Medical Countermeasures for Radiation Induced Health Effects: Report of an Interagency Panel Session Held at the NASA Human Research Program Investigator’s Workshop, January 26, 2017

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An Interagency Panel Session organized by the NASA Human Research Program Space Radiation Program Element (SRPE) was held during the NASA Human Research Program (HRP) Investigator’s Workshop (IWS) in Galveston, Texas on January 26, 2017 to identify complementary research areas that will advance the testing and development of medical countermeasures (MCM) in support of radioprotection and radiation mitigation on the ground and in space. There were several areas of common interest identified among the various participating agencies. This report provides a summary of the topics discussed by each agency along with potential areas of intersection for mutual collaboration opportunities. Common goals included repurposing of pharmaceuticals, neutraceuticals for use as radioprotectors and/or mitigators, low-dose/chronic exposure paradigms, late effects post-radiation exposure, mixed-field exposures of gamma-neutron, performance decrements, and methods to determine individual exposure levels.

Introduction

NASA has been charged with preparing for the next frontier of exploration missions that will include sending astronauts to cis-lunar habitats, the moon and Mars over the next 30 years. This requires NASA to understand the implications to the astronauts’ health with radiation being one of the greater unknowns. The International Space Station (ISS) has provided key evidence on the impact microgravity and living in space has on the human body; however, radiation exposures accumulated on the ISS is a fraction of what the astronauts will experience during longer, deep space missions. While shielding on spacecraft and in the habitats will provide some mitigation, it is impossible to prevent astronauts from being exposed to high-energy, low dose-rates of radiation. To address the impact of radiation-induced health questions, NASA recently upgraded its Galactic Cosmic Ray (GCR) Simulator at the NASA Space Radiation Laboratory (NSRL) to provide a more accurate representation of the space radiation environment to support ground based research. This facility will be critical to support
evaluation of medical countermeasures to protect or mitigate astronauts from GCR exposures. NASA has developed requirements and a plan to pursue medical countermeasures to provide mitigation and reduce the overall radiation risk to astronauts. One aspect of NASA’s plan is to engage with interagency partners to leverage their existing research and development, to learn from them, and potentially expedite NASA’s goals. In order to accomplish this, it is necessary to understand the goals of each agency and identify common areas where collaborations can occur. This prompted the joint session organized by NASA SRPE during the NASA HRP Investigator’s Workshop. The Interagency Panel Session was organized to address specific questions regarding radiation-induced health effects, exposure concerns, and MCM research and development of interest to each participating Agency. It included presentations from the National Institute of Health (NIH)/National Cancer Institute (NCI), NIH/National Institute for Allergy and Infectious Disease (NIAID), NIH/National Heart Lung and Blood Institute (NHLBI), Biomedical Advanced Research and Development Authority (BARDA) and the Defense Threat Reduction Agency (DTRA), with attendance by the Armed Forces Radiobiology Research Institute (AFRRI). A highlight of each Agency’s key areas of interest is illustrated in Figure 1.

Figure 1. Agency areas of interest and the intersection with NASA.
Each Agency has unique requirements for MCM development and implementation. NASA SRPE has four primary risk areas, Acute Radiation Syndrome, Cancer, Degenerative Tissue Effects and Central Nervous System, each with multiple endpoints that overlap with the various Agencies in different areas.

Radioprotectors and radiomitigators have been in the spotlight for more than a decade post-9/11 era. The potential for a nuclear accident or worse, detonation, increased significantly and several efforts were born to develop ways to protect the public and military warfighter including, the National Institute of Health (NIH) National Institute for Allergy and Infectious Diseases (NIAID) Radiation Nuclear Countermeasures Program (RNCP), and the Biomedical Advanced Research and Development Authority (BARDA). Their efforts have focused on the development of end-to-end solutions to respond to mass injuries associated with nuclear and radiological incidents. The primary goal has been rescuing victims from acute radiation exposures that may result in loss of life. Several agents have been developed, FDA approved and stockpiled in a relatively short period to address these needs and many more are in the pipeline as potential candidates to include in the Strategic National Stockpile (SNS). The military has its concerns for the warfighter during these events and other activities that may expose troops to radiation. The possibility of performance decrements exists if troops are exposed to even low doses of radiation during missions or support efforts that may result in mission compromise. However, the negative effects of radiation exposure extend far beyond the potential for a nuclear disaster. Millions of people are treated annually with radiotherapy and suffer from latent effects that disrupt their overall quality of life. The Radiation Research Program, Division of Cancer Treatment and Diagnosis under the NIH National Cancer Institute (NCI) is chartered with protecting normal tissue during radiation therapy and mitigating the radiation induced side effects. Latent effects from radiation exposure involve the vascular system to a great extent, which can compromise multiple organs in the body. The NIH National Heart Lung and Blood Institute (NHLBI) is interested in learning what can be done to mitigate these effects post-radiotherapy. The health effects being addressed terrestrially have benefit to NASA to address potential in-flight and latent effects anticipated post-long duration, deep exploration missions.

**National Institute of Health/National Cancer Institute (NIH/NCI)**

Dr. Pataje Prasanna, Radiation Research Program, Division of Cancer Treatment and Diagnosis under NIH/NCI, gave an overview of “Radioprotectors and Mitigators for Improving Radiotherapy”. Radiotherapy is currently used to treat half of all cancer patients and has become a curative modality. In 2012, there were 14.1M new cancer cases and 7M were treated with radiotherapy. Projections for future cancer cases are staggering. By 2030 it is estimated there will be 24.6M new cancer cases and 12M of those will be treated using radiotherapy.¹ A focus for NCI is how to address post-treatment quality of life. Radiotherapy has been shown to reduce cognitive function anywhere from 50-90% in cancer patients being treated for glioblastoma, and head and neck cancers. Radiation-induced brain injury involves
inflammation, changes in the central nervous system (CNS) microenvironment, signaling dysfunction, vascular damage, and injury to neurons, cellular organelles, demyelination, and collagen deposition. It was noted that apoptosis and necrosis appear to play a major role as well. Development of radioprotectors will allow for dose escalation with the goal of eliminating the tumor while a radiation mitigator will help improve post-treatment quality of life. Figure 2 depicts the pathway for the translation of radiation effect modulators to the radiation oncology clinic. The process involves moving the work through a logical hierarchy of model systems from \textit{in vitro} based assays through \textit{in vivo} tumor models and ultimately to the clinic. Early screening using \textit{in vitro} systems could save resources and time.

**Department of Defense/Defense Threat Reduction Agency (DOD/DTRA)**

The Defense Threat Reduction Agency (DTRA) has two primary objectives 1) to develop prophylaxes to prevent latent effects associated with radiation exposure that occurs during warfighter operations and 2) to develop environmental monitoring solutions for near- to mid-field characterization of nuclear activity. DTRA’s approach for developing prophylaxes is to study intracellular response-recovery modes for different domains of life, with a focus on understanding intrinsic radioresistance. Environmental monitoring surveillance approaches use omics, genotypic, functional and phenotype changes related to exposure. Additional work in this area explores development of materials with multicatalytic centers for successive analyte

![Workflow for development of radioprotectors and mitigators for radiation oncology](image-url)
characterization which increase signal veracity. Studies are designed to develop motifs which can be incorporated into standard optical or electrochemical platforms. Other topics explore changes to local flora and fauna in the surrounding environment that are relatable to exposure of distinct chemical species or level/type/quality of radiation. The demographics, low-dose/low-dose rate and mixed neutron/gamma radiation field are complementary to NASA’s interests. DTRA is also concerned with performance decrements for the warfighter which complements NASA’s interest related to in-flight events that may occur with astronauts on long-duration missions.

**National Institute of Health/National Institute of Allergy and Infectious Disease (NIAID)**

NIAID Program Officers, Drs. Carmen Rios and Lanyn Taliaferro, provided background information on the Radiation Nuclear Countermeasures Program. In 2004, NIAID was directed by the Department of Health and Human Services (HHS) to start a research program to accelerate development of radiation/nuclear medical countermeasures (MCMs) for the Strategic National Stockpile. Their primary mission is to support early to mid-stage research to develop radiation/nuclear MCMs and biodosimetry tools with an emphasis on three key areas 1) drugs to treat or mitigate radiation injury 24 hours post-exposure, 2) drugs to remove radioactive materials from the body and 3) biodosimetry tools.

![EVALUATION OF PRODUCTS BY RNCP PROGRAM AREAS](image)

*Figure 3. NIAIDs portfolio includes the evaluation of numerous MCM candidates and biodosimetry technologies.*
and biomarker identification to determine levels of radiation exposure. This is accomplished through grants, collaborative agreements, contracts, and inter- and intra-agency agreements. Over 200 MCM candidates and biomarkers have been evaluated (Figure 3). Of these, six biodosimetry approaches which have reached higher technology readiness levels (TRL) have transitioned to BARDA for advanced development, and two MCMs are in the DOD pipeline for prophylaxis development. NIAID’s efforts resulted in the first two MCMs, Neupogen® and Neulasta®, approved by the FDA under the Animal Rule with the indication to treat Hematopoietic Acute Radiation Syndrome (H-ARS). Of these, six biodosimetry approaches which have reached higher technology readiness levels (TRL) have transitioned to BARDA for advanced development, and two MCMs are in the DOD pipeline for prophylaxis development. NIAID’s efforts resulted in the first two MCMs, Neupogen® and Neulasta®, approved by the FDA under the Animal Rule with the indication to treat Hematopoietic Acute Radiation Syndrome (H-ARS). 5 NIAID also received an FDA Investigational New Drug authorization to proceed with first-in-human safety/PK evaluation of an oral radionuclide decorporation agent (Hydroxypyridinone – 3,4,3(1,2 - HOPO)). Delayed effects from acute radiation exposure (DEARE) is another area of interest in NIAID’s portfolio. DEARE along with H-ARS mitigators are areas of common interest between NASA and NIAID. NASA is concerned with protecting astronauts from acute exposures caused by solar particle events and mitigating any delayed effects from these exposures that could impact quality of life for crew upon returning to Earth.

**Assistant Secretary for Preparedness and Response/Biomedical Advanced Research and Development Authority (ASPR/BARDA)**

Dr. Mary Homer, BARDA, gave a talk on their “Radiological and Nuclear Countermeasure Program”, addressing areas of focus for preparedness in order to treat injury due to exposure of acute ionizing radiation caused by Improvised Nuclear Device (IND) or Radiological Dispersal Device (RDD) Events with priority given to IND-related injuries since the impact is predicted to be greater. BARDA focuses on MCM candidates that are ready for advanced development.

Due to the complex spectrum of injuries that are anticipated to include combined injuries of acute radiation exposure, trauma, and thermal burn, treatment is expected to require a polypharmacy approach. Over the years, BARDA has evolved its focus away from organ-centric syndromes to focus on more pathophysiological processes involved in

**Figure 4. The five main focus areas for targeted product development include**

- Ischemia
- Vascular Injury / Sepsis
- Coagulopathy/ Fibrinolysis
- Inflammation
- Cell Death
radiation injury. The five main focus areas for targeted product development include: vascular injury, coagulopathies, inflammation, cell death, and ischemia. For the near term, the primary MCM development areas are for treatment of hematopoietic injury, specifically targeting thrombocytopenia and vascular injury. NASA and BARDA are both interested in addressing the systemic pathophysiological processes, along with combined effects of high skin exposures and the impact to the blood forming organs.

Dr. Lynne Wathen, BARDA, gave a brief overview on the development of radiation biodosimetry tests that may be useful during space missions or a mass casualty incident on earth. Biodosimetry is the measurement of the biological response to an absorbed dose of ionizing radiation and offers an added clinical benefit to patient observation for post-irradiation symptoms by estimating qualitative and quantitative absorbed ionizing radiation dose. A point-of-care (POC), immediate qualitative test can deliver dose prediction to triage low- and no-absorption victims from all others. In addition, a quantitative dose absorption test delivered quickly can inform physicians in advance of diagnostic neutropenia and the onset of acute radiation syndrome (ARS). Further, it can substitute a less efficient empirical treatment regimen with better-informed therapeutic management and consequently better allocation of scarce medical countermeasure resources. These two types of tests are currently under development with support from the United States Department of Health and Human Services (HHS). Initial assessments of test accuracy and positive/negative predictive values over a range of 0 to 10 Gray (Gy) are underway using extensive clinical and non-clinical validation studies.

**National Institute of Health/National Heart Lung and Blood Institute (NHLBI)**

Dr. Keith Hoots, NHLBI, gave a presentation on vascular injury and the pathogenesis of endothelial injury. Chronic radiation exposure and its effect on the vascular cell repair machinery was a focus area along with determining if there is an impact of low, chronic radiation exposure due to cross-talk between the endothelium and circulating inflammatory cells. Another area of common interest includes the central nervous system (CNS) implications for chronic low-dose radiation exposure since key endothelial cell regulatory receptor activation appears to be relevant to inflammatory signaling across the blood-brain barrier. Long-term radiation exposure and the impact on long non-coding RNAs in the vascular endothelium and other human cells was a key topic discussed. NASA and NHLBI share areas of research interest in understanding the effect of chronic low-dose radiation on the vascular system along with the mechanisms underlying the impact and the relationship of these events to the CNS.

**National Aeronautics and Space Administration (NASA)**

NASA representative, Dr. Lisa Carnell, gave an overview of the risks from exposure to Space Radiation that may require physical and/or medical countermeasures. There are two different problems to consider on long-duration deep space missions, solar particle events and galactic cosmic radiation. Each needs to be addressed individually. In the case of solar particle events, there is the potential for prodromal and H-ARS effects. Mitigation strategies include: (1) storm
shelters with active dosimetry; (2) space weather forecasting and operations scheduling that reduce exposure during extravehicular activities and provide notification for crew to shelter; and (3) MCMs that may include treatments for nausea and vomiting along with G-CSF for H-ARS, depending on the mission scenario (Table 1).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>MCM Recommendation</th>
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<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>Ondansetron (Zofran*), Granisetron (Kytril*), Aprepitant (Emend*), Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>(Decadron*)</td>
</tr>
<tr>
<td></td>
<td>Immodium*</td>
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<tr>
<td></td>
<td>Intravenous (IV) normal saline</td>
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<tr>
<td></td>
<td>penicillins, cephalosporins, macrolides, ciprofloxacin</td>
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<tr>
<td></td>
<td>prednisone</td>
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<tr>
<td></td>
<td>G-CSF, GM-CSF</td>
</tr>
<tr>
<td></td>
<td>Silver sulfadiazine, sterile gauze, parenteral opioid analgesics, crystalloid solutions, corticosteroid cream</td>
</tr>
</tbody>
</table>

Galactic cosmic radiation is comprised of approximately 86% protons (hydrogen nuclei), 13% helium nuclei, with 1% being the nuclei of heavier elements, called HZE ions. GCR is an even greater challenge to address because there are multiple effects to consider including risk of central nervous systems disorders, degenerative tissue effects in flight, and late effects that may include the central nervous system, cardiovascular and other degenerative tissue effects along with solid and hematological cancers. An ideal MCM will provide cross risk mitigation by targeting common pathways for each health impact. Table 2 provides a definition of an ideal MCM to address GCR. Requirements for a MCM to be used will depend on the mission scenario. A key aspect for consideration by NASA on long-duration missions is storage and shelf-life. A lyophilized form of a MCM may provide longer stability and weight savings. NASA has several areas of complementary interests with each of the Agencies identified beyond what was highlighted already. NASA has a demographic aligned with DOD since the astronaut corps is highly trained and monitored similar to the military, while many of the other Agencies are addressing the general population. There is a common need for extended shelf-life and storage for NASA and BARDA due to the need to include MCMs in the SNS. Determining the exposure dose is of concern to all Agencies as is developing computational modeling scenarios to predict the risk of exposure resulting in adverse health effects to the public and astronauts.
**In Summary**

Several Federal Agencies including NIH/NIAID, NIH/NCI, DoD/DTRA, DoD/AFRRI, NIH/NHLBI and ASPR/BARDA have been studying, testing and developing medical countermeasures in support of anti-terrorism activities that may involve weapons of mass destruction, dirty bombs or other means of radiation exposure. The exposures studied are typically acute, high doses of radiation including both gamma and neutrons. In moving forward with Interagency collaborations, it is important to appreciate and understand that each Agency has unique requirements for medical countermeasures. Determining complementary research interests will help expedite research and maximize cost savings.

**Acknowledgement/Disclaimer**

The views expressed in this manuscript are those of the authors; no endorsement by NCI, NIH, HHS or any other US Government Agency agencies has been given, implied, or inferred. The authors declare that there is no financial conflict of interest.

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