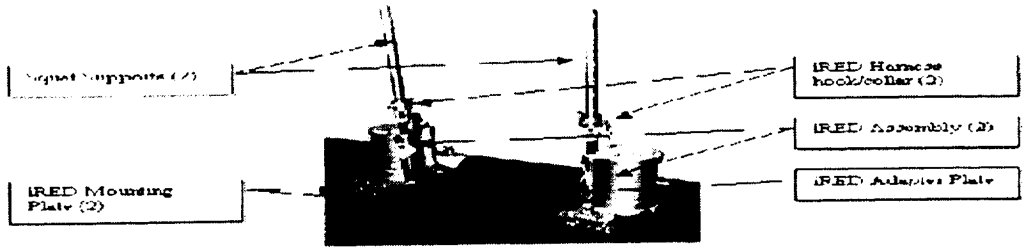
Submitters should take notice that NASA is working in collaboration with the European Space Agency (ESA) on countermeasure evaluation studies being conducted at the Institute for Space Physiology and Medicine (MEDES) facility in Toulouse, France. Both NASA and ESA are using the ITR as a common measure, and studies will be coordinated. For example, one of the countermeasures currently undergoing bed rest evaluation at MEDES is evaluating the efficacy of bisphosphonates as a countermeasure against bone loss. Therefore, studies proposing the use of bisphosphonates will not be considered.

Regular exercise is planned during all ISS operations. Current exercise capabilities are limited to the equipment and protocols defined herein and form the basis of NASA's operational exercise countermeasure program. Exercise prescriptions are tailored to the individual needs of various crewmembers, but all will follow the guidelines defined herein. Nominally, exercise prescriptions are developed based on pre-flight physical fitness testing, and these prescriptions are modified during the mission based on feedback from the crew, operational constraints, or the results of the monthly in-flight Physical Fitness Exam (PFE) conducted on ISS crew. Exercise prescription logs are developed by the NASA-JSC Astronaut Strength, Conditioning, and Rehabilitation (ASCR) group, maintained by the crew, and are downlinked to the ground on a periodic basis.

The following devices and protocols describe the current ISS exercise regimen:

1) **Interim Resistive Exercise Device (iRED)** – The iRED hardware (see Figure 3) provides the ability to perform resistive exercise in a zero gravity environment. The iRED currently resides in the U.S. Node on the ISS. The iRED is comprised of two main canisters, containing rubber "flex packs," which provide a selectable range of resistance from 5 to 150 lbs per canister. The resistance is controlled by rotating a hand crank to preload the flexpacks to the desired resistance, and for loads of 100 pounds or less, adjustability is provided in increments of 5 pounds resistance at an accuracy of ±1 pound or +5% of current reading, whichever is greater. For resistance greater than 100 pounds, adjustability is in increments of 10 pounds resistance at an accuracy of ±1 pound or +5% of current reading, whichever is greater. The canisters may be operated independently or in tandem. A cord exiting the bottom of each canister provides for attachment to a suite of accessories allowing unilateral or bilateral operations, including a deadlift bar, squat harness, ankle cuffs, and handgrips.

Figure 3. Interim Resistive Exercise Device (iRED)



The iRED supports a number of exercises targeting several major muscle groups. Among these are squats, deadlifts, heel raises, knee raises, hip abductions, leg curls, bent-over rows, upright rows, shoulder raises, shoulder presses, bicep curls, tricep extensions, and wrist curls. The iRED provides both concentric and eccentric capability during exercise, with eccentric resistance ranging from 40-60% of the concentric resistance. Due to maximal rotation constraints on the flexpacks, the range-of-motion is limited to 22" for high loads and is progressively higher as loads decrease.

The prescription for iRED exercises varies according to the unique needs and fitness of individual crewmembers, the mission phase, availability of other exercise equipment, and operational and timeline constraints. It is usually updated on a biweekly basis. In general the prescription is written with the intent to alternate lower body and upper body exercises every other day and to minimize the iRED reconfiguration time for the crewmember. Table 1 shows an example of the types of exercise conducted during weekly resistive exercise training program using the iRED. The bottom of the table shows the various phases of training based on mission duration (nominally 4 months).

Table 1. Sample week of inflight iRED exercise

Day 1	Day 3	Day 5
deadlift	squat	deadlift
bent over rows	heel raises	bent over rows
straight leg deadlift	straight leg deadlift	straight leg deadlift
squat	deadlift	squat
heel raises	bent over rows	heel raises

Day 2	Day 4	Day 6
shoulder press	bicep curls	shoulder press
rear raises	tricep kickbacks	lateral raises
front raises	upright rows	front raises
hip abduction	hip flexion	hip abduction
hip adduction	hip extension	hip adduction

2 weeks	adaptation	12-15 reps/2-3 sets
4 weeks	basic strength	10-12 reps/2-4 sets
5 weeks	hypertrophy	8-10 reps/2-4 sets
5 weeks	strength	6-8 reps/2-4 sets

2) **Treadmill with Vibration Isolation System (TVIS)** – The TVIS (see Figure 4) is designed to provide treadmill exercise in a microgravity environment while minimizing the structural loads imparted into the ISS structure during exercise. The treadmill is designed to allow walking, running, and knee bends; and provides cardiovascular exercise, ambulation (neuromuscular patterning), axial skeletal loading (heel strike), and endurance exercise of the

anti-gravity musculature. The vibration isolation system is intended to minimize the transfer of dynamic forces caused by operation of the treadmill to the structure of the Service Module (SM) and other parts of the International Space Station (ISS), while at the same time maintaining a stable running/walking surface.

The TVIS is programmable and can be operated in either motorized tread belt or non-motorized (passive) modes. Speed ranges from 0-10 mph in increments of 0.1 mph. In the passive mode, the TVIS uses the motor as a required resistance. The Subject Load Device, a bungee system that attaches to a harness that impacts the downward force on the crewmembers hips and shoulders, accommodates loading. The load can be varied from 40% to 100% total body weight depending on comfort and desired workout. Nominal exercise usually is conducted at the 60-80% load setting. The operator is constrained in the forward/aft direction by use of the Subject Positioning Device, which provides stabilizer bars attached to the TVIS harness and the TVIS platform. A record of the actual exercise speed, load setting, and duration will be recorded onto the PCMCIA card and will nominally be downloaded to the ground for evaluation. If the optional Heart Rate Monitor is worn, heart rate during the exercise will also be recorded.

As in the iRED, individual prescriptions will vary; however, nominal TVIS usage will be planned for a minimum of four sessions per week and will be complemented on alternate days with the Cycle Ergometer Vibration Isolation System (CEVIS - see next section). A typical weekly prescription between the TVIS and CEVIS would be as follows:

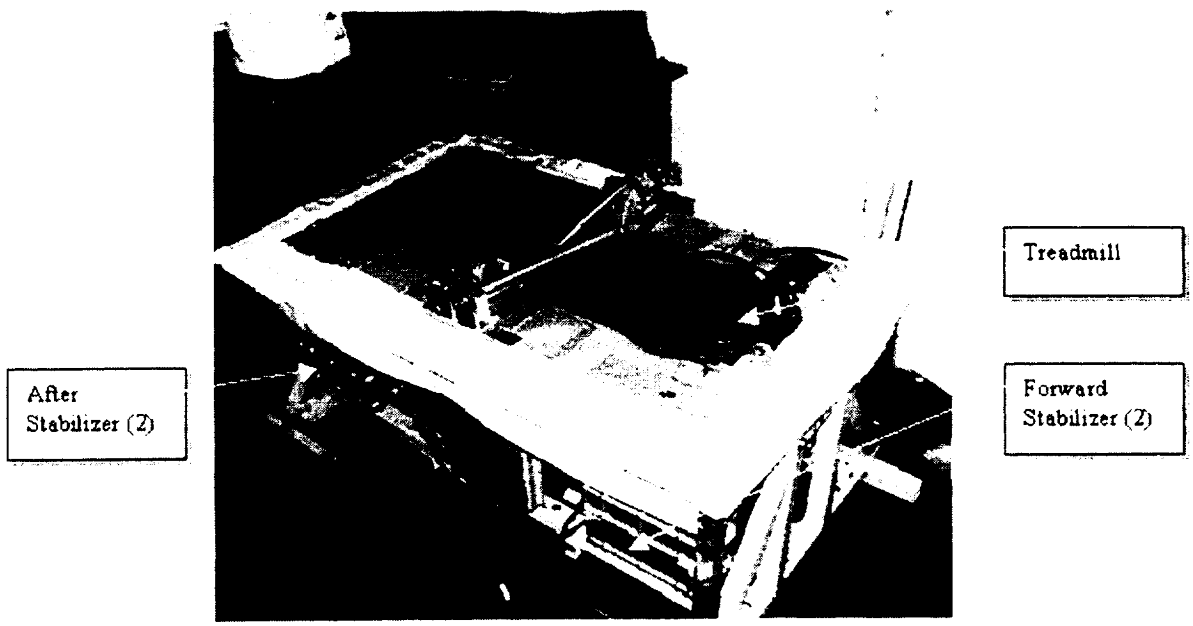
Table 2. Weekly prescription between the TVIS and CEVIS

Day 1	TVIS Interval Training (sprint with walk recovery) (RPMs & length of recovery will vary based upon crewmembers' fitness levels.)
Day 2	CEVIS aerobic training and upper limb resistance training
Day 3	TVIS aerobic training (continuous running) (Time varies based upon crewmembers' fitness levels.)
Day 4	Repeat Day 1
Day 5	Repeat Day 2
Day 6	Repeat Day 3
Day 7	Rest or Interval Training

Individual prescriptions for time and distance exercised will vary depending on preflight and inflight assessments of the crewmember.

Protocols will gain intensity as the mission proceeds. In the final 30 days prior to landing, all aerobic exercise sessions are scheduled on the treadmill (vs. the CEVIS) to promote re-adaptation to earth gravity.

Figure 4. Treadmill with Vibration Isolation System (TVIS)



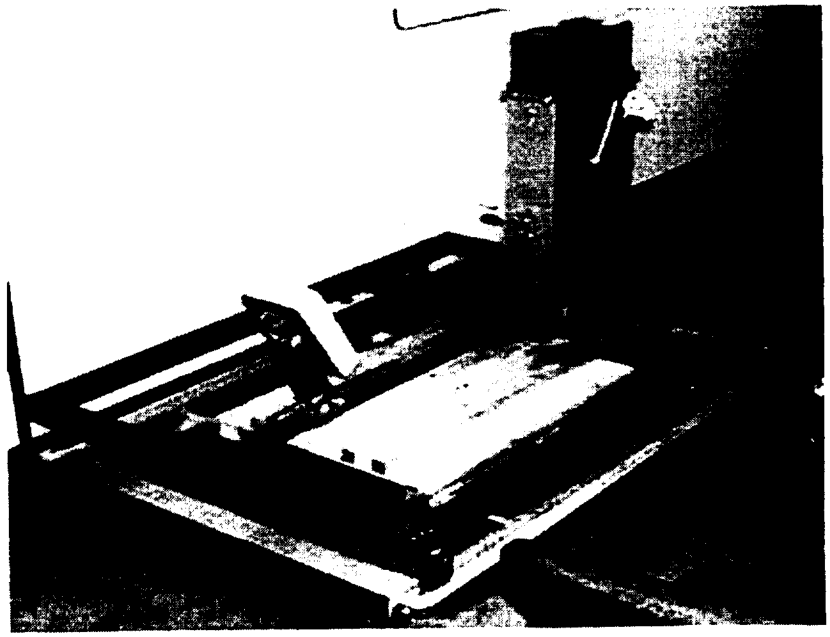
3) **Cycle Ergometer with Vibration Isolation System (CEVIS)** – The CEVIS (see Figure 5) is located in the U.S. Laboratory Module and provides a variable resistive load for maintaining cardiovascular fitness. The CEVIS can provide independent upper and lower limb cyclic training. The CEVIS is also used for the monthly periodic fitness evaluations. The CEVIS incorporates a resistive mechanism actuated by a manual control as well as a remote electronic controller that provides a workload range from 0 to 350 Watts, described below:

a) Using the manual controller, the CEVIS workload is continuously variable between 0 and 350 Watts for pedal speeds between 30 and 120 revolutions per minute (rpm). Pedal speeds are adjustable in 5 rpm increments. The workload is displayed during manual control is adjustable in increments of 25 Watts (+/- 5 Watts).

b) Using the remote electronic controller, the workload may be varied between 25 and 350 Watts, adjustable in discrete units of 1 watt, for pedal speeds between 50 to 120 rpm (+/- 1 rpm).

The nominal prescription for CEVIS is shown in Table 2. A record of the load, speed, and duration is recorded onto the PCMCIA card and downloaded to the ground for evaluation. If the optional Heart Rate Monitor is worn, heart rate during the exercise will also be recorded.

Figure 5. Cycle Ergometer with Vibration Isolation System (CEVIS)



Current contingency exercise capability on ISS

In the event that the nominal ISS exercise equipment (TVIS, CEVIS, or iRED) fails, NASA must develop and maintain contingency capabilities and protocols designed to minimize deconditioning experienced while awaiting repairs. To date, the following contingency capabilities exist:

- TVIS failures – there are a number of potential failures for TVIS that would degrade TVIS performance. Possible failures include the active motor, Subject Load Device, or the tread. Failure of the motor would require "passive" operation, where the operator drives the tread. Failure of the Subject Load Device would necessitate a contingency loading mechanism, such as bungee cords attached to the TVIS harness and 4-point attachment to the TVIS structure. Complete failure of the TVIS would require an alternate running surface, such as the Contingency Exercise Surface (CES). The CES is a Teflon-coated aluminum plate that mounts over the TVIS tread. The user dons slippery booties over their shoes, and then uses the same accessories as the TVIS for loading and positioning (SLD and the user can "moonwalk" across the near frictionless surface, emulating a running motion to the maximum extent possible).

- IRED failures – the iRED has multiple failure modes, which also degrade performance. In the event of failure of one or both of the iRED canisters, the Contingency Resistive Exercise System (CRES) can be used to provide resistive loading. The CRES is comprised of four sets of bungee cords. Each set is comprised of a pair of bungees, with each bungee rated up to 100 lbs at full 36-inch extension; however, at the usual extension (~ 22 inches) for squats, a resistance of 60 lbs is more typical (therefore, squats with four sets of bungees would net 480 lbs resistance at maximum range of motion). The CRES bungees can be installed individually or in pairs to the iRED footplate and attachments.

Note that CEVP proposals will be evaluated for their responsiveness to the critical needs expressed in this NRA. Proposals that are not responsive to these needs will not be selected for funding.

III. Integrated Testing Regimen

A standardized set of operational, medical, physiological and psychological tests have been adapted by the CEVP for obtaining systematic measurements before, during, and after space flight. This complement of tests is called the Integrated Testing Regimen (ITR). The ITR will be used to examine the efficacy of candidate countermeasures on the target physiological system(s) as well as to evaluate the side effects and/or interactions of the countermeasures on non-target systems.

Discipline-specific Integrated Product Teams comprised of flight surgeons, space research experts, and operations experts will establish success/criteria criteria for physiological performance measures in each of the target disciplines and will review/update these criteria on a regular basis. Creation of predetermined, objective ratings of success and failure will facilitate statistical analysis of a countermeasure's efficacy. Success/failure criteria address functional and clinical capabilities projected during long-duration space flight and must be evaluated from test data derived from the CEVP ITR. Given the importance of countermeasure development and validation to the OBPR objectives, all crewmembers on every long-duration ISS mission will be requested to participate in either the ITR alone, or the ITR as part of countermeasure validation. **Ground-based ITR testing in conjunction with this solicited bed rest study will be required.**

Table 3. Integrated Testing Regimen (ITR) – Primary Evaluation Tool

Test	Description	Test Performed in Relation to Bed Rest
Operational Tilt Test	Subject will be tested on the tilt table in supine and standing positions. Measurements of blood pressure, heart rate, stroke volume, cardiac output and peripheral resistance are collected.	*(pre - post)*
Clinical Lab Assessment (fasting)	Blood and urine are collected for analysis.	*(pre - post)*
Clinical Nutritional Assessment	A diet questionnaire is filled out, and height and weight are taken pre-, in-, and post bed rest. Blood, urine and saliva are collected pre and post bed rest, as well as bone densitometry (DEXA) data.	*(pre - post)*
Bone Densitometry	5 DEXA scans are taken: heel, hip, wrist, whole body and lumbar spine.	*(pre - post)*
Functional Neurological Assessment	Subject is placed on the posture platform where tests for balance control and sensory integration are administered.	*(pre - post)*
Functional Fitness	Exercises used for testing are bench press, crunches, leg press, sit & reach, push-ups, and pull-ups.	*(pre - post)*
Isokinetic Muscle Function	Muscle performance testing will be administered using an isokinetic dynamometer on back extensors/abdominal, hamstring/quadricep and tibialis anterior/gastro-soleus groups.	*(pre - post)*
Test of Aerobic Capacity: Cycle Ergometry	A maximal and submaximal upright cycle test will be administered. The max test will establish a max heart rate and V02. The submax test will establish the protocol for in-flight exercise.	*(pre - in - post)*
Neurocognitive Assessment	A computer-based test is administered on the Medical Equipment Computer.	*(pre - in - post)*

IV. Ground Analog Campaign Description

Research selected through this NRA will be managed under NASA's CEVP, an element of the NASA Biomedical Research and Countermeasures Program. Under the CEVP, NASA will provide and support a space flight analog bed rest study for the evaluation of countermeasures targeting bone and muscle loss. Research that proposes bed rest facilities outside of the CEVP facility will not be considered.

The CEVP solicits proposals to evaluate mature candidate countermeasures for testing in a bed rest study. Dependent measures for these studies are defined by the Integrated Testing Regimen (ITR). **Due to the high cost of conducting bed rest studies, proposals selected through this CEVP NRA may be "teamed" and coordination of the protocols will be performed by CEVP and the selected investigators. The bed rest study will be performed at a facility designated by the CEVP, and all subjects participating in countermeasure evaluation studies will be tested using a ground-based version of the ITR.**

CEVP Database for Ground Evaluation Studies

CEVP ITR ground data will be archived in a dedicated CEVP database maintained within the Life Sciences Data Archive infrastructure at JSC. NASA CEVP Project Management will strictly control access to test subject data. Data requests for CEVP ground data will be screened through and approved by a CEVP Review Committee and management configuration control board. Test subjects will be briefed prior to enrolling in the bed rest campaign, and must sign an Informed Consent Form allowing sharing of data with CEVP investigators prior to study enrollment.

Data collected for the CEVP will be coded to assure test subject confidentiality. Protection will include use of unique codes assigned to each test subject on all paper, electronic, audio, and videotape data records. Published results may not identify or be able to identify any test subject unless consent to do so is specifically granted by the test subject.

V. Funding

Since NASA will provide and support the space flight analog infrastructure, including test subjects, supplies, sample analysis, and the ITR, it is anticipated that the proposing PI costs are to be minimal. **It is expected that a typical ground proposal award will average $120,000 (total annual costs). It is anticipated that only two to four ground-based CEVP proposals will be funded by this Research Opportunity due to facility and funding limitations for bed rest studies. Because of this limitation, investigators should very carefully review the focus of this section of the solicitation identified in Section II "Focused Investigation Questions and Opportunities Specific to CEVP."**

VI. Facilities

Sites that may be used by CEVP for ground-based countermeasure evaluations include the NASA Ames Research Center Human Research Facility and/or other facilities local to the NASA Johnson Space Center (JSC). These facilities will provide a core staff of nurses, medical monitoring personnel, technicians, and dieticians to provide a turn-key, end-to-end capability for conducting countermeasure evaluation studies using long-duration bed rest as a space flight analog. In addition, facility personnel will perform the ITR (see Figure 1) on all bed rest subjects.

VII. Test Duration

Current anticipated dates for the bed rest studies solicited by this NRA will be of 30-90 days in duration and will be performed in the January – March 2003 and/or June - August 2003 timeframe.

VIII. Application Procedures for Individual Investigations Proposing to the Countermeasure Evaluation and Validation Project

Instructions for Notice of Intent and Proposal Submission

Proposals for individual investigator grants must comply with the general requirements of this research opportunity as described in this appendix (Appendix D). Appendix E outlines general NASA specified requirements for proposal submission, and should be used for clarification and reference. This appendix supersedes, modifies, or extends the requirements enumerated in Appendix E.

SYS-EYFUS Registration for All Applicants

SYS-EYFUS is an electronic system used by NASA Headquarters to manage research solicitation activity, plan for the receipt of research proposals, track the receipt and peer evaluation of these proposals, and manage funded research (grants, cooperative agreements, etc.) sponsored by NASA's Office of Equal Opportunity (Code E), Office of Earth Science (Code Y), Office of Human Resources & Education Division (Code F), Office of Biological and Physical Research (Code U), Office of Space Science (Code S), and the Office of Space Flight (Code M). SYS-EYFUS also supports the funding and administration of awards pursuant to selection of these research opportunities.

All investigators planning to submit a proposal to this solicitation are requested to register online with SYS-EYFUS. Comprehensive help, instructions, and contact information are provided online. SYS-EYFUS can be accessed at the following address:

http://proposals.hq.nasa.gov/

If you have previously registered with SYS-EYFUS, you are requested to verify and update your user information. If you have forgotten your user ID or password, select the "Forgot Your Password" option and type in your first and last name to search our database. The system will send an automatic email message with your username and password to the email address listed in our database.

Instructions for Preparing a Notice of Intent

All investigators planning to submit a proposal in response to this solicitation are requested to submit a **non-binding** Notice of Intent (NOI) to propose by November 30, 2001, via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

- Login to SYS-EYFUS and select "New Notice of Intent."
- The Division Specific Opportunities screen will appear. In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Notice of Intent submission Form. All fields are required.
    a. For the proposal type field on this form, <u>new/no prior support</u> means that the investigator has not received NASA funding from 1999 through 2001, <u>new/prior support</u> means that the investigator has received NASA funding between 1999 and 2001, and <u>revised</u> means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002.
- Click on "Submit NOI Page."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the NOI. After you are done, click on "Continue." IMPORTANT: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Members Page, your NOI will be displayed. Click on "Resubmit NOI Page" to complete your NOI submission.
- You may edit and resubmit your NOI at any time before the submission deadline of November 30, 2001. Once you submit an NOI, it cannot be deleted. For title, team member, or any other changes, please edit your existing NOI and resubmit changes to avoid duplicate records.

Instructions for the Preparation of Proposals

An original signed proposal, plus twenty (20) complete copies of the proposal, should be mailed to the address indicated and in the manner described of this document.

<u>All</u> proposals submitted to the Bioastronautics' Biomedical Research and Countermeasures Program must include the completed cover page form as described in this Appendix. The name of the Principal Investigator should appear in the upper right hand corner of each page of the proposal, except on the cover page form where special places are provided for this information. Note that the proposal <u>must</u> specify the period of performance for the work described; periods of

performance may be for any duration up to three (3) years but should be suitable for the project proposed.

The proposal must include the following material, in this order:

(1) Proposal Cover Page: Solicited Proposal Application, including certification of compliance with U.S. code (if applicable). One signed original required. Please see "How to Submit Proposal Cover Page Information" below for instructions on how to complete the proposal cover page information.

(2) Transmittal Letter or Prefatory Material, if any (see Appendix E for details)

(3) Proposal Title Page, with Notice on Restriction on Use and Disclosure of Proposal Information, if any (see Appendix E for details)

(4) Project Description

The length of the Project Description section of the proposal cannot exceed 20 pages using regular (12 point) type. Referenced figures must be included in the 20 pages of the Project Description. The Bibliography section is not considered part of the 20-page project description. Proposals that exceed the 20-page limit for the project description (22-page limit for revised proposals; see below) will not be reviewed. The proposal should contain sufficient detail to enable reviewers to make informed judgments about the overall merit of the proposed research and about the probability that the investigators will be able to accomplish their stated objectives with current resources and the resources requested. In addition, the proposal should clearly indicate the relationship between the proposed work and the research emphases defined in this Announcement. Reviewers are not required to consider information presented as appendices or to view and/or consider Web links in their evaluation of the proposal.

New applications, where the investigator has received NASA funding in related fields from 1999 through 2001, must present results and evidence of progress of the associated NASA-supported research as part of the project description.

Revised applications (revisions of 1999, 2000 or 2001 submissions) must be so designated on the proposal cover page and explained in the project description. This explanation should be presented in a separate section of **no more that two pages at the beginning of the project description**, and is in addition to the 20 pages allowed for the project description. Related changes to the research plan should be highlighted in the body of the project description. Changes within the proposal may be highlighted by appropriate bracketing, indenting, or changing of typography. Clearly present any work done since the prior version was submitted. **Revised applications that do not address the criticisms in the previous review will be considered unresponsive and will be returned without review.**

(5) Management Approach

Each proposal must specify a single Principal Investigator who is responsible for carrying out the proposed project and coordinating the work of other personnel involved in the project. In proposals that designate several senior professionals as key participants in the research project, the management approach section should define the roles and responsibilities of each participant and note the proportion of each individual's time to be devoted to the proposed research activity. The proposal must clearly and unambiguously state whether these key personnel have reviewed the proposal and endorsed their participation.

(6) Personnel / Biographical Sketches

The biographical sketch for each investigator should not exceed two pages. If the list of qualifications and publications exceeds two pages, select the most pertinent information (see Appendix E for details).

(7) Other Support (see Appendix E for details)

(8) Facilities and Equipment (see Appendix E for details)

(9) Special Matters (specific information on animal or human subjects protocol approval required, if applicable)

The Special Matters section must contain a statement from the investigator's institution that states that the proposed work will meet all Federal and local human subject requirements and animal care and use requirements, if applicable. Note that no animal subjects may be utilized unless specific information justifying and describing their use is included in the proposal. Policies regarding the protection of human research subjects in NASA-sponsored research are detailed in NASA Management Instruction (NMI) 7100.8B (Protection of Human Research Subjects), and animal care and use requirements are detailed in the NASA Code of Federal Regulations (CFR) 1232 (Care and Use of Animals in the Conduct of NASA Activities), both of which are available from the Office of Biological and Physical Research, Code UB, NASA Headquarters, Washington, DC 20546. Assurance of compliance with human subject or animal care provisions is required on Form A, to be submitted with each proposal. In addition, a letter signed by the chairperson of the Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC), or both, as appropriate, regarding approval of the experimental protocol, should be included with each copy of the proposal. If IRB or IACUC review is unavoidably delayed beyond the submission of the application, enter "Pending" on Line 9b or 10a of Form A, and be advised that the certification must be received within 60 days after the due date for which the application is submitted. If certification is not received within 60 days after the application due date, the application will be considered incomplete, and will not be reviewed. NASA shall require current IRB or IACUC certification prior to each year's award. All U.S., non-NASA proposals providing IACUC approval must also contain the institution's Public Health Assurance number.

(10) Detailed Budget

NASA is expected to be operating on the basis of full cost accounting as soon as possible, including all Civil Service salaries with overhead. In the interim period, proposals should use the accounting method authorized at their institutions at the time proposals are due and for the entire proposed period of performance. Funds to support the Resident Research Assistant (RRA) Postdoctoral Program costs (e.g., stipend, travel, computer time, supplies, etc.) are to be budgeted within the NASA intramural Principal Investigator budget.

The budget must include travel funds for the Principal Investigator to attend a biannual BR&C Principal Investigator meeting. If other travel is planned, the proposal budget should include appropriate travel funds for visits to NASA field centers (as appropriate) and presentation of findings at professional society meetings.

(11) Supporting Budgetary Information

In this solicitation, the terms "cost" and "budget" are used synonymously. Sufficient proposal cost detail and supporting information are required; funding amounts proposed with no explanation (e.g., Equipment: $1,000, or Labor: $6,000) may cause delays in evaluation and award. Generally, costs will be evaluated for realism, reasonableness, allowability, and allocation. The budgetary forms define the desired detail, but each category should be explained in this section. Offerors should exercise prudent judgment in determining what to include in the proposal, as the amount of detail necessarily varies with the complexity of the proposal.

The following examples indicate the suggested method of preparing a cost breakdown:

<u>Direct Labor</u>
Labor costs should be segregated by titles or disciplines with estimated hours and rates for each. Estimates should include a basis of estimate, such as currently paid rates or outstanding offers to prospective employees. This format allows the Government to assess cost reasonableness by various means including comparison to similar skills at other organizations.

<u>Other Direct Costs</u>
Please detail, explain, and substantiate other significant cost categories as described below:

<u>Subcontracts</u>: Describe the work to be contracted, estimated amount, recipient (if known), and the reason for subcontracting.
<u>Consultants</u>: Identify consultants to be used, why they are necessary, the time they will spend on the project, and the rates of pay (not to exceed the equivalent of the daily rate for Level IV of the Executive Schedule, exclusive of expenses and indirect costs).
<u>Equipment</u>: List separately. Explain the need for items costing more than $5,000. Describe basis for estimated cost. General purpose equipment is not allowable as a direct cost unless specifically approved by the NASA Grant Officer. Any equipment purchase requested as a direct charge must include the equipment description, how it will be used in the conduct of the basic research proposed, and why it cannot be purchased with indirect funds.
<u>Supplies</u>: Provide general categories of needed supplies, the method of acquisition, and estimated cost.
<u>Travel</u>: Describe the purpose of the proposed travel in relation to the grant and provide the basis of estimate, including information on destination and number of travelers (if known).
<u>Other</u>: Enter the total of direct costs not covered previously. Attach an itemized list explaining the need for each item and the basis for the estimate.

<u>Indirect Costs</u>
Indirect costs should be explained to an extent that will allow the Government to understand the basis for the estimate. Examples of prior year historical rates, current variances from those rates, or an explanation of other basis of estimates should be included. Where costs are based on allocation percentages or dollar rates, an explanation of rate and application base relationships

should be given. For example, the base to which the General and Administrative (G&A) rate is applied could be explained as: application base equals total costs before G&A less subcontracts.

All awards made as a result of this NRA will be funded as grants. However, while proposals submitted by "for profit" organizations are allowed, they cannot include a "fee."

(12) Appendices, if any (reviewers are not required to consider information presented in appendices)

How to Submit Proposal Cover Page Information:

All investigators planning to submit a proposal in response to this solicitation must electronically submit proposal cover page information online and provide a hard copy of the cover page attached to each proposal copy by January 31, 2002. The proposal cover page can be submitted and printed via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

- Login to SYS-EYFUS.
- To submit a New Proposal Cover Page, click the "New Proposal Cover Page" option from the SYS-EYFUS Options screen, and the New Proposals Cover Page screen will appear.
- If you previously submitted an NOI in response to this solicitation, choose to carry over the existing NOI. This option will populate the cover page fields with the NOI information. Edit the information as necessary, click "Continue" and proceed to the instructions for the Proposal Cover Sheet Submission Form below.
- If you did not previously submit an NOI, click on New Proposal Cover Page option, and the Division Specific Opportunities screen will appear.
- In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Proposal Cover Page Submission Form. Fill in all the fields. All fields are required.
  For the proposal type field on this form, new/no prior support means that the investigator has not received NASA funding from 1999 through 2001, new/prior support means that the investigator has received NASA funding between 1999 and 2001, and revised means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002. Click on "Continue."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the proposal. After you are done, click on "Continue." **IMPORTANT**: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Member Page, the Proposal Options Page appears.

- Please fill out the budget form by clicking on the "Budget" button, filling in project costs, and clicking "Continue." This will bring you to the Proposal Budget Review Page. Click "Continue" if the information is correct.
- After verifying your budget information, you will be returned to the Proposal Options Page. Click the "Show/Print" button.
- At the Page entitled Proposal Information Item List click "Continue" to preview your Proposal Cover Page. Print the cover page from your Internet browser once you have reviewed the information. The cover page must be signed by both the Principal Investigator and the authorizing official and attached to the font of your proposal before submission of hard copies to NASA.
- You may edit and resubmit your proposal cover page at any time before the submission deadline of January 31, 2002. Please note that once you submit a proposal cover page, it cannot be deleted. For title, team member, budget or any other changes, please edit your existing proposal cover page and resubmit changes to avoid duplicate records.
- One (1) signed original and twenty (20) copies of the proposal must be received by 5:00 PM on January 31, 2002, at the following address:
  NASA Peer Review Services
  Subject: 01-OBPR-07
  500 E Street SW, Suite 200
  Washington, DC 20024

CEVP proposals submitted by investigators from the International Space Life Sciences Working Group Agencies' (ISLSWG) members and approved for funding by the ISLSWG member agencies will be reviewed. U.S. co-investigators who are collaborating on such proposals with non-U.S. entities must ensure that their scientific role is clearly delineated in the proposal, that their expertise is shown to make a substantial contribution, and that their funding requirements are included in the proposal. Any proposals from non-U.S. entity must be endorsed by the respective government agency or funding/sponsoring institution in that country from which the non-U.S. participant is proposing. Such endorsement should indicate that the proposal merits careful consideration by NASA, and if the proposal is selected, sufficient funds will be made available to undertake the activity as proposed. This Letter of Endorsement from the sponsoring non-U.S. government agency or funding/sponsoring institution should be forwarded along with the proposal.

IX. Evaluation and Selection Process

Investigators should refer to Appendix A, Section IV, for a description of the review and selection process. Elements of review and selection unique to the CEVP are as follows:

Upon receipt, proposals will be reviewed for compliance with the requirements of this NRA.

Information resulting from the four levels of review noted below will, in turn, be used for making a selection recommendation by CEVP Science Managers for each of the program elements described in this NRA. This recommendation will be based on

1. Operational Relevance/Feasibility of Implementation
2. Countermeasure maturity/Scientific pedigree
3. Scientific or technical merit review score from the peer review panel

4. Programmatic cost of each proposal

The most important element in the evaluation process is the merit review, which carries the highest weight in final evaluation and selection. The other factors are approximately equal in weight to each other. Funding determination will be made by the Director of the Bioastronautics Research Division at NASA Headquarters for those proposals recommended by the CEVP Science Managers.

Instructions for Responding to NASA Research NRAs
NFS 1852.235-72

(a) General.

(1) Proposals received in response to a NASA Research Announcement (NRA) will be used only for evaluation purposes. NASA does not allow a proposal, the contents of which are not available without restriction from another source, or any unique ideas submitted in response to an NRA to be used as the basis of a solicitation or in negotiation with other organizations, nor is a pre-award synopsis published or individual proposals.

(2) A solicited proposal that results in a NASA award becomes part of the record of that transaction and may be available to the public on specific request; however, information or material that NASA and the awardee mutually agree to be of a privileged nature will be held in confidence to the extent permitted by law, including the Freedom of Information Act

(3) NRAs contain programmatic information and certain requirements which apply only to proposals prepared in response to that particular announcement. These instructions contain the general proposal preparation information which applies to responses to all NRAs.

(4) A contract, grant, cooperative agreement, or other agreement may be used to accomplish an effort funded in response to an NRA. NASA will determine the appropriate instrument. Contracts resulting from NRAs are subject to the Federal Acquisition Regulation and the NASA FAR Supplement. Any resultant grants or cooperative agreements will be awarded and administered in accordance with the NASA Grant and Cooperative Agreement Handbook (NPG 5800.1).

(5) NASA does not have mandatory forms or formats for responses to NRAs; however, it is requested that proposals conform to the guidelines in these instructions. NASA may accept proposals without discussion; hence, proposals should initially be as complete as possible and be submitted on the proposers' most favorable terms.

(6) To be considered for award, a submission must, at a minimum, present a specific project within the areas delineated by the NRA; contain sufficient technical and cost information to permit a meaningful evaluation; be signed by an official authorized to legally bind the submitting organization; not merely offer to perform standard services or to just provide computer facilities or services; and not significantly duplicate a more specific current or pending NASA solicitation.

(b) NRA-Specific Items. Several proposal submission items appear in the NRA itself: the unique NRA identifier; when to submit proposals; where to send proposals; number of copies required; and sources for more information. Items included in these instructions may be supplemented by the NRA.

(c) The following information is needed to permit consideration in an objective manner. NRAs will generally specify topics for which additional information or greater detail is desirable. Each proposal copy shall contain all submitted material, including a copy of the transmittal letter if it contains substantive information.

(1) Transmittal Letter or Prefatory Material.

(i) The legal name and address of the organization and specific division or campus identification if part of a larger organization;

(ii) A brief, scientifically valid project title intelligible to a scientifically literate reader and suitable for use in the public press;

(iii) Type of organization: e.g., profit, nonprofit, educational, small business, minority, women-owned, etc.;

(iv) Name and telephone number of the principal investigator and business personnel who may be contacted during evaluation or negotiation;

(v) Identification of other organizations that are currently evaluating a proposal for the same efforts;

(vi) Identification of the NRA, by number and title, to which the proposal is responding;

(vii) Dollar amount requested, desired starting date, and duration of project;

(viii) Date of submission; and

(ix) Signature of a responsible official or authorized representative of the organization, or any other person authorized to legally bind the organization (unless the signature appears on the proposal itself).

(2) Restriction on Use and Disclosure of Proposal Information. Information contained in proposals is used for evaluation purposes only. Offerors or quoters should, in order to maximize protection of trade secrets or other information that is confidential or privileged, place the following notice on the title page of the proposal and specify the information subject to the notice by inserting an appropriate identification in the notice. In any event, information contained in proposals will be protected to the extent permitted by law, but NASA assumes no liability for use and disclosure of information not made subject to the notice.

Notice: Restriction on Use and Disclosure of Proposal Information

The information (data) contained in [insert page numbers or other identification] of this proposal constitutes a trade secret and/or information that is commercial or financial and confidential or privileged. It is furnished to the Government in confidence with the understanding that it will not, without permission of the offeror, be used or disclosed other than for evaluation purposes; provided, however, that in the event a contract (or other agreement) is awarded on the basis of this proposal the Government shall have the right to use and disclose this information (data) to the extent provided in the contract (or other agreement). This restriction does not limit the Government's right to use or disclose this information (data) if obtained from another source without restriction.

(3) Abstract. Include a concise (200-300 word if not otherwise specified in the NRA) abstract describing the objective and the method of approach.

(4) Project Description.

(i) The main body of the proposal shall be a detailed statement of the work to be undertaken and should include objectives and expected significance; relation to the present state of knowledge; and relation to previous work done on the project and to related work in progress elsewhere. The statement should outline the plan of work, including the broad design of experiments to be undertaken and a description of experimental methods and procedures. The project description should address the evaluation factors in these instructions and any specific factors in the NRA. Any substantial collaboration with individuals not referred to in the budget or use of consultants should be described. Subcontracting significant portions of a research project is discouraged.

(ii) When it is expected that the effort will require more than one year, the proposal should cover the complete project to the extent that it can be reasonably anticipated. Principal emphasis should be on the first year of work, and the description should distinguish clearly between the first year's work and work planned for subsequent years.

(5) Management Approach. For large or complex efforts involving interactions among numerous individuals or other organizations, plans for distribution of responsibilities and arrangements for ensuring a coordinated effort should be described.

(6) Personnel. The principal investigator is responsible for supervision of the work and participates in the conduct of the research regardless of whether or not compensated under the award. A short biographical sketch of the principal investigator, a list of principal publications and any exceptional qualifications should be included. Omit social security number and other personal items which do not merit consideration in evaluation of the proposal. Give similar biographical information on other senior professional personnel who will be directly associated with the project. Give the names and titles of any other scientists and technical personnel associated substantially with the project in an advisory capacity. Universities should list the approximate number of students or other assistants, together with

information as to their level of academic attainment. Any special industry-university cooperative arrangements should be described.

(7) Facilities and Equipment.

(i) Describe available facilities and major items of equipment especially adapted or suited to the proposed project, and any additional major equipment that will be required. Identify any Government-owned facilities, industrial plant equipment, or special tooling that are proposed for use. Include evidence of its availability and the cognizant Government points of contact.

(ii) Before requesting a major item of capital equipment, the proposer should determine if sharing or loan of equipment already within the organization is a feasible alternative. Where such arrangements cannot be made, the proposal should so state. The need for items that typically can be used for research and non-research purposes should be explained.

(8) Proposed Costs (U.S. Proposals Only).

(i) Proposals should contain cost and technical parts in one volume: do not use separate "confidential" salary pages. As applicable, include separate cost estimates for salaries and wages; fringe benefits; equipment; expendable materials and supplies; services; domestic and foreign travel; ADP expenses; publication or page charges; consultants; subcontracts; other miscellaneous identifiable direct costs; and indirect costs. List salaries and wages in appropriate organizational categories (e.g., principal investigator, other scientific and engineering professionals, graduate students, research assistants, and technicians and other non-professional personnel). Estimate all staffing data in terms of staff-months or fractions of full-time.

(ii) Explanatory notes should accompany the cost proposal to provide identification and estimated cost of major capital equipment items to be acquired; purpose and estimated number and lengths of trips planned; basis for indirect cost computation (including date of most recent negotiation and cognizant agency); and clarification of other items in the cost proposal that are not self-evident. List estimated expenses as yearly requirements by major work phases.

(iii) Allowable costs are governed by FAR Part 31 and the NASA FAR Supplement Part 1831 (and OMB Circulars A-21 for educational institutions and A-122 for nonprofit organizations).

(iv) Use of NASA funds--NASA funding may not be used for foreign research efforts at any level, whether as a collaborator or a subcontract. The direct purchase of supplies and/or services, which do not constitute research, from non-U.S. sources by U.S. award recipients is permitted. Additionally, in accordance with the National Space Transportation Policy, use of a non-U.S. manufactured launch vehicle is permitted only on a no-exchange-of-funds basis.

(9) Security. Proposals should not contain security-classified material. If the research requires access to or may generate security-classified information, the submitter will be required to comply with Government security regulations.

(10) Current Support. For other current projects being conducted by the principal investigator, provide title of project, sponsoring agency, and ending date.

(11) Special Matters.

(i) Include any required statements of environmental impact of the research, human subject or animal care provisions, conflict of interest, or on such other topics as may be required by the nature of the effort and current statutes, executive orders, or other current Government-wide guidelines.

(ii) Proposers should include a brief description of the organization, its facilities, and previous work experience in the field of the proposal. Identify the cognizant Government audit agency, inspection agency, and administrative contracting officer, when applicable.

(d) Renewal Proposals.

(1) Renewal proposals for existing awards will be considered in the same manner as proposals for new endeavors. A renewal proposal should not repeat all of the information that was in the original proposal. The renewal proposal should refer to its predecessor, update the parts that are no longer current.

and indicate what elements of the research are expected to be covered during the period for which support is desired. A description of any significant findings since the most recent progress report should be included. The renewal proposal should treat, in reasonable detail, the plans for the next period, contain a cost estimate, and otherwise adhere to these instructions.

(2) NASA may renew an effort either through amendment of an existing contract or by a new award.

(e) Length. Unless otherwise specified in the NRA, effort should be made to keep proposals as brief as possible, concentrating on substantive material. Few proposals need exceed 15-20 pages. Necessary detailed information, such as reprints, should be included as attachments. A complete set of attachments is necessary for each copy of the proposal. As proposals are not returned, avoid use of "one-of-a-kind" attachments.

(f) Joint Proposals.

(1) Where multiple organizations are involved, the proposal may be submitted by only one of them. It should clearly describe the role to be played by the other organizations and indicate the legal and managerial arrangements contemplated. In other instances, simultaneous submission of related proposals from each organization might be appropriate, in which case parallel awards would be made.

(2) Where a project of a cooperative nature with NASA is contemplated, describe the contributions expected from any participating NASA investigator and agency facilities or equipment which may be required. The proposal must be confined only to that which the proposing organization can commit itself. "Joint" proposals which specify the internal arrangements NASA will actually make are not acceptable as a means of establishing an agency commitment.

(g) Late Proposals. Proposals or proposal modifications received after the latest date specified for receipt may be considered if a significant reduction in cost to the Government is probable or if there are significant technical advantages, as compared with proposals previously received.

(h) Withdrawal. Proposals may be withdrawn by the proposer at any time before award. Offerors are requested to notify NASA if the proposal is funded by another organization or of other changed circumstances which dictate termination of evaluation.

(i) Evaluation Factors.

(1) Unless otherwise specified in the NRA, the principal elements (of approximately equal weight) considered in evaluating a proposal are its relevance to NASA's objectives, intrinsic merit, and cost.

(2) Evaluation of a proposal's relevance to NASA's objectives includes the consideration of the potential contribution of the effort to NASA's mission.

(3) Evaluation of its intrinsic merit includes the consideration of the following factors of equal importance:

(i) Overall scientific or technical merit of the proposal or unique and innovative methods, approaches, or concepts demonstrated by the proposal.

(ii) Offeror's capabilities, related experience, facilities, techniques, or unique combinations of these which are integral factors for achieving the proposal objectives.

(iii) The qualifications, capabilities, and experience of the proposed principal investigator, team leader, or key personnel critical in achieving the proposal objectives.

(iv) Overall standing among similar proposals and/or evaluation against the state-of-the-art.

(4) Evaluation of the cost of a proposed effort may include the realism and reasonableness of the proposed cost and available funds.

(j) Evaluation Techniques. Selection decisions will be made following peer and/or scientific review of the proposals. Several evaluation techniques are regularly used within NASA. In all cases, proposals are subject to scientific review by discipline specialists in the area of the proposal. Some proposals are reviewed entirely in-house; others are evaluated by a combination of in-house and selected external reviewers; while yet others are subject to the full external peer review technique (with due regard for conflict-of-interest and protection of proposal information), such as by mail or through assembled panels. The final decisions are made by a NASA selecting official. A proposal which is scientifically and programmatically meritorious, but not selected for award during its initial review, may be included in subsequent reviews unless the proposer requests otherwise.

(k) Selection for Award.

(1) When a proposal is not selected for award, the proposer will be notified. NASA will explain generally why the proposal was not selected. Proposers desiring additional information may contact the selecting official who will arrange a debriefing.

(2) When a proposal is selected for award, negotiation and award will be handled by the procurement office in the funding installation. The proposal is used as the basis for negotiation. The contracting officer may request certain business data and may forward a model award instrument and other information pertinent to negotiation.

(l) Additional Guidelines Applicable to Foreign Proposals and Proposals Including Foreign Participation.
Only ground-based proposals submitted in response to this NRA from U.S. entities, or from non-U.S. entities that involve substantive co-investigator collaboration from a U.S. entity, will be reviewed. U.S. co-investigators who are collaborating on such proposals with non-U.S. entities must ensure that their scientific role is clearly delineated in the proposal, that their expertise is shown to make a substantial contribution, and that their funding requirements are included in the proposal. Proposals from non-U.S. entities with significant co-investigator collaboration from a U.S. entity must be endorsed by the respective government agency or funding/sponsoring institution in that country from which the non-U.S. participant is proposing. Such endorsement should indicate that the proposal merits careful consideration by NASA, and if the proposal is selected, sufficient funds will be made available to undertake the activity as proposed. This Letter of Endorsement from the sponsoring non-U.S. government agency or funding/sponsoring institution should be forwarded along with the proposal.

All proposals from non-U.S. entities which involve substantive co-investigator collaboration from a U.S. entity must be typewritten in English and comply with all other submission requirements stated in this NRA. These proposals will undergo the same evaluation and selection process as those originating in the U.S. All proposals must be received before the established closing date. Sponsoring foreign government agencies or funding institutions for proposals from non-U.S. entities meeting the above guidelines may, in exceptional situations, forward a proposal without endorsement to the above address if endorsement is not possible before the announced closing date. In such cases, the NASA sponsoring office should be advised when a decision on endorsement can be expected.

Successful and unsuccessful non-U.S. proposers will be contacted directly by the NASA sponsoring office. Copies of these letters will be sent to the sponsoring government agency or funding institution. Should a non-U.S. proposal with significant U.S. participation be selected, NASA's Office of External Relations will arrange with the foreign sponsoring agency or funding institution for the proposed participation on a non-exchange-of-funds basis, in which NASA and the non-U.S. sponsoring agency or funding institution will each bear the cost of discharging their respective responsibilities.

Depending on the nature and extent of the proposed cooperation, this arrangement may entail:

(1) a letter of notification by NASA;
(2) an exchange of letters between NASA and the sponsoring foreign governmental agency; or
(3) a formal Agency-to-Agency Memorandum of Understanding (MOU).

Export Control Guidelines Applicable to Foreign Proposals and Proposals Including Foreign Participation.

Proposals including foreign participation must include a section discussing compliance with U.S. export laws and regulations, e.g., 22 CFR Parts 120-130 and 15 CFR Parts 730-774, as applicable to the circumstances surrounding the particular foreign participation. The discussion must describe in detail the proposed foreign participation and is to include, but not be limited to, whether or not the foreign participation may require the prospective proposer to obtain the prior approval of the Department of State or the Department of Commerce via a technical assistance agreement or an export license, or whether a license exemption/exception may apply. If prior approvals via licenses are necessary, discuss whether the license has been applied for or if not, the projected timing of the application and any implications for the schedule. Information regarding U.S. export regulations is available at http://www.pmdtc.org and http://www.bxa.doc.gov. Proposers are advised that under U.S. law and regulations, spacecraft and their specifically designed, modified, or configured systems, components, and parts are generally considered "Defense Articles" on the United States Munitions List and subject to the provisions of the International Traffic in Arms Regulations (ITAR), 22 CFR Parts 120-130.

(m) Cancellation of NRA. NASA reserves the right to make no awards under this NRA and to cancel this NRA. NASA assumes no liability for canceling the NRA or for anyone's failure to receive actual notice of cancellation.

CERTIFICATION REGARDING DEBARMENT, SUSPENSION, AND OTHER RESPONSIBILITY MATTERS

PRIMARY COVERED TRANSACTIONS

This certification is required by the regulations implementing Executive Order 12549, Debarment and Suspension, 14 CFR Part 1269.

A. The applicant certifies that it and its principals:

(a) Are not presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from covered transactions by any Federal department or agency;

(b) Have not within a three-year period preceding this application been convicted or had a civil judgment rendered against them for commission of fraud or a criminal offense in connection with obtaining, attempting to obtain, or performing a public (Federal, State, or Local) transaction or contract under a public transaction; violation of Federal or State antitrust statutes or commission of embezzlement, theft, forgery, bribery, falsification or destruction of records, making false statements, or receiving stolen property;

(c) Are not presently indicted for or otherwise criminally or civilly charged by a government entity (Federal, State, or Local) with commission of any of the offenses enumerated in paragraph A.(b) of this certification; and

(d) Have not within a three-year period preceding this application/proposal had one or more public transactions (Federal, State, or Local) terminated for cause or default; and

B. Where the applicant is unable to certify to any of the statements in this certification, he or she shall attach an explanation to this application.

C. Certification Regarding Debarment, Suspension, Ineligibility and Voluntary Exclusion - Lowered Tier Covered Transactions (Subgrants or Subcontracts)

a) The prospective lower tier participant certifies, by submission of this proposal, that neither it nor its principles is presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from participation in this transaction by any federal department of agency.

b) Where the prospective lower tier participant is unable to certify to any of the statements in this certification, such prospective participant shall attach an explanation to this proposal.

This page has been included for your information.

CERTIFICATION REGARDING LOBBYING

As required by S 1352 Title 31 of the U.S. Code for persons entering into a grant or cooperative agreement over $100,000, the applicant certifies that:

(a) No Federal appropriated funds have been paid or will be paid by or on behalf of the undersigned, to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, in connection with making of any Federal grant, the entering into of any cooperative, and the extension, continuation, renewal, amendment, or modification of any Federal grant or cooperative agreement;

(b) If any funds other than Federal appropriated funds have been paid or will be paid to any person for influencing or attempting an officer or employee of any agency, Member of Congress, an or an employee of a Member of Congress in connection with this Federal grant or cooperative agreement, the undersigned shall complete Standard Form - LLL, "Disclosure Form to Report Lobbying," in accordance with its instructions.

(c) The undersigned shall require that the language of this certification be included in the award documents for all subawards at all tiers (including subgrants, contracts under grants and cooperative agreements, and subcontracts), and that all subrecipients shall certify and disclose accordingly.

This certification is a material representation of fact upon which reliance was placed when this transaction was made or entered into. Submission of this certification is a prerequisite for making or entering into this transaction imposed by S1352, title 31, U.S. Code. Any person who fails to file the required certification shall be subject to a civil penalty of not less than $10,000 and not more than $100,000 for each such failure.

This page has been included for your information.

CERTIFICATION OF COMPLIANCE WITH THE NASA REGULATIONS PURSUANT TO NONDISCRIMINATION IN FEDERALLY ASSISTED PROGRAMS

The (Institution, corporation, firm, or other organization on whose behalf this assurance is signed, hereinafter called "Applicant") hereby agrees that it will comply with Title VI of the Civil Rights Act of 1964 (P.L. 88-352), Title IX of the Education Amendments of 1962 (20 U.S. 1680 et seq.), Section 504 of the Rehabilitation Act of 1973, as amended (29 U.S. 794), and the Age Discrimination Act of 1975 (42 U.S. 16101 et seq.), and all requirements imposed by or pursuant to the Regulation of the National Aeronautics and Space Administration (14 CFR Part 1250) (hereinafter called "NASA") issued pursuant to these laws, to the end that in accordance with these laws and regulations, no person in the United States shall, on the basis of race, color, national origin, sex, handicapped condition, or age be excluded from participating in, be denied the benefits of, or be otherwise subjected to discrimination under any program or activity for which the Applicant receives federal financial assistance from NASA; and hereby give assurance that it will immediately take any measure necessary to effectuate this agreement.

If any real property or structure thereon is provided or improved with the aid of federal financial assistance extended to the Applicant by NASA, this assurance shall obligate the Applicant, or in the case of any transfer of such property, any transferee, for the period during which the real property or structure is used for a purpose for which the federal financial assistance is extended or for another purpose involving the provision of similar services or benefits. If any personal property is so provided, this assurance shall obligate the Applicant for the period during which the federal financial assistance is extended to it by NASA.

This assurance is given in consideration of and for the purpose of obtaining any and all federal grants, loans, contracts, property, discounts, or other federal financial assistance extended after the date hereof to the Applicant by NASA, including installment payments after such date on account of applications for federal financial assistance which were approved before such date. The Applicant recognized and agrees that such federal financial assistance will be extended in reliance on the representations and agreements made in this assurance, and the United States shall have the right to seek judicial enforcement of this assurance. His assurance is binding on the Applicant, its successors, transferees, and assignees, and the person or persons whose signatures appear below are authorized to sign on behalf of the Applicant.

This page has been included for your information.

Appendix O

NATIONAL
SPACE BIOMEDICAL
RESEARCH INSTITUTE

EDUCATION AND PUBLIC OUTREACH
PROJECT SUMMARIES
YEAR 5 - FY 2002

September 30, 2002

NSBRI EDUCATION AND PUBLIC OUTREACH PROGRAM FUNDED PROJECTS

Team Leader: **MacLeish, M. T.** **Morehouse School of Medicine**

NSBRI AREA:	**Education and Public Outreach**
PRINCIPAL INVESTIGATOR:	**Patrick J. Gannon, Ph.D.**
ORGANIZATION:	**Mount Sinai School of Medicine**
PROJECT:	**Defying Gravity: Enduring Life in Space**

Project Executive Summary

The 1996 National Science Education Standards (NSES) reported that scientific literacy has become increasingly important in the US workplace where people are more often required to learn, reason, think creatively, make informed decisions and solve problems. However, results of the 3rd International Mathematics and Science Survey reported a marked decline in science and mathematical knowledge from 8th-12th grades in the US compared to an international average of 41 countries, many of which have invested in creation of a scientifically literate workforce. As such, we have chosen to focus our science educational outreach efforts on the 9th grade, which we consider to represent a potentially pivotal, formative educational stage at which to confront this underperformance and to help them prepare for the new NY Regents Living Environment exam.

NSES also recommended that inquiry-based curricula should be the new educational model applied for generation of enthusiasm, learning, understanding and a respect of science. We propose to extend the NSES strategy by generation of a genuine enthusiasm for learning science and math, via presentation in the classroom by MSSM scientists and mathematicians of "working models" of space biomedical research. Subsequently, development of a stand-alone curriculum will allow science teachers to utilize the theme in various courses of study. In order to address issues related to goals stated within NSBRI's educational outreach mission, we plan to integrate fundamental concepts of biomedicine with basic science and mathematics in the rich and enticing framework of space exploration. We propose a novel research-based educational outreach program entitled "DEFYING GRAVITY: Enduring Life in Space" to symbolize how a basic body plan, that evolved over many millions of years for life on earth within "Normal Gravity," may adapt to endure and solve any problems encountered in "Microgravity" and function efficiently. Goals for exploration of this compelling concept are to provide: 1) a "unifying theme" that will afford meaningful links between the wide breadth of issues related to human health in Earth's "normal" gravity and in space's microgravity; 2) insight into the scientific knowledge essential for formulation of countermeasures, and how they will be implemented to ensure the well being of humans who spend long periods of time in space, and 3) working models of scientific and mathematical principles.

The basic *Defying Gravity* curriculum will be fine-tuned, primarily assessed, and then adjusted as considered necessary within partnership/teams of MSSM scientists/educators, high school science teachers and students of the "MSSM Teacher's Summer Institute 2001: A Space Research Odyssey" (TSI). This will represent the penultimate formulation phase of the program's curriculum.

A fully formed first-run curriculum, presented as semi-formal "research lab meeting" style seminars/workshops followed by hands-on laboratory sessions with group discussion, will demonstrate: 1) current paradigms and unifying principles that relate research to space biomedicine; 2) approaches used to devise and test hypotheses (i.e., the Scientific Method); 3) integration of mathematical principles as they relate to concepts and common themes with the biological and physical sciences and technology; and 4) how to formulate components of, collect, organize, analyze, graph, and interpret, data. The new Life Sciences Secondary School, with an "underrepresented" and academically challenged, minority (>95%) student population, will represent a first level test site over the second and third years. Selected curriculum components will also be applied during the third year by MSSM-TSI participant 'lab mentor' teachers, as a stand-alone product to a wide and more diverse group of 9th-11th grade students and to other teachers and students within the well-established Gateway Program (Slater and Iler, 1991; Iler and Slater, 1998). These schools will represent second level, broader spectrum, test sites. Additional curriculum components will be incorporated within these test sites as the program progresses. Both formative and summative measures will be used for example: to determine mid point progress, clarify program strengths and weaknesses and sum up overall program impact.

Products derived from the *Defying Gravity* program will include: 1) A hard copy of the stand-alone curriculum with lesson plans and hands-on laboratory experiences; 2) An interactive www-site version of the stand-alone curriculum with downloadable text, images and digital video/audio sessions; live (scheduled) scientist discussion room; teacher's lounge email FAQ and questions (modeled on the well designed and tested "NEURON NEUROLAB ONLINE" www page; 3) Interactive CD Rom's of selected curriculum components, produced by NSBRI's Morehouse School of Medicine with Public Broadcasting Atlanta's studio (Dr. Marlene MacLeish with Milton Clipper and Wayne C. Sharpe, in years 2 and 3); 4) "High School Teaching for Biomedical Scientists" handbook; 5) An interactive, hands-on exhibit at the New York Hall of Science, of selected curriculum components; and 6) National multi-media outreach/dissemination via MSSM and NSBRI/PBA channels.

NSBRI AREA:	**Education and Public Outreach**
PRINCIPAL INVESTIGATOR:	**Deborah L. Illman, Ph.D.**
ORGANIZATION:	**University of Washington - *Northwest Science and Technology* Magazine**
PROJECT:	**Northwest Outreach Program on Space Biomedical Research**

Project Executive Summary

The overall goals of this outreach project at the University of Washington (UW) are to develop new ways to communicate more effectively with the public about space biomedical science and technology, and to attract bright young minds to careers in this field.

Our project objectives are to:
1. Develop and disseminate articles on space biomedical research via *Northwest Science & Technology* (*NWS&T*) Magazine, a new regional science publication with a circulation of over 30,000 in the Pacific Northwest region and beyond, and furthermore, to involve student writers in our science writing curriculum and in development of these articles;
2. Develop/adapt and disseminate special materials on space biomedical research for middle school students and their parents and teachers by means of an insert in *NWS&T*;
3. Improve the ability of scientists and public information officers to communicate with general audiences by developing and delivering a science writing workshop for NSBRI consortium members; and
4. Attract students in the pipeline to careers in space biomedical research by means of a summer experience for high school students in the laboratories of NSBRI projects at the UW.

During the first year of the project, we have accomplished the following tasks in support of these objectives:

1. Magazine Articles on Space Biomedical Research

- Developed a series of articles for *Northwest Science & Technology* Magazine on space biomedical topics:

  "UW Joins Effort to Advance Space Biomedical Technology," Holli Riebeek, *NWS&T*, Autumn 2001, pp. 6-8.

  "Flying Higher and Faster: An Interview with Astronaut Susan Helms," Cover Story by Holli Riebeek and Deborah Illman, *NWS&T*, Winter 2002, pp. 14-20.

  "Great Expectations: Virtual Reality," Holli Riebeek, *NWS&T*, Spring 2002, pp. 22-28.

  "Biomedical Studies Should Take Priority on International Space Station: Research on human adaptation to space is likely to benefit terrestrial medicine," Editorial by Martin J. Kushmerick, *NWS&T*, Spring 2002, p. 58.

  SciScape insert for middle school students, Spring 2002, by Holli Riebeek.
- Provided support and experiential learning opportunities for a master's level science writing student, Holli Riebeek, to develop these articles. Ms. Riebeek graduated in June 2002 and is

currently serving as technology journalism intern in New York at *IEEE Spectrum*, the flagship publication of the Institute for Electrical and Electronics Engineers.

- Added 4,500 names of middle school science teachers and administrators from Washington, Oregon, Idaho, Montana, and Alaska to our magazine distribution list to receive these articles and insert.
- Published and disseminated an announcement by Baylor College of Medicine on the NSBRI-funded teaching series "From Outerspace to Innerspace" in the Autumn 2001 issue.
- Published and disseminated full-page color displays about NSBRI in Winter, Spring, and Autumn 2002 issues.
- Technical Communication undergraduate student Sara Causey helped to develop a second issue of *SciScape* on space/biomedical content to be published in a future issue of *NWS&T*.
- Provided support for Technical Communication student Marita Graube to develop an article on space exercise for inclusion in the Winter 2003 issue.

2. Middle School Insert

- Developed the concept and design for *NWS&T SciScape*, our insert for middle school students, with input from educators and writers with special expertise for this age group.
- The first of two NSBRI-sponsored inserts was published in Spring 2002 and copies supplied to the outreach team leader.
- Developed an evaluation tool to obtain feedback from users of *SciScape*.

3. Improving Communication with General Audiences

- With funding from the UW College of Engineering for UW School of Communications Ph.D. student Fiona Clark, we completed a content analysis of recent *New York Times* coverage of space-related events and issues. Our objective was to characterize current journalistic practices with regard to space exploration and space biomedical research, and to provide a benchmark against which future developments in coverage can be assessed.

4. Summer Experience for High School Students

- Implemented a recruitment plan in conjunction with Washington Space Grant to identify high school students to work in the laboratories of UW-NSBRI investigators during summer quarter 2002. The plan was carried out through the 2001-02 academic year culminating in the placement of 4 students in NSBRI-related laboratories at the University of Washington and successful completion of the program by all 4 students.
- Developed a participation plan for UW-NSBRI investigators to take part in the selection process and tours for 40 high school seniors who are applying for Washington Space Grant scholarships, thereby highlighting topics in space biomedical research for a wider pool of students in the pipeline.

NSBRI AREA:	**Education and Public Outreach**
PRINCIPAL INVESTIGATOR:	**Robert K. James, Ph.D.**
ORGANIZATION:	**Texas A&M University**
PROJECT:	**NSBRI Teacher Academy Project**

Project Executive Summary

The Vision

The vision of NSBRI TAP is to engage middle level students in the highly motivational study of manned space flight to Mars. The project is designed as an avenue to promote improvement in and to contribute to the reform science education in this country. One of the critical pathways to reform is through the nation's classrooms and the conduit to those classrooms is through teachers. NSBRI TAP has developed the exciting concept of producing a national cadre of 90 Fellows of the Academy, trained to lead space science workshops in each state of the nation with the focus on NSBRI research. The Teacher Academy is being developed and refined as a model that can be disseminated nationally.

The Mission

The mission of NSBRI TAP is to prepare this national cadre of space science teacher-leaders that can assist other local middle school teachers to implement cutting-edge, space-based science activities in their classrooms. These activities are related to NASA's planned Mission to Mars. There are approximately half a million middle school classrooms in the nation and space-based science provides exciting, creative and inclusive instructional activities that engage middle level students. The goal is for the Fellows of the Academy to have a significant impact on the space science teaching of their peers and their students nationwide. Through the joint efforts of NSBRI scientists and Fellows of the Academy, information about and the vision needed for public support of a Mission to Mars is being shared.

The Impact

The impact on teachers of NSBRI TAP is already being felt after the first year:
Over one thousand teachers estimated to serve at least 100,000 students were reached through Academy Teachers' workshops and this has made the job of recruiting teachers for this year's summer institute much easier. Word has spread that this is an exciting project that provides good teacher support and is looked upon favorably by schools and their districts.

There is a long waiting list of applicants and it appears likely that after three years the project will have managed to recruit a teacher/leader from each state in the nation.

Sessions, delivered at regional and national conferences by both teacher participants and TAP staff, have been well attended. This suggests that NSBRI research is a topic that interests teachers and their students.

Teacher participants in the program bring with them an infectious enthusiasm and a passion for space science. The teachers thirst after the kind of information that can be imparted to them about NSBRI research. NSBRI scientists at Texas A&M University volunteer their time during the summer institute to share this research information enthusiastically with the teachers. Four of these NSBRI scientists serve on the project's Advisory Board.

Future Plans

Plans are already in place for this year's NSBRI TAP Summer Institute, held partly at Texas A&M University, College Station with research contributions from NSBRI scientists on site and at Johnson Space Center, Houston, Texas. One of these scientists, Dr. Michael Delp, will educate the teachers about his experiment that will fly on STS-107 in July 2002. This is certainly exposing them to science at the cutting-edge. Participating teachers will be welcomed to the Academy by Dr. Ron White, Associate Director of NSBRI and they will hear a closing presentation from Dr. John Charles, a NASA Code U Mission Scientist, on the future directions of manned space flight. It promises to be an exciting and productive year, building on the good foundation laid during 2001-2002 with the help of synergistic partnerships that have been developed.

NSBRI AREA:	**Education and Public Outreach**
PRINCIPAL INVESTIGATOR:	**Marlene Y. MacLeish, Ed.D.**
ORGANIZATION:	**Morehouse School of Medicine**
PROJECT:	**Secondary and College Education for the Next Generation of Space Life Scientists**

Project Executive Summary

Three schools – Baylor College of Medicine (BCM), Morehouse School of Medicine (MSM), and Texas A&M University (TAMU) – have strategic responsibility to effect the National Space Biomedical Research Institute's (NSBRI) education and pubic outreach mission. MSM has been funded by the NSBRI for the past three years to support national science education reform through the production of innovative secondary education curriculum supplements and the development of a pipeline of minority group science students. MSM is requesting continued funding for four ongoing projects and one new initiative to support this mission.

The four ongoing projects are: the NSBRI Teacher Fellowship Program, a collaboration with the DeKalb School System - Fernbank Space Station and Georgia State University SECME programs; the Summer Research Program which enrolls college students to do summer research in a MSM science laboratory; an undergraduate level course, The Human Body in Space, taught at Spelman College; and the NSBRI Film Archive. MSM is proposing a fifth initiative - the production of an undergraduate textbook on the human body and weightlessness.

The Teacher Fellowship Program aims to support the professional development of secondary teachers by engaging them in the production of innovative problem-based science cases. The fellow is using the Harvard problem-based case model to write a cardiovascular case, *Bobby's Beat*. The fellow will attend the TAMU Teacher Academy Program to introduce this method to science teachers enrolled in that program and to learn leadership skills to effect change when the fellow returns to their home system. Georgia State University SECME will sponsor the 2001 teacher fellow. This Program also enrolls one student intern. The 2000 student intern produced the video, *Immortal Heavens*. A second intern will be selected in Spring 2001 to work on *Bobby's Beat*.

The Summer Research Program provides research opportunities for four undergraduate students to engage in a research intensive internship at MSM, learn about space biomedical research from an eminent space sciences guest lecturer, and meet role models involved in space biomedical research. To date, 13 students, selected from a competitive applicant pool, have participated in the intensive 12-week research program. A longitudinal database exists on the students to measure the outcome of the program.

The NSBRI Film Archive contains over 150 hours of video relating to NASA's Neurolab mission, NSBRI team science, and the Human Body in Space course. Film and design footage are made available to NSBRI consortium member schools as well as other organizations. The Discovery Channel, ZDF-German TV, RDF Television-London, the Atlanta and DeKalb public schools, and the SciTrek and Fernbank museums have used materials from the archive. This one-of-a-kind repository will be used to develop interactive Internet accompaniments to the proposed textbook and the problem-based cases written by the teacher fellows.

The proposed textbook on the human body and weightlessness will enrich teaching of space biological sciences at the undergraduate level. A well-designed textbook that uses a multidisciplinary perspective to elicit their understanding of the world is timely. The need for such a text is amply demonstrated by the Spelman College, Colorado State University and Johns Hopkins University courses that rely on collated materials from disparate sources. Existing course materials do not adequately meet national undergraduate science education standards and are not uniformly appropriate for an undergraduate audience.

NSBRI AREA:	**Education and Public Outreach**
PRINCIPAL INVESTIGATOR:	**Dava J. Newman, Ph.D.**
ORGANIZATION:	**Massachusetts Institute of Technology**
PROJECT:	**Space Biomedical Sciences and Engineering Curriculum and Outreach Program**

Project Executive Summary

Mission:
Our mission is to provide the National Space Biomedical Research Institute (NSBRI) with a multi-level Space Life Sciences curriculum, and to excite and educate the public about the wonders of science, engineering and medicine by disseminating knowledge gained in NSBRI research areas. Our project is directly contributing to the need for developing graduate and undergraduate level curriculum, as well as to the need for transfer of advanced space life sciences knowledge into material appropriate for younger students and the general public.

Basic Approach:
The team includes academia and two small businesses, both of whom significantly contribute to our outreach program. We are developing and teaching graduate level courses at the Massachusetts Institute of Technology. The curricula are modular and cover eight of the twelve NSBRI research areas, and hence they can be distributed and used in other NSBRI affiliated universities. The two graduate courses are: "Space Biomedical Engineering and Life Support" (SBE) and "Sensori-Neural Systems: Spatial Orientation from Vestibular End Organs to Behavior and Adaptation" (SNS).

The curriculum and student term projects from the SBE course serves as a starting point for the development of undergraduate level curriculum and provide the topical areas for outreach at the high school and public outreach levels. We are developing and will teach a freshman course devoted to the same space biomedical topics that are covered in the graduate level course. The high school level outreach encompasses Anatomy and Physiology class laboratories that focus on the debilitating effects of long duration microgravity on the human body. These are part of a greater engineering design curriculum, entitled "Spacercise", which challenges students to design the best countermeasure exercise machine for space. For the public, we have completed a conceptual design for the 'knowledge station' that allows learners to interact with curricular materials via state-of-the-art information technology and a physical platform that is designed specifically to facilitate human interaction and learning.

Attention to assessment has been paramount in our curricular efforts and learning will be assessed in all our efforts. We have developed two Assessment Guideline Tutorials that give advice to teachers/instructors on 1) effective feedback and 2) learning styles and teaching. A third tutorial is under development and explores the topic of 'Questioning' and getting students involved in taking responsibility for their own learning.

Strengths and Major Accomplishments:
Within Year 1, we have taught the two proposed graduate level courses. "Space Biomedical Engineering and Life Support" was taught in the Fall of 2001 and the "Sensori-Neural Systems" was piloted in the Spring of 2002 at MIT through the Harvard-MIT Health Sciences and

Technology Program. Both courses had NSBRI affiliated researchers, from several different disciplines, participation as guest or active lecturers.

Development of the undergraduate version of "Space Biomedical Engineering" (SBE UG) has begun with the identification of appropriate level materials as well as a website that parallels the graduate site. Extensive discussions and planning with three external academic sites that wish to offer the SBE UG curriculum have commenced, namely, Smith College, the Naval Academy, and the University of Maryland. In Year 2 of our efforts we will assist with teaching and implement the SBE UG course at Smith College in conjunction with their new undergraduate degree in engineering. We are also planning on offering a Fall 2003 (grant Year 2) freshman seminar at MIT.

Three "Spacercise" laboratories are being developed, of which two are scheduled to be piloted in the Fall 2002 (grant Year 2). During Year 1, the Everett Public High School (Everett, MA) was identified as a possible site for piloting the Spacercise labs. Three Everett High School teachers are currently working with us to develop the inquiry-based labs for the Anatomy and Physiology classes. Based on discussions with the teachers, it was decided that three labs should be developed, each covering one of the following topics: the Skeletal, Muscular, and the Cardiovascular systems. Within each unit, students will gain an understanding of the basic anatomy and physiology of each system as well as an application of the effects of long duration spaceflight on each system.

Three conceptual designs for a "Knowledge Station" were completed and a final concept chosen, namely, the "Knowledge Sphere" design. Visualizations of the Knowledge Sphere, Knowledge Spider, and Knowledge World designs were completed and electronic visualizations and 3D models have been completed for the Knowledge Sphere and Spider concepts.

Future:
In Year 2, our goals include further curriculum development of graduate and undergraduate courses. Our assessment and feedback gained during Year 1 will lead to re-designed and enhanced curriculum content for both graduate courses. The graduate curriculum development efforts will lead to SBE and SNS being taught again in academic year 2003-2004 (grant Year 3). In Year 2, we will focus on finishing developing the undergraduate "Space Biomedical Engineering" (SBE UG) course, and plan to offer it at MIT (grant Year 3) and Smith College (grant Year 2). The "Spacercise" laboratories will be completed and piloted in the Fall of 2002 at the Everett Public High School. The prototyping of the Knowledge Sphere commences and plans for deployment and a pilot study at the Peabody Essex Museum (Salem, MA), the Museum of Science (Boston, MA), and a public mall (Cambridge, MA) will be finalized.

NSBRI AREA:	**Education and Public Outreach**
PRINCIPAL INVESTIGATOR:	**Roland B. Smith, Jr., Ed.D.**
ORGANIZATION:	**Rice University**
PROJECT:	**Outreach Program for the Professional Development of Students and Teachers on Studies Related to Biomedicine in Outer Space**

Project Executive Summary

The United States continues to feel the effects of declining student interest in science and scientifically related careers. At the same time, high school science teachers have limited opportunity to enhance their scientific knowledge in a manner that would inspire the interest of their students in science careers. In response to these challenges, the Rice/UTMB Outreach Program is dedicated to furthering the NSBRI mission to communicate the significance of space life sciences and microgravity biotechnology to local and national audiences, while disseminating the biomedical knowledge gained through research programs to the classroom and community.

Our goals are to attract young people to space-related enrichment programs, promote excellence and innovation in America's science education system, and enhance the scientific background among teachers, students, their families, and the community as a whole. This is achieved through a program consisting of two parts: 1) the Academic Development of High School Students (Student Research) and 2) the Teacher Institute for the Advancement of Space Science Education (Teacher Institute). Students and teachers were involved in the ongoing space biomedicine research projects conducted at Rice and UTMB, including those in the areas of i) bone and musculoskeletal loss, ii) integrated human function, iii) immunology, infection, and hematology, iv) neurovestibular adaptation, and v) technology development.

For the Student Research component, twelve high school students conducted laboratory research from June to August, taking advantage of the academic environment at both Rice and UTMB. Their interactions extended beyond those in their own laboratory through a series of workshops designed to expose young scientists to researchers and the wide variety of research being conducted in the field of space biomedicine. The research experiences were supplemented by field trips designed to motivate students to pursue scientific research as a career.

The Teacher Institute continued throughout the academic year after beginning with an intensive two-week session held in June. Sixteen secondary teachers enhanced their scientific knowledge of space biomedicine through interactive discussions with space biomedical researchers, a one-day, hands-on research experience performing activities in some of the existing NSBRI and NASA educational modules, and special tours of NASA Johnson Space Center and Space Center Houston. Teachers applied their knowledge toward the design of a space biomedicine mini-module/unit plan to be taught in class during the academic year and refined for publishing on the educational resources web sites of Rice, UTMB and the NSBRI. Both student and teacher components were monitored and evaluated by an external evaluator.

Rice University has a long-standing commitment to the greater Houston area through its 54 K-12 outreach initiatives, many of which are programs for student enrichment and professional development of teachers focused in the area of science and mathematics education. Rice University, founded in 1892, is consistently ranked one of America's best teaching and research universities. It is distinguished by its size, with 2,700 undergraduates, 1,500 graduate students, an undergraduate student-to-faculty ratio of 5-to-1, selectivity (10 applicants for each place in the freshman class), and the fourth largest endowment per student among private American universities. Rice maintains a residential college system, which builds communities that are both close-knit and diverse. Its collaborative culture crosses disciplines and integrates teaching, research and service throughout the University community. Rice University's K-12 outreach projects number 67 separate programs, of which over half are specifically designed to enhance science and mathematics education in area schools.

UTMB has a long-term interactive partnership with the nine Galveston County school districts through a variety of K-12 programs including summer science research camps for 7-12 grade students, science teacher workshops, and an annual Regional Science Teacher Conference. The University of Texas Medical Branch at Galveston (UTMB), founded as a medical school in 1891, has grown into a major health science center comprising four schools, two institutes, and seven hospitals. Its campus lies on the East End of the Galveston Island, encompassing 64 acres and consisting of more than 50 major buildings. The total space allocated at UTMB is approximately 332,000 net square feet. During the last fiscal year approximately 500 research projects were conducted with external funding. An estimated 250 additional projects were conducted without external funding. The graduate school of biological sciences, consisting of about 275 faculty members and 300 students, confers the Ph.D. degree mainly in the fields of Biochemistry, Human Genetics, Cell Biology, Microbiology, Neuroscience, and Pharmacology and Toxicology.

The collaborative, interdisciplinary spirits of both institutions extend beyond their campuses to the Texas Medical Center, Baylor College of Medicine, NASA – Johnson Space Center, and other educational institutions. The synergy created by the combined scientific and educational expertise at Rice and UTMB has culminated in an outstanding program that will not only benefit the participating students and teachers, but also the community at-large.

Assisting Dr. Roland B. Smith, Jr., Associate Provost - Rice University and Chair of the Educational Outreach Council and Dr. Clifford W. Houston, Associate Vice President for Educational Outreach – The University of Texas Medical Branch, who serve as Co-Principal Investigators were the following individuals. For the Student Research Component, Dr. Kate Beckingham – Professor in the Department of Biochemistry and Cell Biology, Rice University and Dr. Vimlarani Chopra – Assistant Professor in the Department of Obstetrics and Gynecology, The University of Texas Medical Branch, served as Co-Investigators and managed the laboratory research activities of students assigned to their respective campus, 6 each for a total of 12. For the Teacher Institute, team members from Rice University were Ms. Nanda Kirkpatrick – Director of Precollege Science Education Programs and Ms. Debbie Jensen – Science Curriculum Specialist in the Department of Biochemistry and Cell Biology. Teams members from the University of Texas Medical Branch included Ms. Marsha Ricks – Director of Science Education Programs (through August, 2001) and Dr. Marguerite Sognier –Assistant Director of Science Education Programs. Dr. Sognier is also a Staff Scientist at NASA/JSC/USRA. Ms. Marty Daniel - Instructional Technology Specialist in the Pre-College Science Education Program at Rice University was responsible for creating and maintaining the web site for both the student research and teacher professional development components of the grant. Administrative support for programs on both the Rice and UTMB campuses was provided by Ms. Sharon Bush – Educational Outreach Administrator, Office of the Associate Provost, which included budget management, procurement, administrative reports, and serving as the administrative liaison for the NSBRI Education Outreach Team, Dr. Marlene MacLeish-Morehouse College and Dr. William Thomson – Baylor College of Medicine, Co-Directors. Administrative support for the UTMB campus was provided by Ms. Sylvia Torres – Administrative Manager, Education Outreach Office.

NSBRI AREA:	**Education and Public Outreach**
PRINCIPAL INVESTIGATOR:	**William A. Thomson, Ph.D.**
ORGANIZATION:	**Baylor College of Medicine**
PROJECT:	**From Outer Space to Inner Space: Sharing NSBRI Progress with the Community**

Project Executive Summary

NSBRI's Education and Public Outreach Team activities are developed and implemented jointly by Team partners, in coordination with the NSBRI leadership, to assure that Team projects address NSBRI program objectives. The Education and Public Outreach Team's mission is to communicate the significance and excitement of space life sciences to local, national and international audiences, while transferring and disseminating knowledge gained by the biomedical advances achieved by other NSBRI Research Teams. This mission is being accomplished through an integrated array of programs that focus on students and educators at all grade levels, as well as the general public. Specific Team objectives address (1) Teacher Professional Development, (2) Curriculum Development, (3) Science Literacy and Public Awareness and (4) Access and Career Awareness.

Each partner institution within NSBRI's Education and Public Outreach Team has created its own specific aims (based on individual strengths, expertise and other factors) to address larger Team objectives. BCM elected to focus its NSBRI-sponsored outreach activities on elementary and middle school students, teachers and families. These activities include the creation of unique teaching materials, delivery of professional development to teachers by multiple partners, and use of broadcast media to convey general science and health messages to the target populations. Original project aims at Baylor College of Medicine (BCM) are as follow.

1. Collaboratively create, evaluate and disseminate one interdisciplinary teaching unit per year, based on NSBRI research themes for middle school students.
2. Improve teacher practice and content knowledge through multiple professional development opportunities conducted in formal and informal educational settings.
3. Develop an online workshop resource for NSBRI scientists to use for outreach to teachers, students and the community-at-large.
4. Create and implement cost-effective models for communicating NSBRI research to local and national populations through television and radio short-format news and newsmagazine stories.

<u>Key Findings</u>. Activities carried out by BCM during the 2001-2002 Award Year relate directly to our original NSBRI proposal and the aims described therein. We currently are examining evaluation data from BCM's Year One NSBRI activities, and the results will be presented in our Year Two report. However, preliminary results and anecdotal evidence reinforce the encouraging findings of our initial NSBRI outreach efforts.

During Year One, more than 750 teachers, representing about 18,000 students nationwide, were reached through BCM's NSBRI professional development at various venues, including Space Center Houston. Field tests results are showing that our NSBRI instructional units are effective, interesting to students and teachers, and simple enough for teachers to use without participating in special training.

In addition, we are finding that space life science topics are appealing to the general public when presented via television or radio formats. During Year One, approximately 9,000,000 potential viewers had an opportunity to see NSBRI-focused stories on Houston Public Television. BCM also produced three NSBRI *Radio HealthLine* stories, which were distributed to 2,900 radio stations nationwide.

The enthusiastic response from a diverse and large audience demonstrates that space life sciences provide an interesting, flexible and effective foundation for educational outreach activities at numerous levels. Equally important, we are finding that the space exploration is an excellent introduction to any number of science, health and other educational topics.

Impacts of Findings. Through its educational and outreach efforts, BCM is working to transfer the excitement and real-world applications of NSBRI research into the nation's classrooms and homes. Teachers and students across the US are using activities guides created by BCM to bring NSBRI science to the elementary and middle school level. Meanwhile, BCM is working with the local Houston public television affiliate (KUHT-TV) to produce and broadcast television news spots and programs that bring space life sciences to the general public.

Based on our project evaluators, BCM's NSBRI efforts have had a significant positive impact in classrooms. We are using teacher feedback to continue refining the instructional model upon which we base our teaching materials. In particular, we are working to ensure that BCM's NSBRI-related programs address identified needs of students to develop problem-solving and critical thinking abilities, as well as language skills within a real world context.

Research Plan for Coming Year. The experiences of Year One and data gathered during the previous funding period are guiding the development of BCM's NSBRI Education and Public Outreach activities over the coming year. BCM's original project aims (listed on page 1) will remain largely intact during Year Two and in future years. However, our aims and strategic plan will be slightly revised to address identified shortcomings and maximize Team strengths. Year Two objectives and strategies are described below.

Year Two Objectives

1. Analyze field test results and reviews by specialists of the *Food and Fitness* unit, and produce a final version of this teacher guide for national dissemination by institutional members of the Education and Public Outreach Team and other NSBRI partners.
2. Create, evaluate and disseminate an interdisciplinary, teaching unit (tentatively entitled "Disease and Infection") for middle school students, based on NSBRI research themes.
3. Improve teacher practice and content knowledge through multiple professional development opportunities conducted in formal and informal educational settings
4. Continue to develop and implement cost-effective models for communicating NSBRI research to local and national populations through public media.

These objectives will be achieved through teacher professional development and space life science curricular materials development. In addition, BCM will work with the media, particularly KUHT-TV and BCM's TV HealthLine, to promote the overarching NSBRI objectives and educate the general population about exciting developments among NSBRI scientific teams and the broader space life sciences community.

Appendix P

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

Annual Program Report: *Education and Public Outreach Team*

October 31, 2002

Team Leader
Marlene MacLeish, Ed.D.
Professor, Medical Education
Morehouse School of Medicine
720 Westview Drive, SW
Atlanta, Georgia 30310
Phone: 404-756-5706; Fax: 404-752-1043
Email: macleim@msm.edu

Associate Team Leader
William A. Thomson, Ph.D.
Professor, Family and Community Medicine
Baylor College of Medicine
1709 Dryden, Suite 519
Houston, Texas 77030
Telephone: 713-798-8200; Fax: 713-798-8201
Email: wthomson@bcm.tmc.edu

EDUCATION AND PUBLIC OUTREACH TEAM PROJECTS

Defying Gravity: Enduring Life in Space

Principal Investigator: Patrick J. Gannon, Ph.D.

Address:	Mount Sinai School of Medicine Box 1189 One Gustave L. Levy Place New York, New York 10029-6574
Telephone:	212-426-1549
Fax:	212-831-3700
E-mail:	Patrick.gannon@mssm.edu

Northwest Outreach Program on Space Biomedical Research

Principal Investigator: Deborah L. Illman, Ph.D.

Address:	University of Washington Box 352195 Seattle, Washington 98195-2195
Telephone:	206-685-9317
Fax:	206-685-9210
E-mail:	illman@u.washington.edu

National Space Biomedical Research Institute Teacher Academy Project

Principal Investigator: Robert James, Ph.D.

Address:	Texas A&M University College of Education, MS 4232 College Station, Texas 77843-4232
Telephone:	979-845-8185
Fax:	979-845-9663
E-mail:	rjames@tamu.edu

Secondary and College Education for the Next Generation of Space Life Scientists

Principal Investigator: Marlene MacLeish, Ed.D.

Address:	Morehouse School of Medicine 720 Westview Drive, S.W. Atlanta, Georgia 30310-1495
Telephone:	404-756-5706
Fax:	404-752-1043
E-mail:	macleim@msm.edu

Space Biomedical Sciences and Engineering Curriculum and Outreach Project

Principal Investigator: Dava J. Newman, Ph.D.

Address:	Massachusetts Institute of Technology 77 Massachusetts Ave., Room 33-307 Cambridge, MA 02139
Telephone:	617-258-8799
Fax:	617-253-4196
E-mail:	dnewman@mit.edu

Outreach Program for the Professional Development of Students and Teachers on Studies Related to Biomedicine in Outer Space

Principal Investigator: Roland B. Smith, Ed.D.

Address:	Rice University Office of Associate Provost-MS 3 P.O. Box 1892 Houston, Texas 77251-1892
Telephone:	713-348-5688
Fax:	713-348-5759
E-mail:	rbsmith@rice.edu

From Outer Space to Inner Space: Sharing NSBRI Progress with the Community

Principal Investigator: William A. Thomson, Ph.D.

Address:	Baylor College of Medicine 1709 Dryden, Suite 519 Houston, Texas 77030
Telephone:	713-798-8200
Fax:	713-798-8201
E-mail:	wthomson@bcm.tmc.edu

TABLE OF CONTENTS

I. ABSTRACT

The Nation's education needs have been framed by the President's challenge to, "leave no child behind" and the 21st century workplace requirement for a science literate society. Such ambitions require bold vision and strong leadership for systemic change across the educational spectrum. NASA Administrator Sean O'Keefe has taken up this challenge, stating, "Education is part of our [NASA's] core mission." That mission includes the goal, "to inspire the next generation of explorers. . . as only NASA can."

The National Space Biomedical Research Institute (NSBRI) Education and Public Outreach Team has been working to achieve these directives through a coordinated, multi-institutional strategy that helps to meet our nation's education needs. This strategy is designed specifically to assist in educating the next generation of space biomedical researchers and to transfer the medical and biomedical findings of space research to the scientific community, the home and the classroom. The Team's mission is to communicate the significance and excitement of space life sciences to local, national and international audiences, while transferring and disseminating knowledge gained by the biomedical advances achieved by other NSBRI Research Teams. This mission currently is being accomplished through an integrated array of programs that focus on students and educators at all grade levels, as well as the general public. The Education and Public Outreach Team develops and implements activities that address the following four major goals:

- Design and conduct a variety of **teacher professional development** programs to help teachers understand space life sciences and change their practices and behaviors to improve the learning experiences they provide students.
- Develop **curricular materials** that span the educational continuum; are aligned with national science education standards; provide accurate, balanced, effective and inquiry-based instruction; and expand students' understanding of and interest in ongoing NSBRI research.
- Promote **educational access and career awareness** in bioastronautics research among high school and undergraduate students, as well as high school teachers.
- Increase **scientific literacy and public awareness** of the real-life impacts of NSBRI research through media, informal science activities, direct mailings and journal publications.

The Education and Public Outreach Team is comprised of seven primary partners: Baylor College of Medicine (BCM); Massachusetts Institute of Technology (MIT); Morehouse School of Medicine (MSM); Mount Sinai School of Medicine (MSSM); Rice University and The University of Texas Medical Branch (RU/UTMB); Texas A&M University (TAMU); and the University of Washington (UW). Twenty-seven other organizations and institutions—including state public school systems, public television and radio stations, state space grant programs and museums—are working with the Team to promote its mission and to ensure the widest possible dissemination of its products and programs.

The Education and Public Outreach Team is helping NSBRI to address the educational goals set forth by President Bush and Administrator O'Keefe. Hundreds of teachers and thousands of students have benefited from the Team's NSBRI-sponsored programs; and the public has been reached through television and radio news programs and national magazine articles. The Team's ongoing efforts are establishing NSBRI as a leading resource for bringing the excitement and importance of NSBRI space life science research into the nation's classrooms and homes.

II. INTRODUCTION

The mission of the NSBRI Education and Public Outreach Team is to communicate the significance and excitement of space life sciences to local, national and international audiences, while transferring and disseminating knowledge gained via the biomedical advances achieved by NSBRI Research Teams. This mission is being accomplished through an integrated array of programs focusing on students and educators at all grade levels, as well as the general public. Team goals are as follows:

- Design and conduct a variety of **teacher professional development** programs to help teachers understand space life sciences and change their practices and behaviors to improve the learning experiences they provide students.
- Develop **curricular materials** that span the educational continuum; are aligned with national science education standards; provide accurate, balanced, effective and inquiry-based instruction; and expand students' understanding of and interest in ongoing NSBRI research.
- Promote **educational access and career awareness** in bioastronautics research among high school and undergraduate students, as well as high school teachers.
- Increase **scientific literacy and public awareness** of the real-life impacts of NSBRI research through media, informal science activities, direct mailings and journal publications.

III. PROGRAM STRUCTURE AND DESIGN

The Education and Public Outreach Team is comprised of seven primary partners: Baylor College of Medicine (BCM) in Houston, Texas; Mt. Sinai School of Medicine (MSSM) in New York, New York; Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts; Morehouse School of Medicine (MSM) in Atlanta, Georgia; Rice University and The University of Texas Medical Branch (RU/UTMB) in Houston and Galveston, Texas; Texas A&M University (TAMU) in College Station, Texas; and the University of Washington (UW) in Seattle, Washington.

A number of major organizations and institutions are working with NSBRI's Education and Public Outreach Team. Notable among these partners are (in alphabetical order): Aldine Independent School District, Atlanta Public Television and Radio, DeKalb Public Schools, Emory University, Fernbank Museum, the nine Galveston County school districts, Georgia Institute of Technology-SECME Program, Georgia State Partnership for Excellence in Education, Harvard Medical School, Houston Independent School District, Houston Public Television, Johnson Space Center, New York Public Schools, New York Hall of Science, Space Center Houston, Spelman College, Texas Alliance for Science, Mathematics and Technology, Texas Rural Systemic Initiative, the Texas Statewide Systemic Initiative, and the Washington Space Grant program.

Synergy among individual project goals is achieved through the following four themes: teacher professional development; curriculum development; science literacy and public awareness; and access and career awareness. The following charts show how the teams work with each other.

NSBRI Education and Public Outreach Team Activities, 2001-2002

	GOAL ADDRESSED				PHASE I	PHASE II
PI/PROJECT	**Teacher Professional Development**	**Curriculum Development**	**Science Literacy and Public Awareness**	**Career Awareness and Access**	**Planning Implementation Evaluation**	**Dissemination**
Patrick J. Gannon *Defying Gravity: Enduring Life in Space*	Science Teacher Summer Workshops, Institutes	9th Grade Curriculum	Museum Exhibits Newsletter and Websites	Museum Exhibits Newsletter and Websites	Project Year 2	
Deborah L. Illman *Northwest Outreach Program on Space Biomedical Research*			NSBRI Magazine Stories; Science Communications Workshops	NSBRI Magazine Stories; Middle School "SciScape" Inserts	Project Year 2	
Robert James *NSBRI Teacher Academy Project*	Master NSBRI Teacher Program Teacher Workshops				Project Year 2	
Marlene MacLeish *Secondary and College Education for the Next Generation of Space Life Scientists*	Year-long Residency Program for 16 Secondary School Teachers	Undergraduate Course Problem-based Cases: 5-12 Grade	NSBRI Film Archive	Undergraduate Summer Program	Project Year 5	Curriculum Materials Available
Dava J. Newman *Space Biomedical Sciences & Engineering Curriculum and Outreach Project*		Undergraduate and Graduate Courses; K-12 Materials	Modular *Knowledge Stations* (Interactive Exhibit)	Modular *Knowledge Stations* (Interactive Exhibit)	Project Year 2	
Roland B. Smith *Outreach Program for Development of Students and Teachers on Studies Related to Biomedicine in Outer Space*	Year-long Program for 16 Secondary School Teachers	Teacher-developed Units		Summer Research Experiences for 12 High School Students	Project Year 2	
William A. Thomson *From Outer Space to Inner Space: Sharing NSBRI Progress with the Community*	Summer Workshops and Workshops at Professional Meetings	Three NSBRI-focused Teacher Units Completed (for Middle School)	Radio and television stories; Space Center Houston Activities	Radio and television stories; Space Center Houston Activities	Project Year 5	Curriculum Materials Available

IV. PROGRAM ACCOMPLISHMENTS, NOVEMBER 2001-OCTOBER 2002

Baylor College of Medicine—*From Outer Space to Inner Space: Sharing NSBRI Progress with the Community*.

- Conducted 11 NSBRI unit workshops for 221 teachers, representing more than 5,000 students. Workshops received an overall 4.9 rating by participants (out of a possible 5.0).
- Filled requests from around the US for more than 3,200 copies of BCM's NSBRI Teacher Guides and more than 1,600 NSBRI classroom posters.

- Space Center Houston (at NASA) also disseminated more than 1,500 copies of BCM's *From Outer Space to Inner Space* materials.
- Incorporated NSBRI activities into other programs:
  - used in a summer professional development program, funded by the National Science Foundation, for 120 lead science teachers in the Houston Independent School District;
  - implemented in workshops for eight scientists and 16 teachers participating in BCM's Science Education Leadership Fellows program, funded by the Howard Hughes Medical institute; and
  - utilized by Space Center Houston in its annual Teacher Camp-in, held in April for approximately 300 Houston-area teachers.
- Completed and field-tested (with 22 teachers) a new NSBRI Teachers Guide, *Food and Fitness*. This third unit in the *From Outer Space to Inner Space* series produced statistically significant increases on pre- /post-test student scores related to awareness and knowledge of issues involving to cardiovascular fitness, nutrition and the importance of diet and exercise.
- Began developing the fourth unit in the *From Outer Space to Inner Space* series, entitled *Infection and Disease*.
- BCM's Office of Public Affairs created and aired one NSBRI-focused radio broadcast as part of its Radio Healthline series, which is distributed nationally via the Associated Press. This spot is entitled "Living in Cramped Quarters."
- BCM's Office of Public Affairs created and aired one NSBRI-focused television broadcast for its TV HealthLine series, which is distributed to 80 TV stations around the nation and is shown on Continental Airlines. This piece is entitled "Helping Astronauts Adjust to Gravity."
- Collaborated with KUHT-TV, Houston Channel, Public Broadcasting affiliate, to produce and air four live television segments on science and health for families, based on BCM's NSBRI educational materials.
- Published an article entitled "Night and Day in One Class Period" in the *Texas Science Teacher*. This article, which discusses one of the activities in BCM's NSBRI Teacher Guide, *Sleep and Daily Rhythms*, will appear in the upcoming October issue of the journal.

Massachusetts Institute of Technology – *Space Biomedical Sciences and Engineering Curriculum and Engineering Curriculum and Outreach Project*

- Taught graduate level course: "Space Biomedical Engineering and Life Support" (Fall 2001).
- Developed and taught graduate level course: "Sensori-Neural Systems: Spatial Orientation from Vestibular End Organs to Behavior and Adaptation" (Spring 2002).
- Developing undergraduate version of "Space Biomedical Engineering" for dissemination in multiple universities.
- Developed high school level anatomy and physiology laboratories that focus on space biomedical sciences and engineering principles.
- Completed conceptual designs for "Knowledge Stations," to be used by the public at large.
- Developed two assessment guidelines tutorials for teachers/instructors on 1) effective feedback and 2) learning styles and teaching.

Morehouse School of Medicine—*Educating the Next Generation of Space Life Scientists*.

The MSM Teacher Institute

- Admitted 15 science teachers to a yearlong Teacher Institute representing 1,760 students.
- Complete three modules: National/Local Education Challenges; Metacognition Workshop; *A Private Universe:* Science Misconceptions. Modules received 5.0 rating (out of possible 5.0) by participants.
- Sponsored guest lecturer – SECME Executive Director, Dr. Yvonne Freeman.
- Provided support for two science teachers to attend SECME, Howard University 2002.
- Provided leadership training for the Texas A&M Teacher Academy Program.
- Completed second draft of a cardiovascular problem-based case, *Bobby's Beat*.
- Initiated design work for *Bobby's Beat*, Fall 2002.

Summer Research Program

- Four undergraduate students completed a ten–week intensive research program including: circadian biology laboratory research; weekly journal club presentations; school-wide poster session/final oral presentation; science writing workshop; core laboratory skills and ethics training.
- Longitudinal database maintained to measure program outcomes.
- Exit interviews and evaluation completed by each student.
- Conducted three space life sciences modules for 26 National Youth Leadership Forum students.

NSBRI Film Archive

- Provided graphics and other technology support for all MSM programs and products.
- Responded to NSBRI Public Affairs requests for film footage.
- Provided initial art for cardiovascular problem-based case.

Mt. Sinai School of Medicine—*Defying Gravity: Enduring Life in Space*

- Completed Beta-testing of 8 (multi - component; twice-monthly) educational modules
- Produced digital video of all lessons, scientist presentations and labs, to be utilized for site testing.
- Produced *End Of DG Beta Phase* Newsletter with a "Beta Test Student Spectacular" component that featured chosen commentary articles written by seven student participants and editorial piece "Teaching to the Future."
- Presented 3 DG modules to participants of NSBRI-TAP.
- Design and produced teachers workshop on feedback/evaluation mechanism.
- Collected workshop feedback/evaluation (& site-test recruitment) forms from 25 NSBRI-TA-02 participants.
- Conducted *Mini Summer Institute:* Five day meeting with program assessment faculty to rank 8 beta tested modules; fine tune teacher's workshop feedback/evaluation mechanism; design and produce site testing feedback/evaluation mechanism.
- Produced kits and lesson components for use in modules during the off site-testing phase.
- Established partnerships with nationally recognized Gateway Institute for Pre-College Education and local school districts for site testing and evaluation.
- Prepared manuscript for NSTA journal *The Science Teacher*, "Defying Gravity: A Partnership for Research, Teaching and Learning."

Rice University/University of Texas Medical Branch—*Space Science Education*

- Enrolled 16 high school teachers in a yearlong residence to develop space biomedicine curriculum modules.
- Completed a special tour for selected teachers of NASA Johnson Space and Center and The University of Texas Medical Branch laboratories to support curriculum content and design.
- Teachers participated in a regional science conference and exhibited curriculum exercises developed during the two-week summer program.
- Initiated field-testing of instructional activities developed during the two-week professional development program.
- Completed summer research internship program for 12 high school students that included laboratory research, weekly research seminars series conducted by faculty, field trips to Johnson Space Center/NASA, and a brown bag lunch discussion of career opportunities.

Texas A&M University—*Teacher Academy Program (TAP)*

- Completed an 11-day summer institute (at Texas A&M University and Johnson Space Center, Houston) for 21 participants from 17 states.
- TAP 2002 included Dr. Richard Braeucker from the German Institut fur Luft und Raumfahrtmedizin (DLR), with the expectation that he will adapt various components of the TAP model for use in Germany.
- Delivered workshops for teachers at Texas Science Teachers' Conference (CAST) November 2001, Austin, TX; Civil Air Patrol (CAP) November 2001, Cocoa Beach, FL; Texas Science Summit November 2001, San Antonio, TX; National Science Teachers' Conference (NSTA) December 2001, Memphis, TN; International Space Station Conference, February 2002, Houston, TX; National Science Teachers' Annual Conference, March 2002, San Diego, CA; Alabama Aerospace Teachers' Conference, March 2002, Opelika, AL; Civil Air Patrol National Conference, April 2002, Arlington, VA.
- Delivered a paper at the Association for Educators of Teachers of Science (AETS) March 2002, Charlotte, NC.
- Taught 2,630 students, of whom 161 are African-American, 191 are Asian, 611 are Hispanic and 34 are Native American.
- Delivered a workshop for 250 teachers at the National Middle School Conference in Portland, OR, November 1, 2002.
- Established a website and a discussion group on-line.
- Developed a NSBRI-TAP teacher training resource book, which is been tested by 2002-3 participants.
- Initiated recruitment for TAP-2003 to target 17 states that have yet to send a teacher to the Institute.
- From the first cohort of teachers (2001-2002), 24 have earned the distinction of becoming Fellows of the NSBRI-TAP.

The University of Washington—*Northwest Outreach Program on Space Biomedical Research*

- Developed and disseminated articles on space biomedical research in *Northwest Science & Technology (NWS&T)* magazine, including a cover story on Astronaut Susan Helms, to approximately 30,000 readers.
- Recruited four students who completed the 2002 high school summer research program.

- Developed insert for young readers, called *SciScape*, on space biomedical research and disseminated to secondary school teachers throughout the greater Pacific Northwest.
- Furnished articles in electronic form to NSBRI for website.
- Completed a study of media coverage of space; article submitted to *Science Communication*.

V. IMPLICATIONS OF CURRENT ACCOMPLISHMENTS

The National Space Biomedical Research Institute (NSBRI) Education and Public Outreach Team is addressing NASA's educational mission and increasing the visibility of NSBRI research through teacher professional development, curriculum development, science literacy/public awareness and career awareness and access. An impressive array of programs has been planned and implemented. From November 2001 through October 2002, NSBRI teacher professional development reached close to 2,000 teachers nationally and up to 100,000 students through teacher summer institutes at Baylor College of Medicine and Mt Sinai School of Medicine, year-long teacher residency programs at Morehouse School of Medicine, Rice University/University of Texas at Galveston, and Texas A&M University. These NSBRI teams also presented NSBRI educational workshops at national meetings and in informal science settings, including Space Center Houston.

Curriculum materials development during the 2001-2002 project year included development of graduate and undergraduate level courses at MIT and the University of Maryland ("Space Biomedical Engineering and Life Support;" "Sensori-Neural Systems: Spatial Orientation from Vestibular End Organs to Behavior and Adaptation;" and "Space Biomedical Engineering").

Teacher and scientist teams at Morehouse (*Bobby's Beat*), Mt. Sinai (*Defying Gravity: Enduring Life in Space*) and MIT (*Spacercise*) are focusing on the continued need to transfer space life science knowledge to younger students. These three projects have developed innovative high school materials and instructional strategies that are being field tested in multiple settings. NSBRI middle school teacher guides developed by Baylor (*From Outer Space to Inner Space* series) have been disseminated throughout the nation and have attracted the interest of a major commercial publisher. Negotiations are currently underway to license these materials to promote worldwide distribution of NSBRI teacher materials.

Also, during 2002, the University of Washington developed magazine stories and special magazine inserts in *Northwest Science* that promote space life science and NSBRI awareness throughout the Northwest. Television stories and appearances by BCM faculty and museum partnerships with Mt. Sinai and MIT also have enhanced awareness of NSBRI among the general public. In addition, public awareness and pipeline activities include the Morehouse School of Medicine, Rice/UTMB, and Mt. Sinai summer research and enhancement programs for high school and undergraduate students.

Between November 2001 and October 2002, the NSBRI Education and Outreach Team significantly increased interaction with NASA-based education activities. These collaborations have included teacher professional development (JSC, KSC, Space Center Houston and Space Grant Consortium Lift-Off Institute). NSBRI is now invited to participate in national meetings and workshops with other NASA educators. Indeed, as demonstrated in this report, Team members have begun to make more NSBRI-focused presentations at national and international meetings. The NSBRI Education Team Lead, along with a BCM faculty member, will present a NSBRI education overview and a workshop on NSBRI-developed educational materials at the OBPR Leading Great Research in Space Annual Educational and Public Outreach Training Retreat, November 16-22, 2002 in Montana.

In combination, the accomplishments of the 2001-2002 project year have helped to establish NSBRI Education and Public Outreach as an important national participant across the educational continuum in space life science education. As additional exposure occurs through ongoing and new activities, NSBRI Education and Public Outreach will continue to advance and gain greater levels of national/international recognition. Despite this progress, however, Team institutions must pay more attention to manuscript development and submission. Team members have agreed on the importance of this activity and have established the goal of one publication per team each year. When this very realistic goal is reached, NSBRI Education and Public Outreach will truly have established itself and NSBRI as a national leader in space education.

Marlene MacLeish, Ed. D.
Team Leader
Education and Public Outreach Team

Appendix Q

NSBRI Summer Interns at JSC

INTERNS	UNIVERSITY	LAB SUPERVISOR	LAB ASSIGNMENT
Batdorf, Niles J.	University of Minnesota, Twin Cities	Todd Schlegel	JSC Neurosciences Lab
Beck, Ryann H.	Georgia Institute of Technology	Todd Schlegel	JSC Neurosciences Lab
Douglas, Pamela	Johns Hopkins University	Todd Schlegel	JSC Neurosciences Lab
Evans, Richard (Todd)	Johns Hopkins University	Alan Feiveson	JSC Statistical Analysis Lab
Graham, Christine	Vanderbilt University	Kathy Major	NSBRI Public Affairs 1st 6 weeks/JSC Public Affairs 2nd 6 weeks
Hughes, Catherine Smith	Texas A&M University	Mihriban Whitmore	JSC Usability Testing and Analysis Facility
Leskin, Katherine	Massachusetts Institute of Technology	William Paloski	JSC Neurophysiology Biomechanics Lab
Moore, Mary Kim	Baylor University	Janice Meck	JSC Cardiovascular Lab