Biofabrication 2024

Biofabrication in space - A Perspective

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Outline

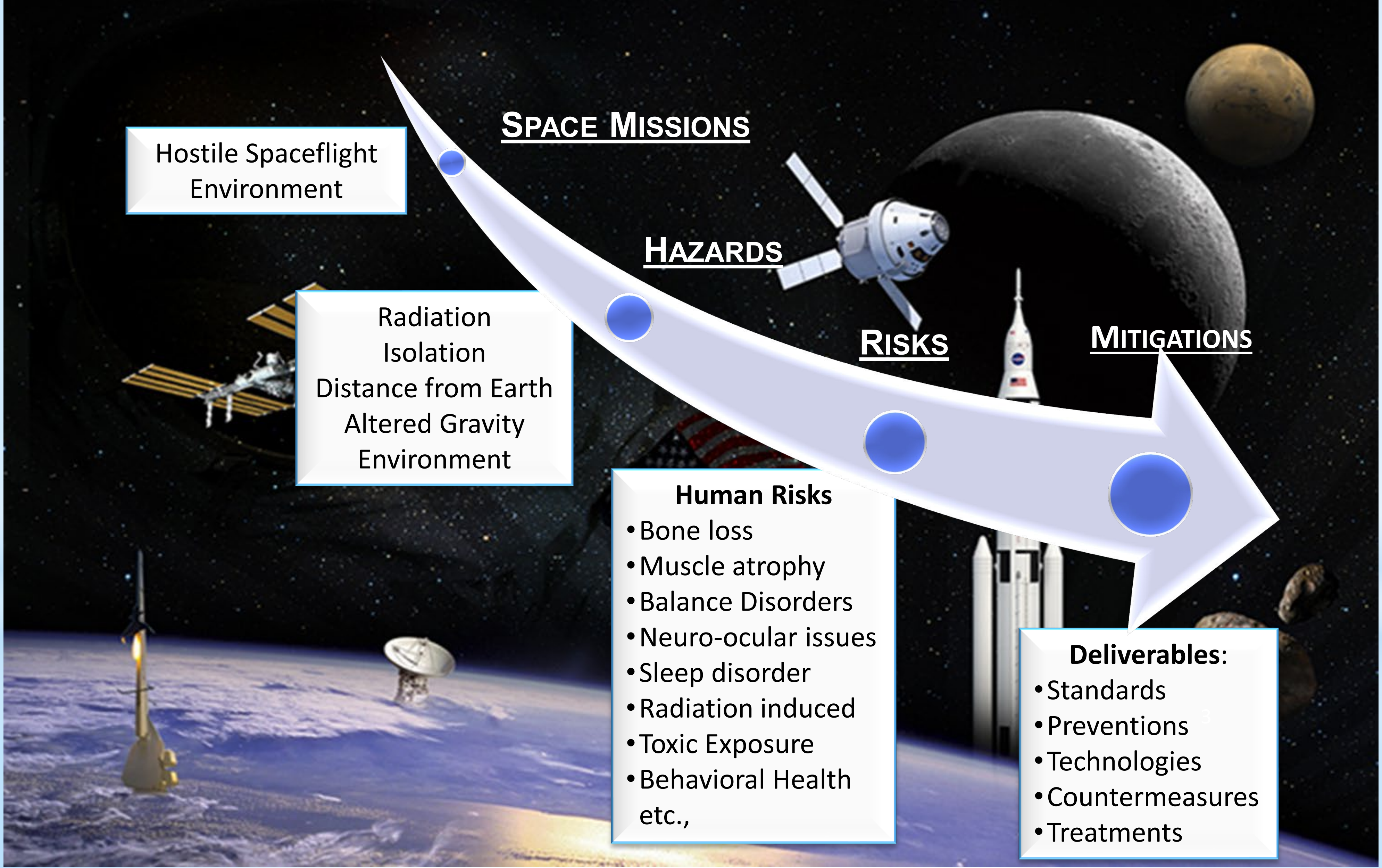
- Human System level Perturbations during long term (more than three months) space missions at ISS

- Tissue Engineering efforts in Space Shuttle and ISS

- Tissue regeneration in Space

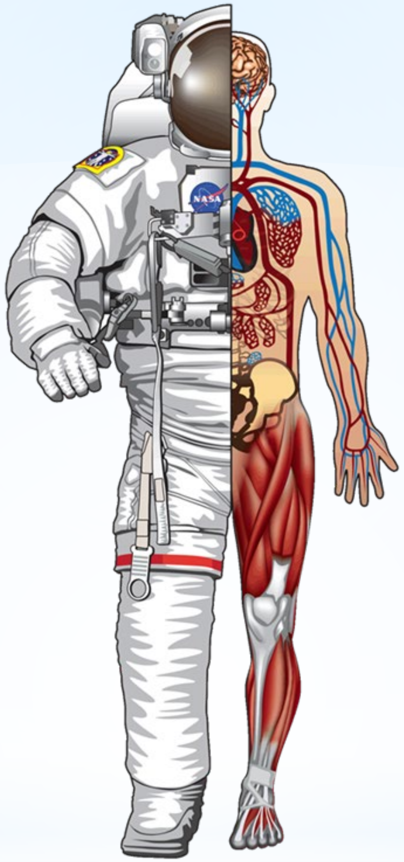
Human Health & Performance

Enable successful space exploration by minimizing the Human System Risks of spaceflight hazards



Hazards of Spaceflight (RIDGE)
Hazards Drive Human Spaceflight Risks

Human Health and Performance
NASA Johnson Space Center
Exploring Space | Enhancing Life



Radiation

Acute In-flight effects
Long term cancer risk

Isolation & Confinement

Behavioral aspect of isolation
Sleep disorders

Distance from earth

Autonomous Medical Care and Operations;
Communication Delay

Altered Gravity - Physiological Changes

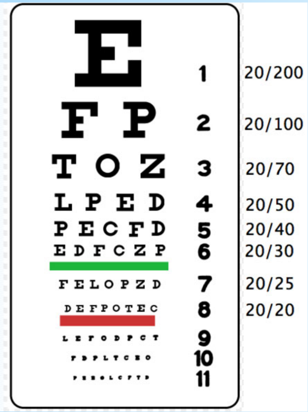
Balance Disorders
Fluid Shifts, Eye issues
Cardiovascular Deconditioning
Decreased Immune Function
Muscle Atrophy
Bone Loss

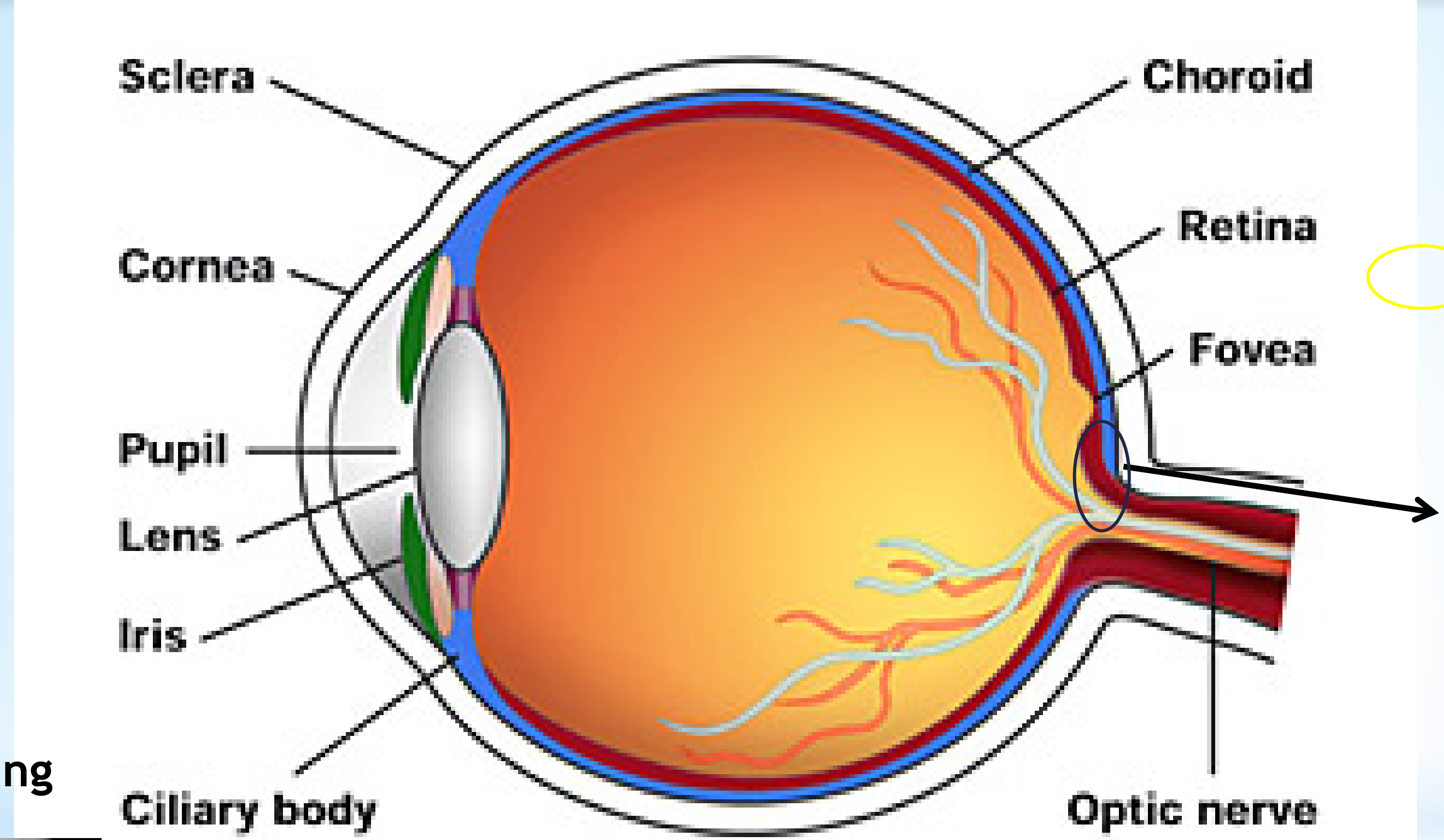
Environment (Closed/Hostile)

Vehicle Design
Environmental – CO_2 Levels, Toxic Exposures, Water, Food

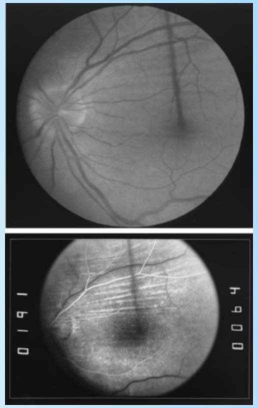
Space Adaptation Neurocular Syndrome (SANS)

- Hyperopic Shifts
  - Up to +1.75 diopters



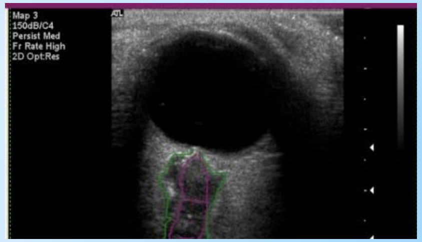


- Choroidal Folds - parallel grooves in the posterior pole

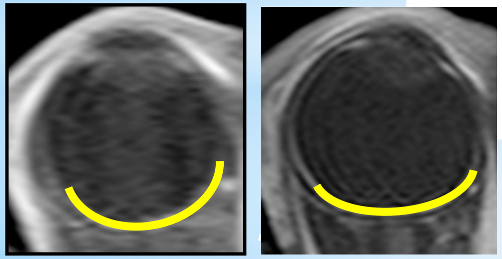


- Optic Disc Edema (swelling)

- Increased Optic Nerve Sheath Diameter



- Globe Flattening

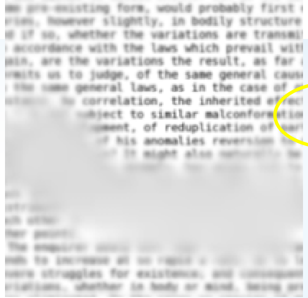


Normal Globe Flatten Globe

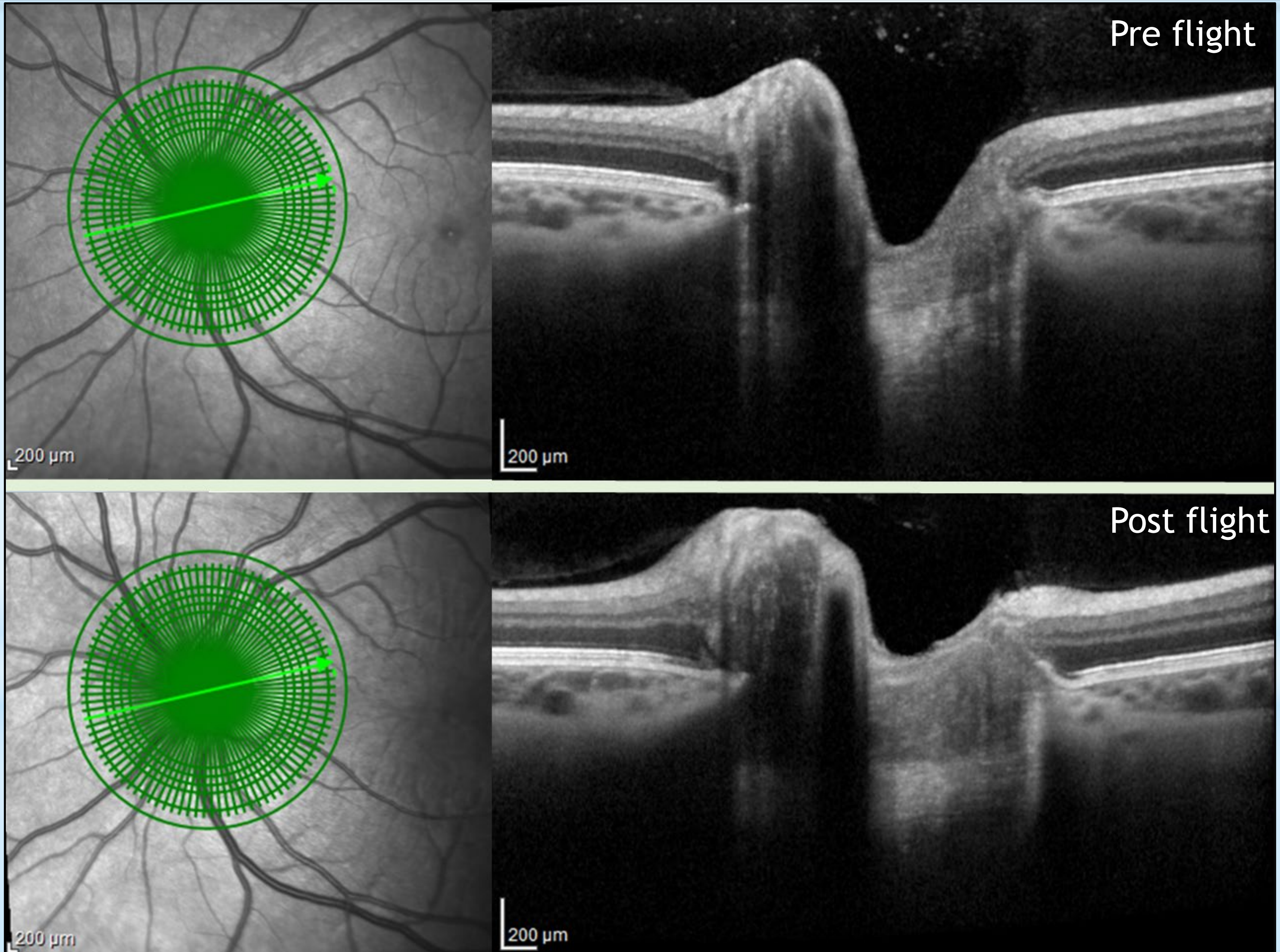
MRI Orbital Image showing globe flattening

Macias, JAMA Opthalmology, 2020

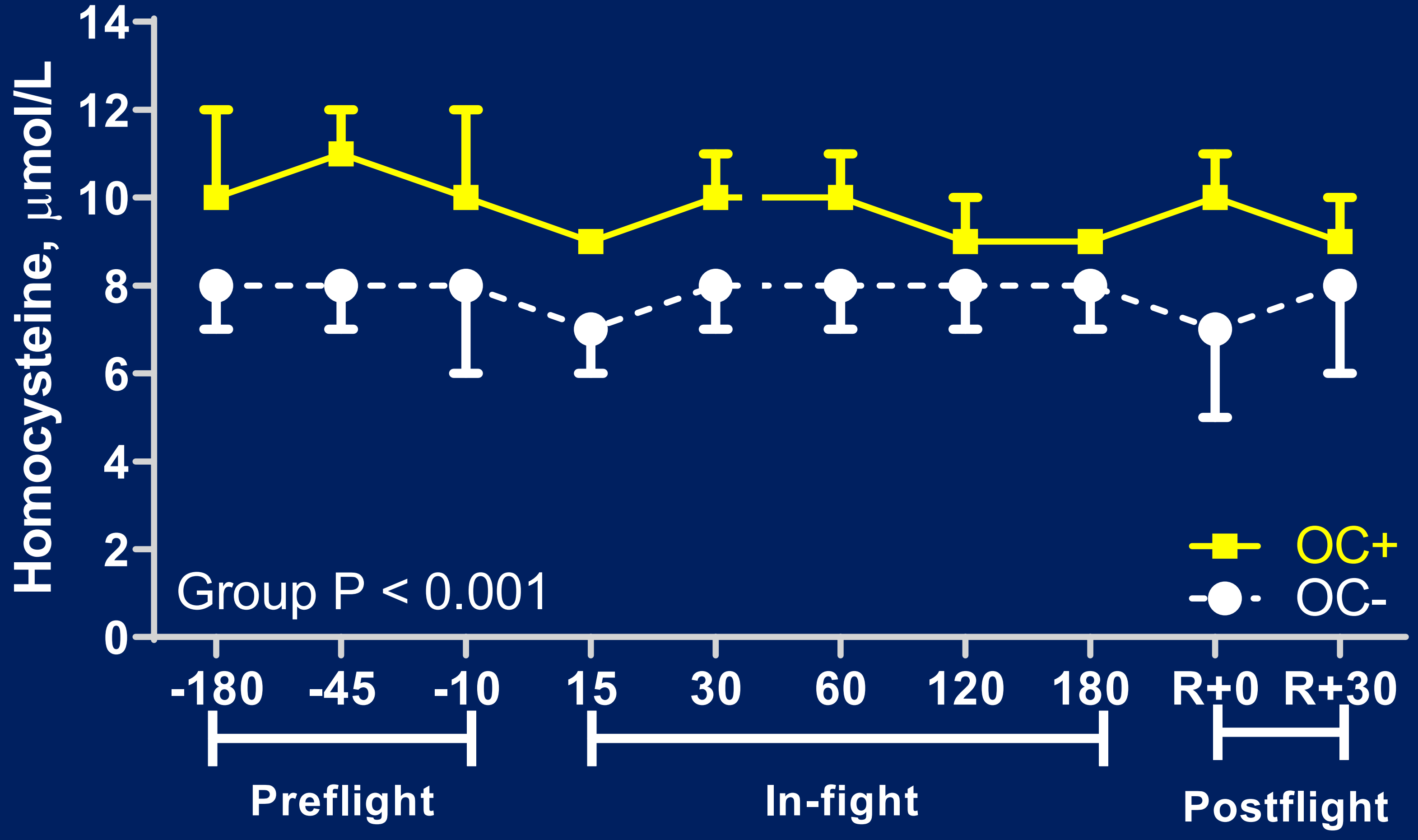
- Altered Blood flow
  - "cotton wool" spots



Retinal Images using OCT



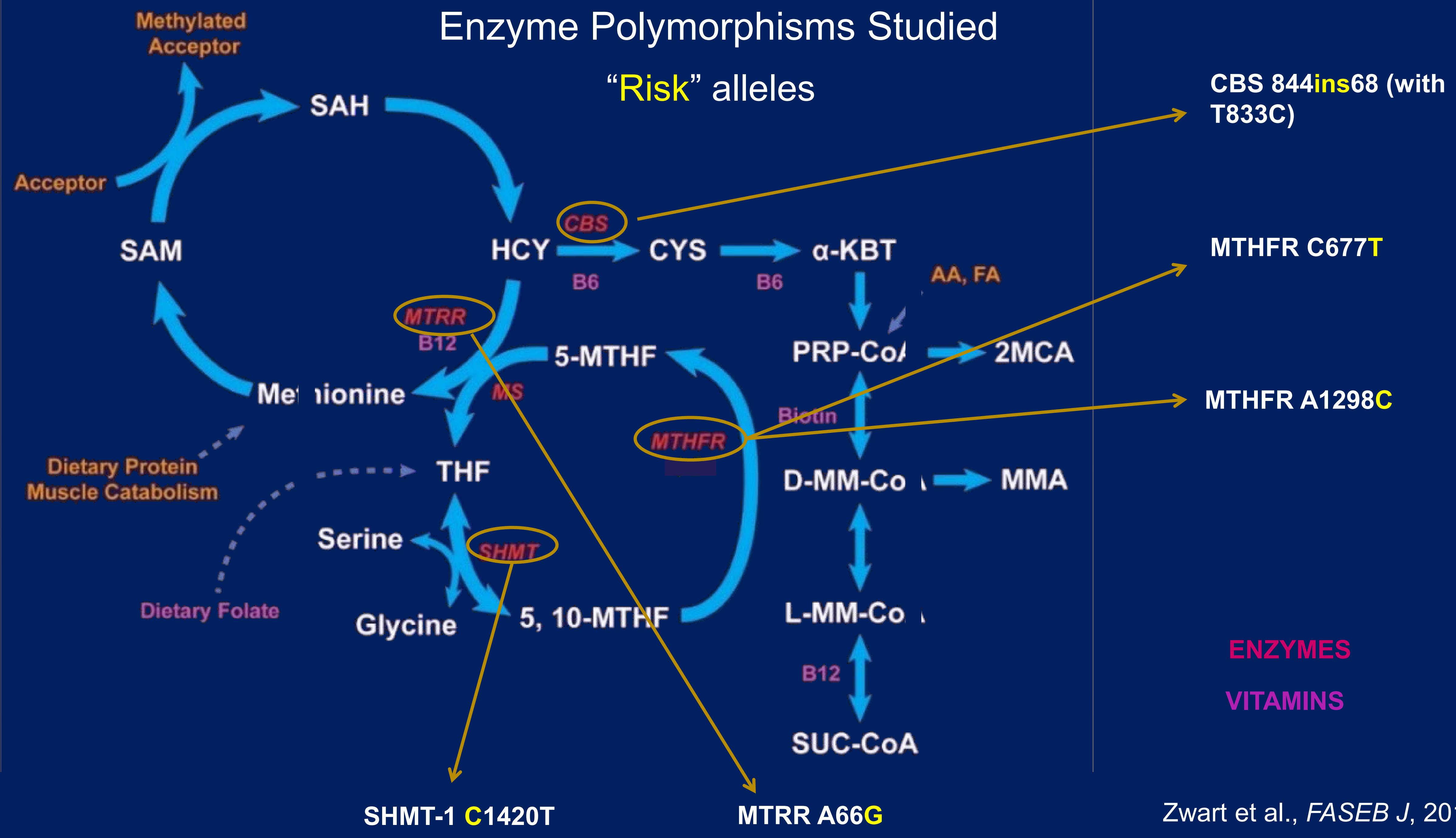
Astronauts with ocular changes had higher serum homocysteine concentration than astronauts without ocular changes. *Before* flight.



Zwart et al., Vision changes after spaceflight are related to alterations in folate- and vitamin B-12-dependent one-carbon metabolism.. *J Nutrition*, 2012

Enzyme Polymorphisms Studied

"Risk" alleles



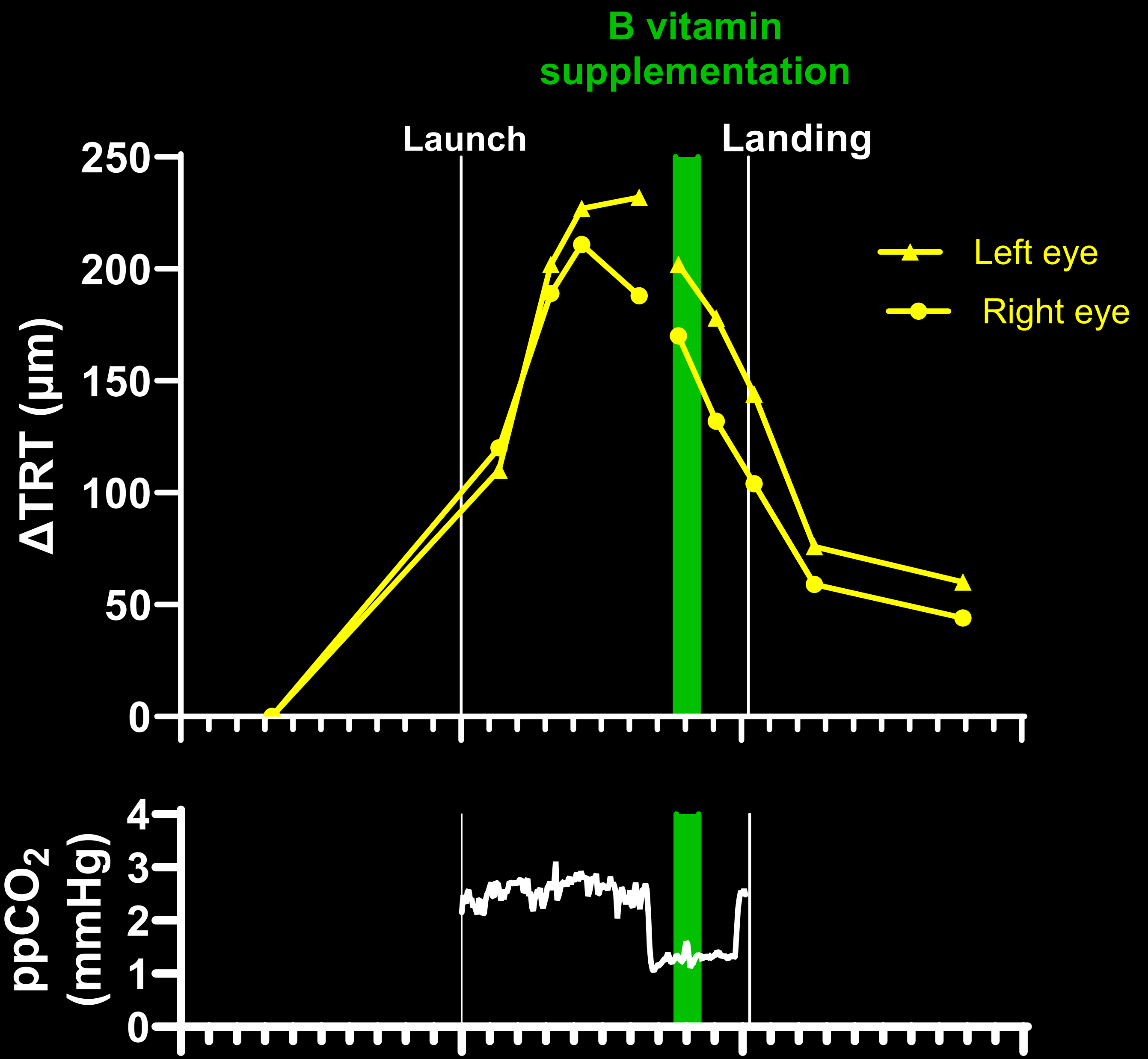
ENZYMES

VITAMINS

Zwart et al., *FASEB J*, 2016

Case Report

B vitamin supplementation was initiated, and there was a coincident drop in cabin CO_2, and a mitigation of retinal edema



Brunstetter, Zwart, et al., *JAMA Ophthalmology*, 2024

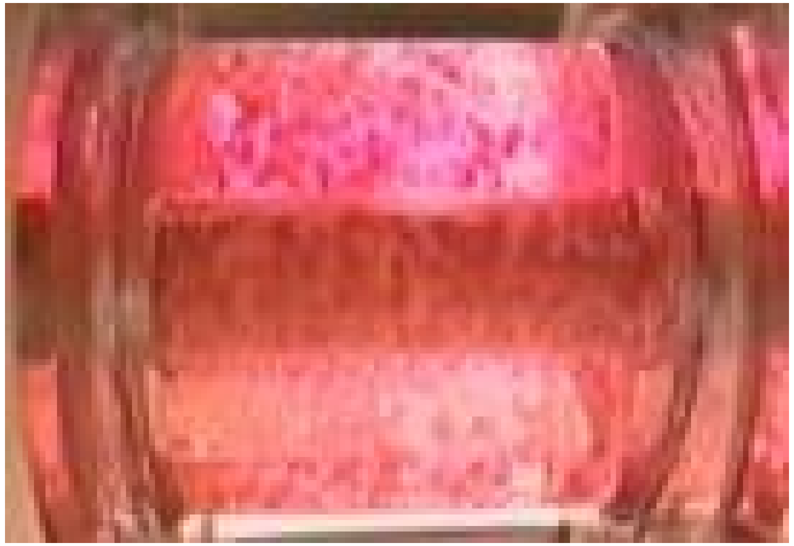
Pioneers in developing Tissue Engineering Technologies at NASA

Dr. David Wolf, Astronaut
Attending the bioreactor at MIR Space Station

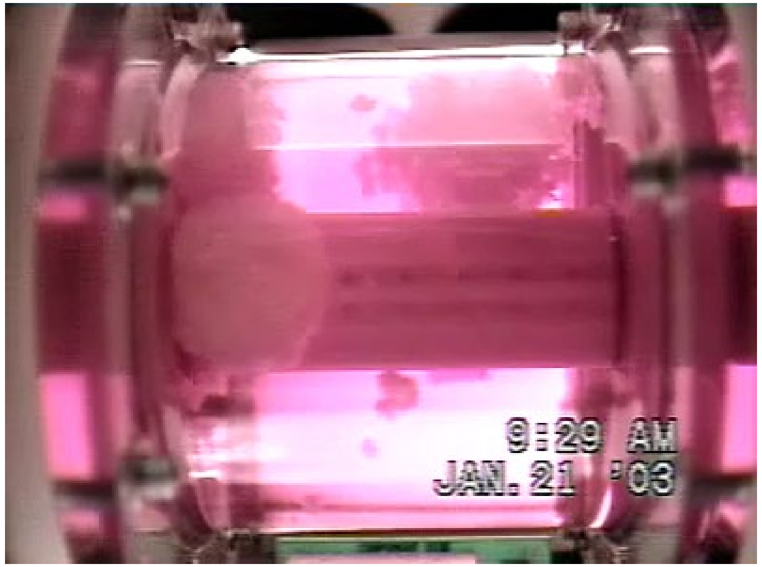
Dr. Neal Pellis, Director
NASA Biotechnology Program

STS-107 Results

GROUND



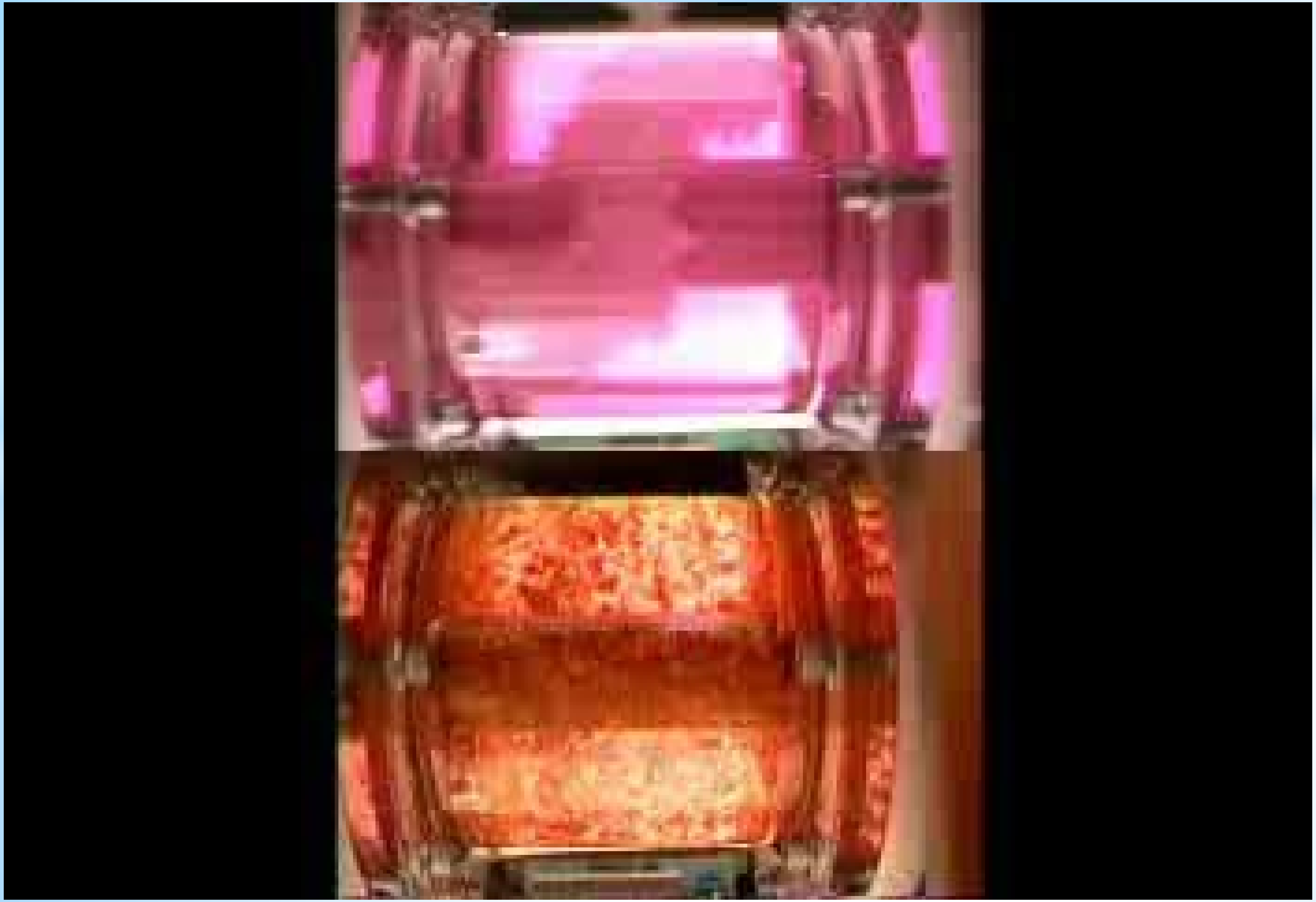
FLIGHT



- Bone stromal cells and prostate carcinoma co-culture
- On-orbit tissue aggregates spanned width of bioreactor

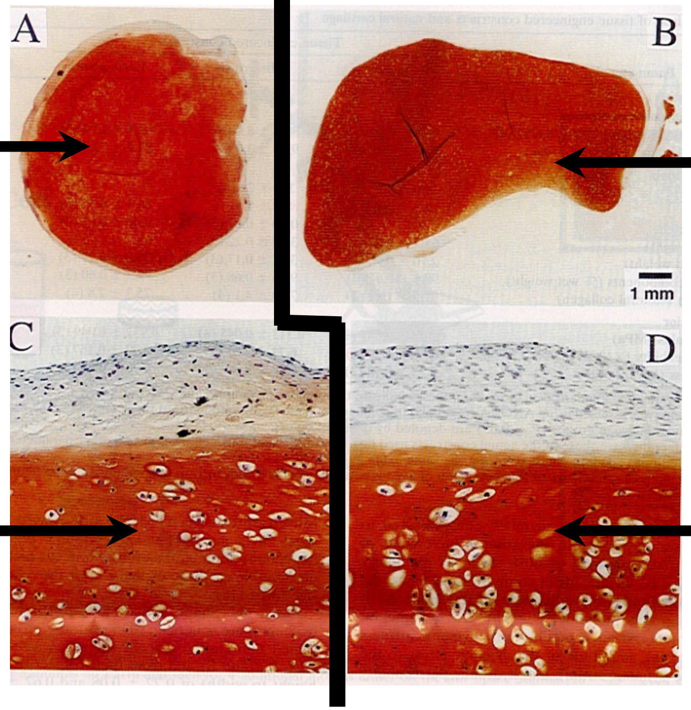
PI: Dr. Leland Chung, Emory University

Bone stromal cells and prostate carcinoma co-culture



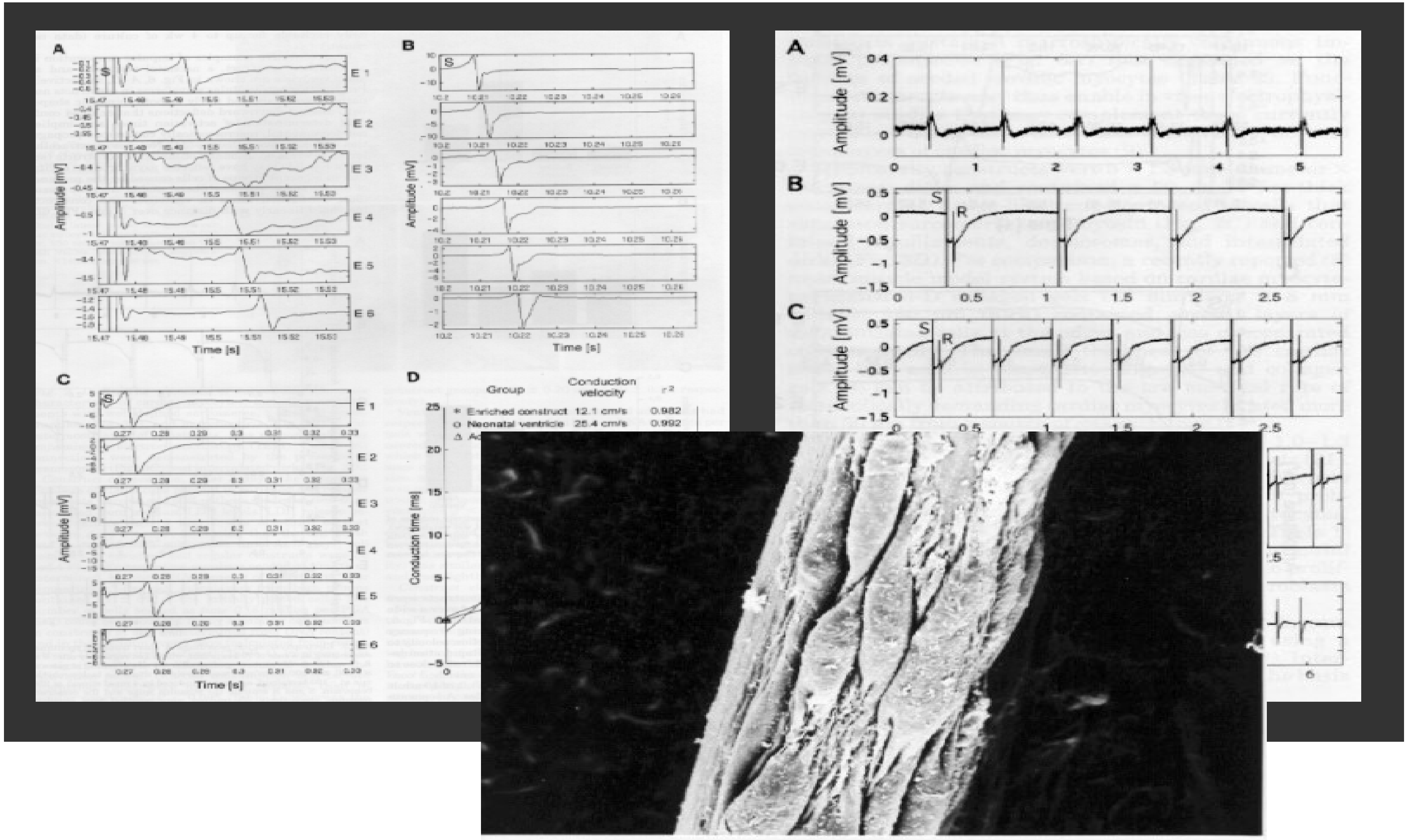
The Cellular Biotechnology Program

Johnson Space Center   Houston, Texas

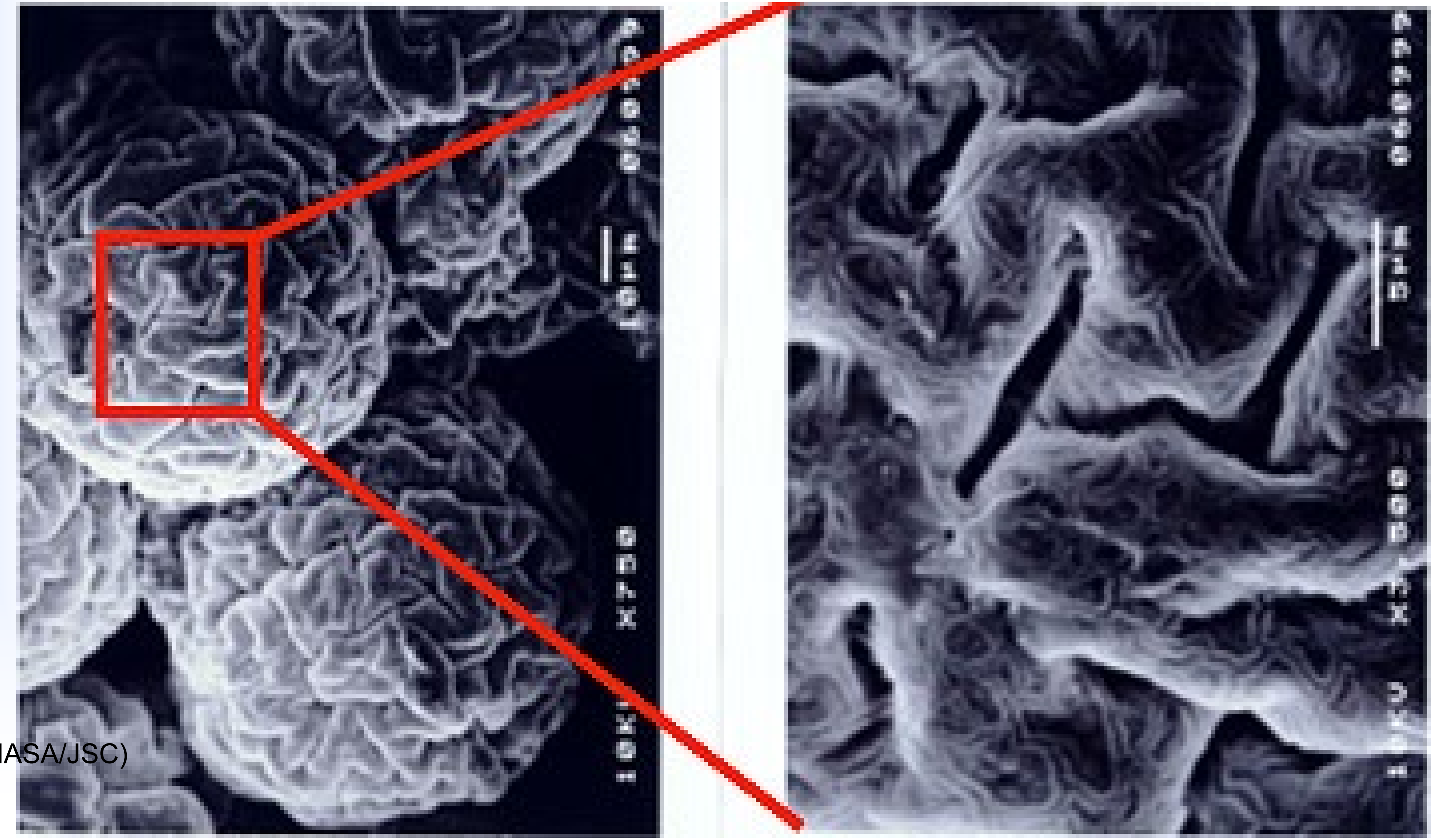


PI : Dr. Lisa Freed, MIT, *Proc. Natl. Acad. Sci. 94*, (1997) pp 1385-1389.

Heart muscle cell Aligning and growing on Connective Tissue Fiber

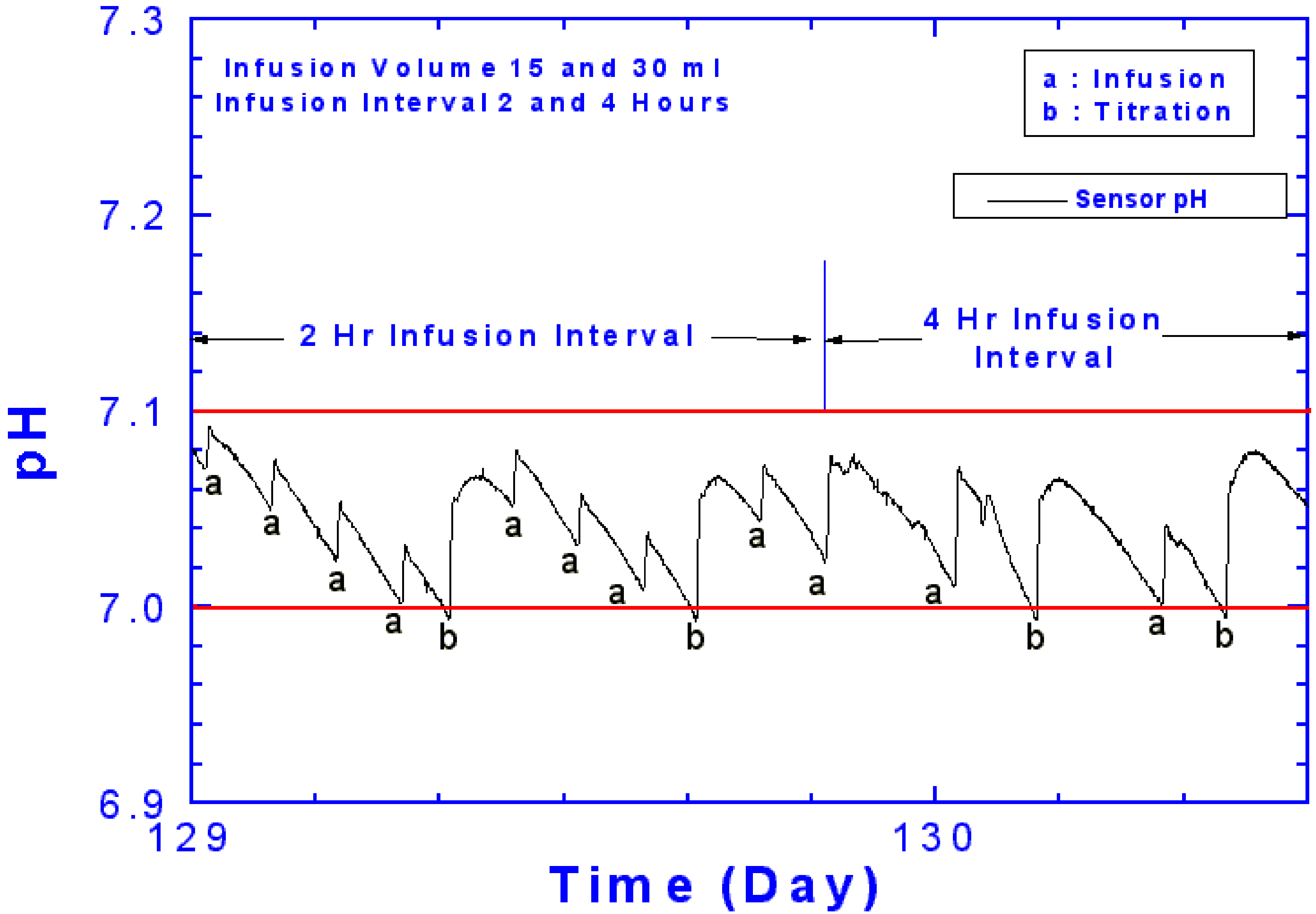


Bowhead Whale Kidney Cells
Response of Mammals to Environmental Toxins

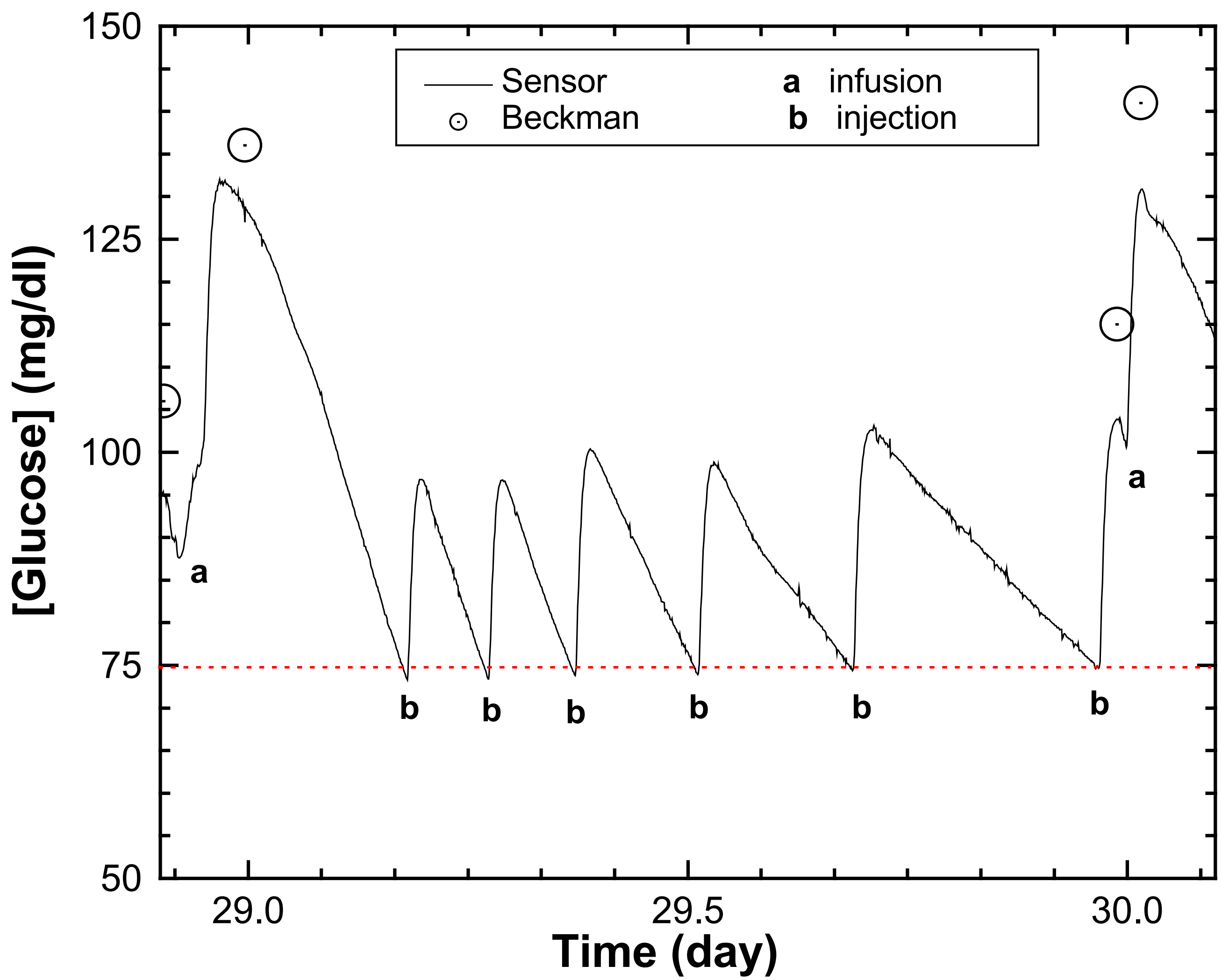


(T. Goodwin, NASA/JSC)

pH Control in a Perfused Bioreactor



Performance of the Glucose Control (75 to 100 mg/dl) System



A. Jeevarajan / NASA-JSC

Propagation of Cells for Tissue

Cancer Models

- Breast
- Colon
- Endocrine
- Ovarian
- Prostate

Normal Tissue

- Cardiac
- Cartilage
- Liver
- Lymphoid for HIV
- Kidney
- Skin
- Thyroid
- Neuro endocrine
- Pancreatic Islets

Propagation for Cell Biology

- Cellular Movement
- Signal Transduction
- Gene Expression
- Immunomodulation
- Invitro Model for Renal toxicity
- Angiogenesis : formation of blood vessels
- Virus Replication
- Cellular basis for space adaptation phenomenon

Competing Forces in Microgravity

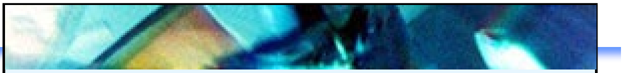
Physical Forces

- Surface Tension
- Cell-Matrix Adhesion
- Cell-Cell Communication
- Fluid Shear Forces
- Maintain Physiological Conditions
- Uniform concentrations of gases and nutrients
- Removal of waste and toxic products

Other Factors

- Quality Cell Source
- Proliferation and Differentiation Required
- Pluri-potent Stem Cells
- Biomaterial Scaffold: Biopolymers
- Bioreactors
- Specific Factors
- Growth factors, hormones, metabolites
- Depends on tissue type and developmental stage

Bioreactor Research – Applications to NASA/Human Health on Earth

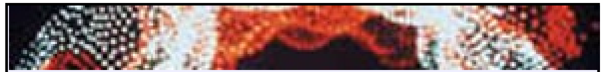


INFECTIOUS DISEASES

• Established the NASA/NIH Center for Three Dimensional Tissue Culture which provides researchers bioreactors and an opportunity to develop new model systems for diseases whose pathology cannot be reproduced by merely growing the right cells in monolayer culture.

- Human Immunodeficiency Virus (HIV)
- Ebola viral transmittal
- Borrelia, the etiologic agent of Lyme disease
- Norwalk virus

• Model for Salmonella pathology in engineered colon tissue



DRUG EFFICACY

• Facilitating testing of drugs to determine their safety without using animals and reducing the need to use human volunteers in final testing

• Bio-production of an enzyme that HIV needs to reproduce, analysis of enzyme structure, and designer drugs to inhibit the HIV virus

• Studying human metabolism of drugs

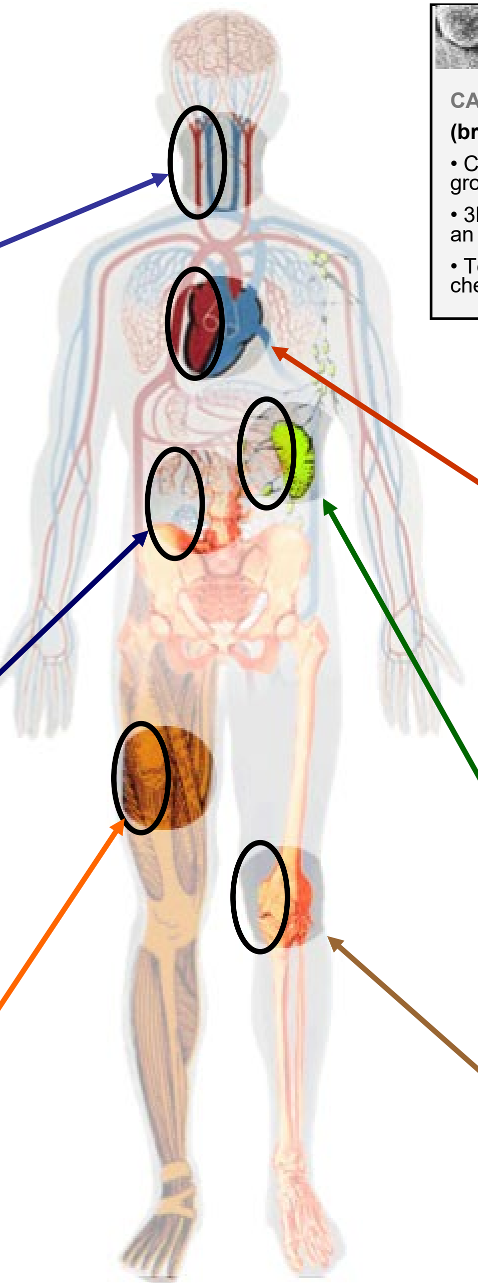
ACUTE INJURY AND RECONSTRUCTIVE SURGERY

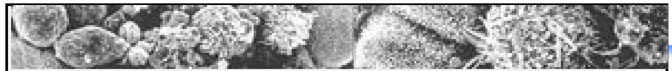
• Biodegradable scaffolds to grow cartilage cells needed for reconstructive surgery

• Models and transplantable cartilage tissues that could revolutionize treatment for joint diseases and injuries

• Cytokine synthesis in analog culture to address wound healing

A.





CANCER

(breast, skin, prostate, ovary, bone and colon)

• Co-culture of cancer and somatic cells to understand cancer growth and human immune system response

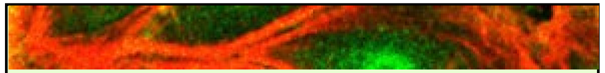
• 3D tumor disease models for studies in proliferation, signaling, an apoptosis

• Testing three-dimensional tissues for sensitivity to chemotherapy and hormonal therapy

HEART DISEASE

• Engineered heart tissue for research in drug testing, and the eventual growth of transplantable heart tissue

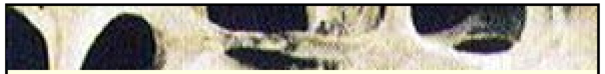
• Studying how heart cells interact to form cardiac structures outside the body



DIABETES

• Working on pancreatic tissue for transplantation

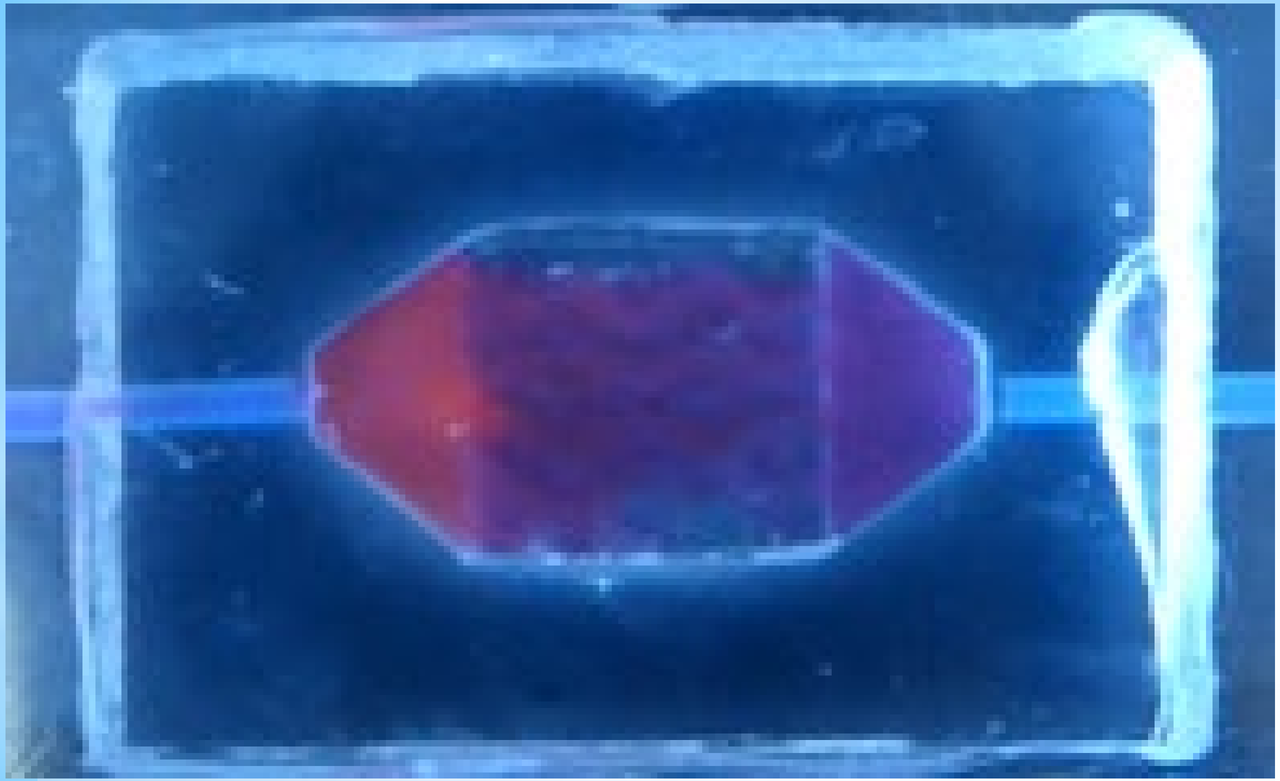
•Cultivating and transplanting beta cells into Type I diabetics

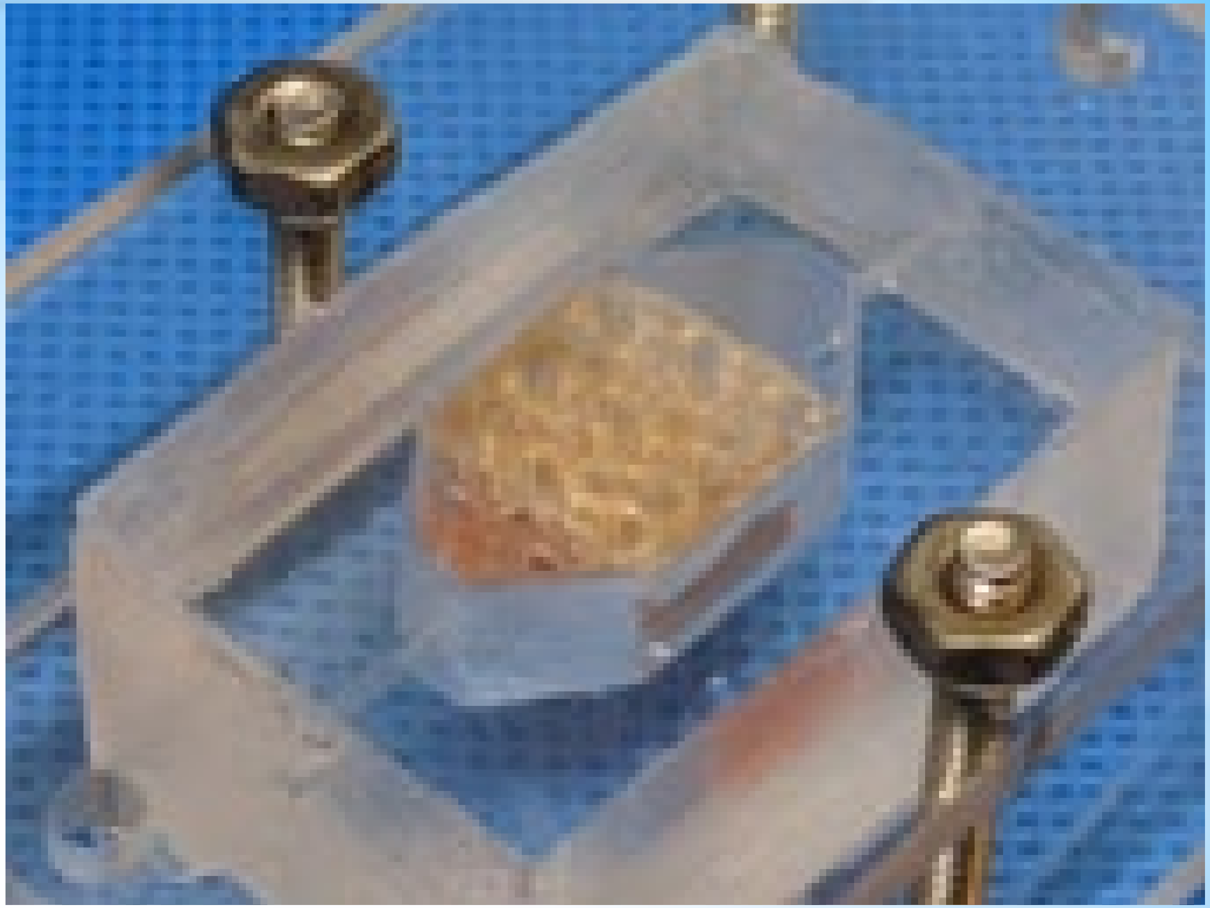


BONE LOSS

• Mechanisms involved in bone loss related to microgravity

• Optimal characteristics of micro-beads for growing bone tissue





Vascularized Human Liver Tissue (1 cm3; 30 day Survival)
Wake Forest Institute for Regenerative Medicine, NC

* Ax-2: May 2023

Published Oct 13, 2024

npj | microgravity Article

Surface tension enables induced pluripotent stem cell culture in commercially available hardware during spaceflight

Maedeh Mozneb[1,2,3,4], Madelyn Arzt[1,2,3,4], Pinar Mesci[5], Dylan M. N. Martin[6], Stephany Pohlman[1,2,3,4], George Lawless[1,2], Shankini Doraisingam[6], Sultan Al Neyadi[7], Rayyanah Barnawi[5,8], Ali Al Qarni[5,8], Peggy A. Whitson[5], John Shoffner[5], Jana Stoudemire[5], Stefanie Countryman[6], Clive N. Svendsen[1,2] ✉ & Arun Sharma [1,2,3,4] ✉

**The 1st stem cell transfection (DNA introduction) in space

**The 1st use of terrestrial, off-the-shelf hardware for cell culture in space

Cedars Sinai

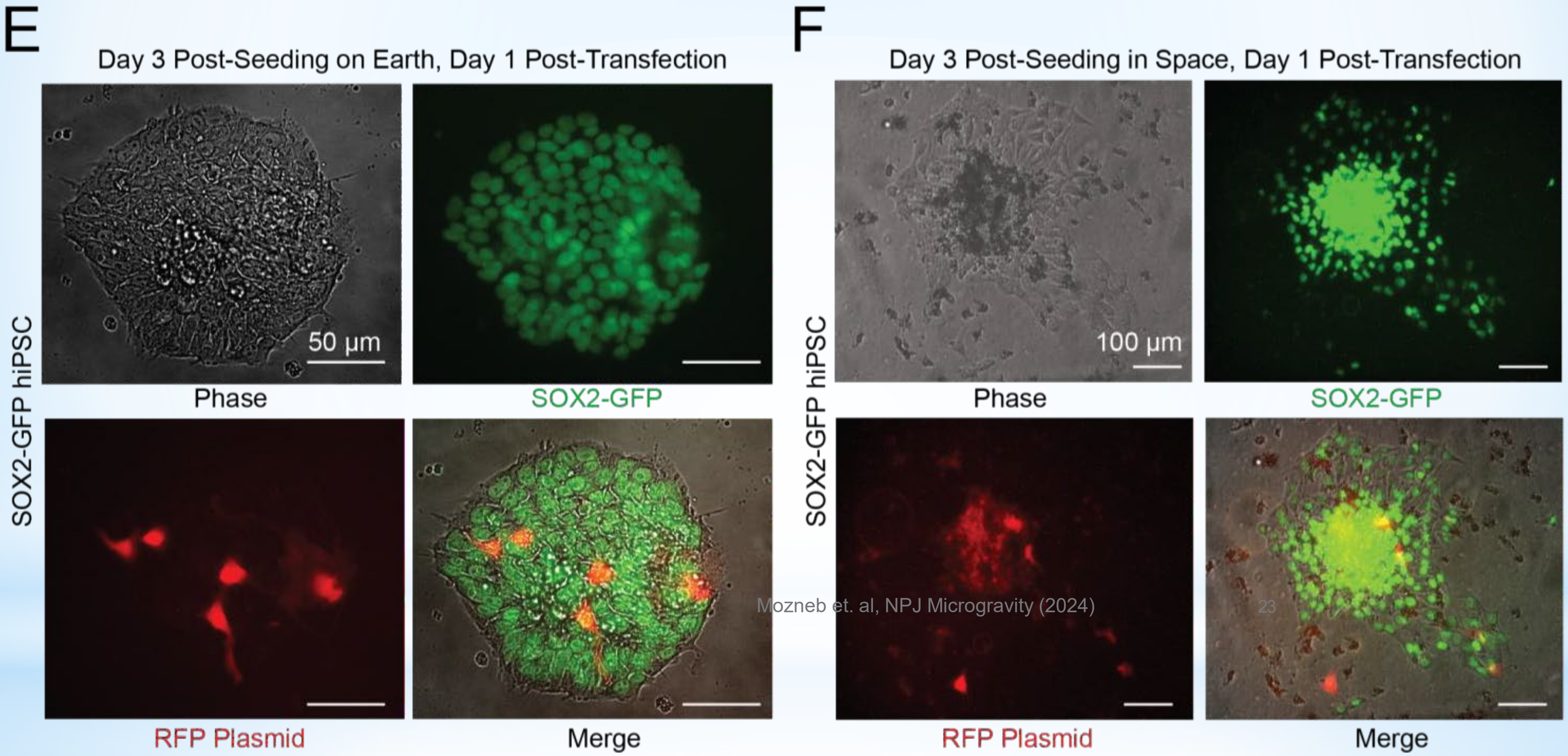
IN SPACE FOR EARTH InSPA

AXIOM SPACE

BIOSERVE SPACE TECHNOLOGIES

AX-2

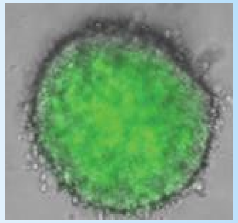
Successful DNA Transfection of hiPSCs in Space



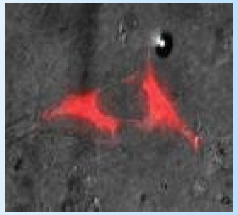
Mozneb et. al, NPJ Microgravity (2024)

Cedars-Sinai NASA In-Space Manufacturing Projects Summary

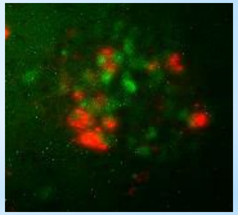
- Successful first demonstration of using commercial off-the-shelf, cost-effective terrestrial hardware for 3D cell culture in LEO, via surface tension (May 2023)
  - Enables improved accessibility of space life sciences, rapid organoid production



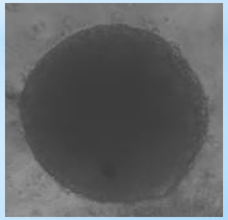
- Successful first transfection of stem cells with DNA in LEO (May 2023)
  - Enables advanced applications including stem cell production and CRISPR gene editing



- Successful first production of induced pluripotent stem cells in LEO (August 2024)
  - Enables in-space tissue production, differentiation, and clinical applications



- Differentiation of stem cells in LEO in progress (2025)



Funding Resources

BIOLOGICAL SYSTEMS OFFICE
JSC

HUMAN RESEARCH PROGRAM

IN SPACE FOR EARTH
InSPA

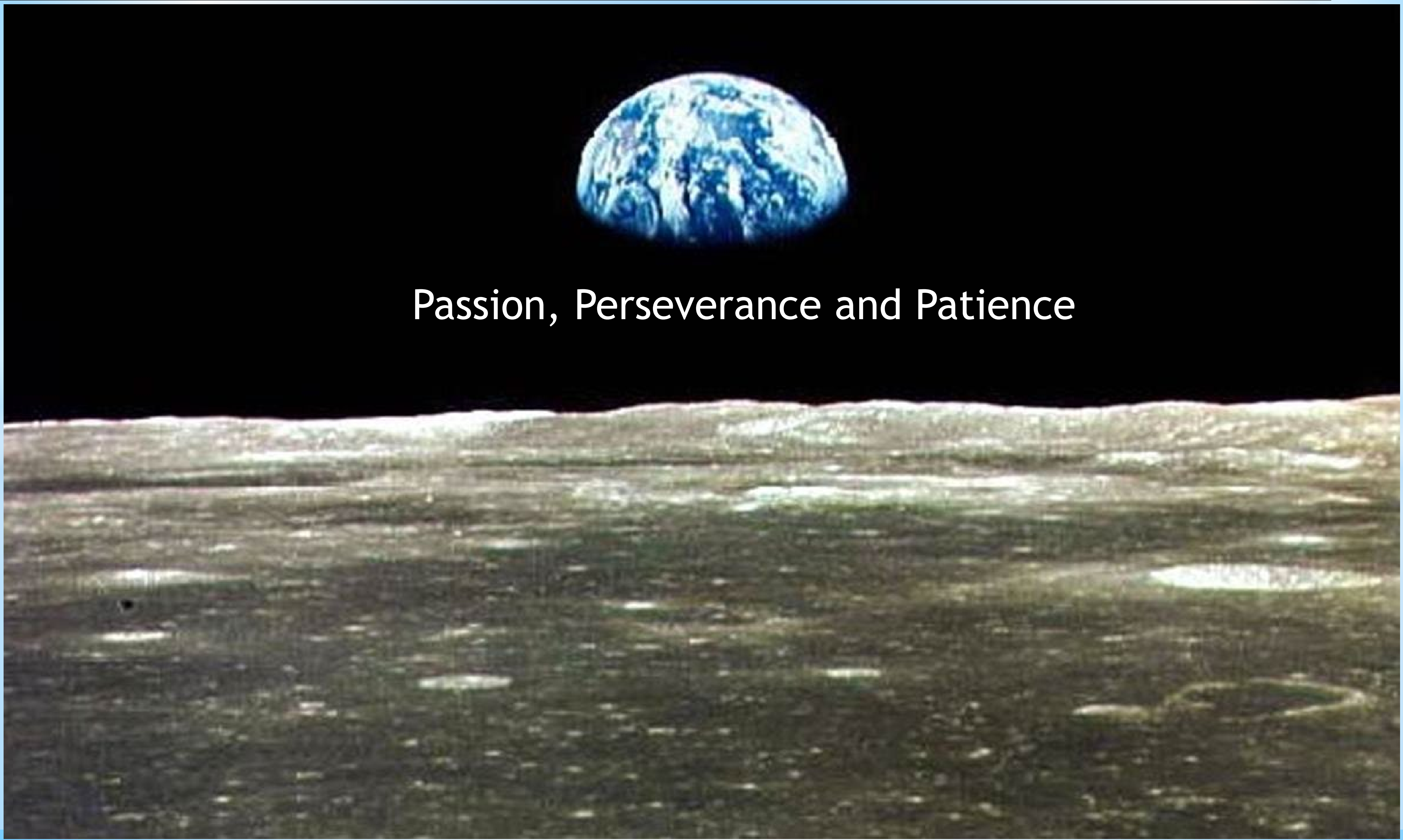
ISS NATIONAL LABORATORY®

Acknowledgment

Engineers, Scientists
Physicians and Astronauts

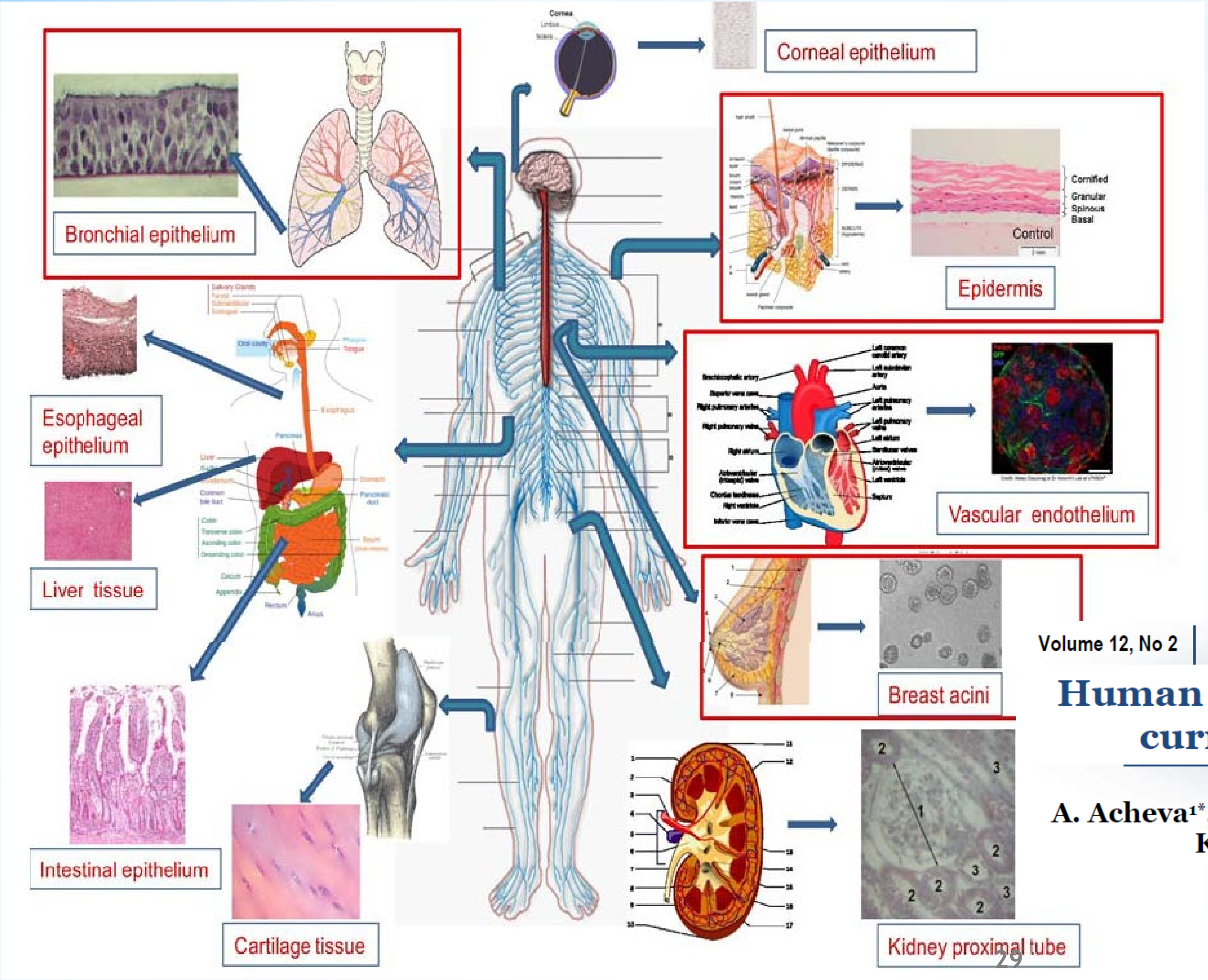
Thanks

Beautiful Fragile Blue Planet



BACK-UP

3-D monotypic and organotypic models in radiobiology studies



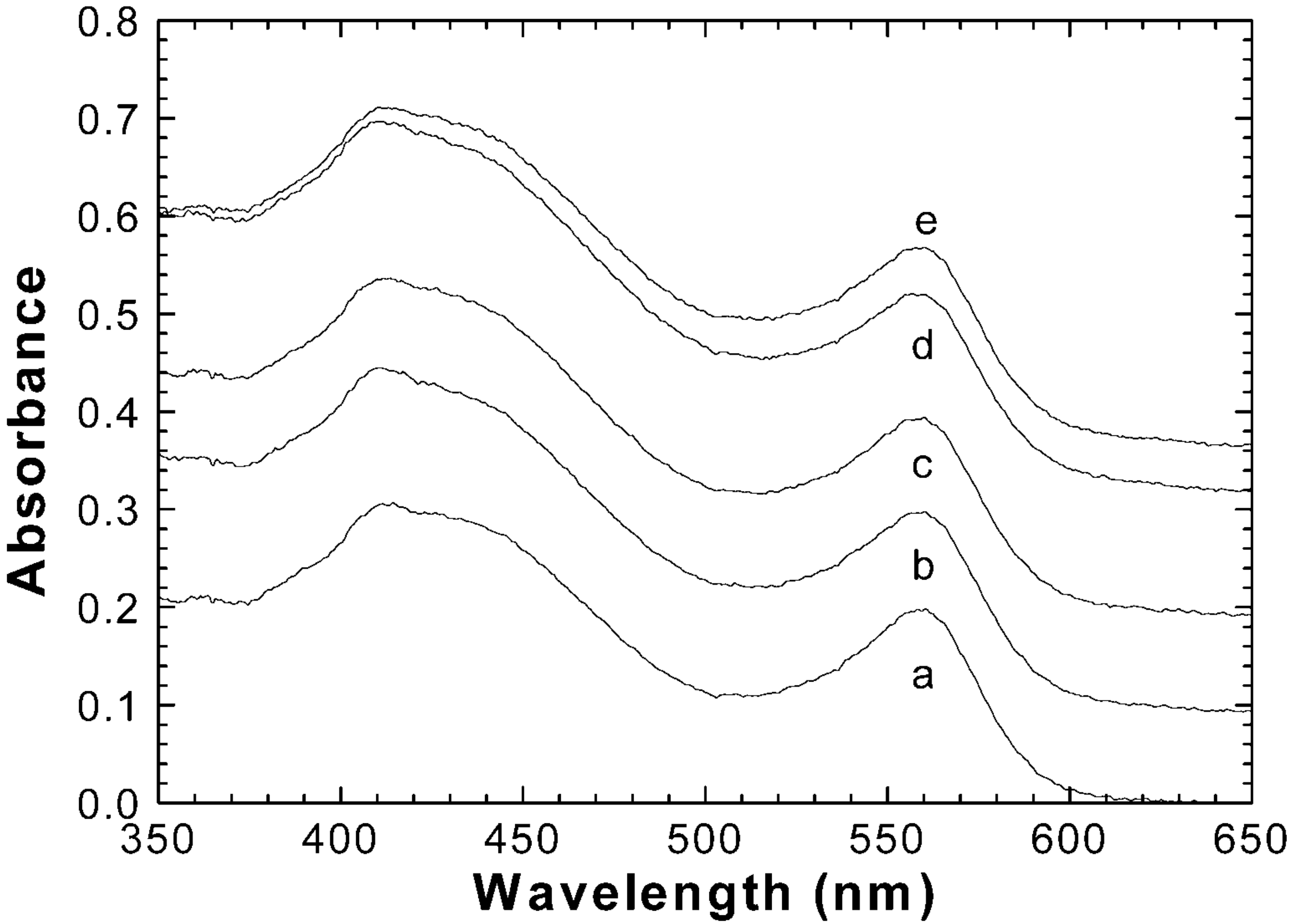
- ECM, Extra cellular matrix
- Bystander effect, mm range
- DNA damage Recovery
- Genetics
- Radiosensitivity

Volume 12, No 2 | International Journal of Radiation Research, April 2014

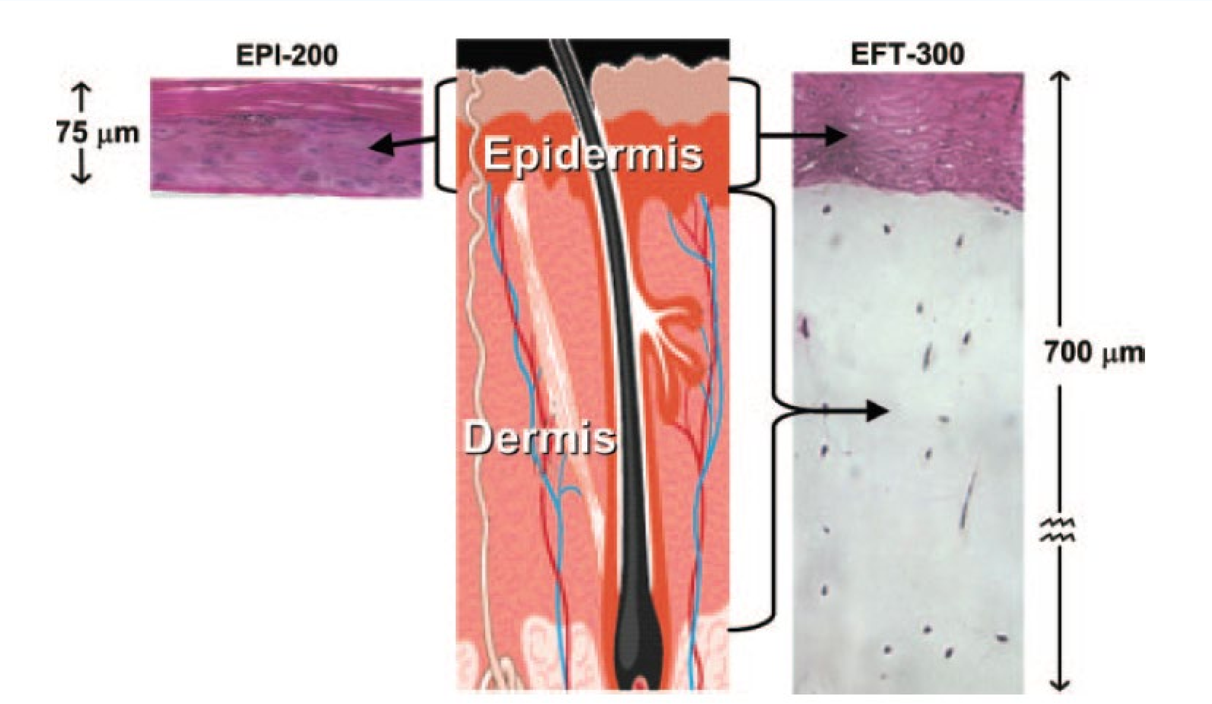
Human 3-D tissue models in radiation biology: current status and future perspectives

A. Acheva[1*], A. Aerts[2], Ch. Rombouts[2,3], S. Baatout[2,3], S. Salomaa[1], K. Manda[4], G. Hildebrandt[4], M. Kämäräinen[1]

Biofilm Formation inside the Optical Cuvette of the pH Sensor Monitored by Fiber-optically Coupled Spectrophotometer at 4, 9, 15, 17 and 21 Days



Human skin tissue model



Human skin tissue system consists of a dermal layer containing fibroblasts and an epidermal layer containing keratinocytes.

From PNAS, 2005

Biological effects in unirradiated human tissue induced by radiation damage up to 1 mm away

Oleg V. Belyakov*†, Stephen A. Mitchell*, Deep Parikh‡, Gerhard Randers-Pehrson*, Stephen A. Marino*, Sally A. Amundson*, Charles R. Geard*, and David J. Brenner*§

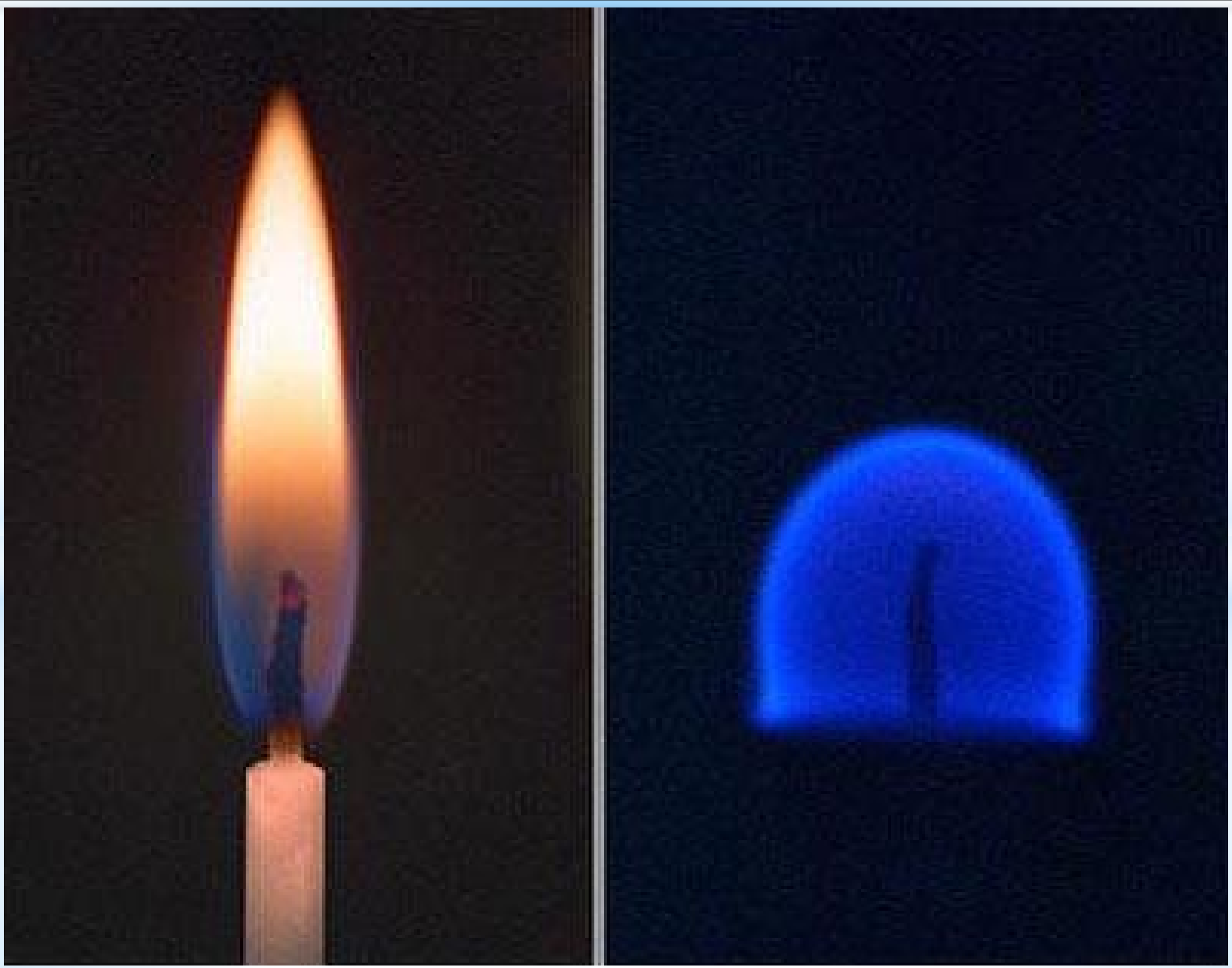
*Center for Radiological Research, Columbia University, New York, NY 10032; †Radiation Biology Laboratory, Research and Environmental Surveillance, Radiation and Nuclear Safety Authority, P.O. Box 14, FIN-00881, Helsinki, Finland; and ‡Stuyvesant High School, New York, NY 10282

Edited by Richard B. Setlow, Brookhaven National Laboratory, Upton, NY, and approved August 3, 2005 (received for review June 16, 2005)

Q&A

1) Exploration of space affecting environment
2) Solving biomedical problems through space exploration
3) Sensing systems in bioreactors; what is the impact?
4) How can University students engage in space exploration
    a) Internship across the globe
    b) Engage in a global competition ('genes in space',ISU, Mars architecture, new generation space vehicles, etc.)
5) How can you take a giant leap?
    a) Understanding our own planet and human race using the technologies developed in space exploration
    b) New generation propulsion technologies
    c) Space travel for everyone (see your only home; 'honey moon in moo')
    d) Protection of our planet
    e) Life beyond our planet and what we can learn

Flame Behavior



https://www.youtube.com/watch?v=BxxqCLxxY3M

Big Bang : An Artistic Rendering