
2015 Space Radiation Standing Review Panel

Research Plan Review for:
The Risk of Radiation Carcinogenesis

Status Review for:
*The Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs),
The Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure,
and
The Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation
Exposure*

Final Report

I. Executive Summary and Overall Evaluation

The 2015 Space Radiation Standing Review Panel (from here on referred to as the SRP) met for a site visit in Houston, TX on December 8 – 9, 2015. The SRP met with representatives from the Space Radiation Element and members of the Human Research Program (HRP) to review the updated research plan for the Risk of Radiation Carcinogenesis Cancer Risk. The SRP also reviewed the newly revised Evidence Reports for the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (Acute Risk), the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (CNS Risk), and the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation (Degen Risk), as well as a status update on these Risks.

The SRP would like to commend Dr. Simonsen, Dr. Huff, Dr. Nelson, and Dr. Patel for their detailed presentations. The Space Radiation Element did a great job presenting a very large volume of material. The SRP considers it to be a strong program that is well-organized, well-coordinated and generates valuable data. The SRP commended the tissue sharing protocols, working groups, systems biology analysis, and standardization of models.

In several of the discussed areas the SRP suggested improvements of the research plans in the future. These include the following:

- It is important that the team has expanded efforts examining immunology and inflammation as important components of the space radiation biological response. This is an overarching and important focus that is likely to apply to all aspects of the program including acute, CVD, CNS, cancer and others. Given that the area of immunology/inflammation is highly complex (and especially so as it relates to radiation), it warrants the expansion of investigators expertise in immunology and inflammation to work with the individual research projects and also the NASA Specialized Center of Research (NSCORs).
 - Historical data on radiation injury to be entered into the Watson “big data” study must be used with caution. The general scientific issues of reproducibility, details of experimental methods and data analysis from preclinical and basic research laboratories have been raised broadly over the last few years (not specific to this work) and indicate
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that caution must be applied in the ways these data are used. This pertains to preclinical data and also to phase 3 clinical trials in radiation oncology and medical oncology. Of course, appropriate use and analysis of these “big-data” sets also offer the potential of pinpointing limitations and extracting remaining useful information. Emphasis should be placed on the latter possibility.

- A key target is risk reduction from radiation exposure. Progress of the entire space program, now moving towards the Mars mission, requires timely answers to key components of human risk, which are known to be complex. Periodic review of progress should be conducted with additional resources directed into achieving critical milestones. Turning the long red bars to yellow and green (or for some risks such as CNS possibly to grey) must be high priority. That such progress will require new science and not engineering means that it should be viewed in a knowledge-based light. The technology-based aspects of engineering issues are certainly as important, however, science and knowledge-based problems are solved in a different way than engineering. Timelines for engineering are more predictable, while for science, progress can be methodical with occasional major incremental findings that can rapidly change the rate of progress. As opportunities for rapid incremental changes arise, periodic enhancement of investment is strongly recommended to enable such new knowledge to be quickly and efficiently exploited.
- Collaborations and linkages with National Institute of Allergy and Infectious Diseases (NIAID), the Biomedical Advanced Research and Development Authority (BARDA) and the Department of Defense (DoD) are in place and more are encouraged, where possible, with the radiation injury and medical countermeasure studies. This could include utilizing some of their animal model testing contracts to facilitate obtaining results using common platforms. Such approach will facilitate the comparison of results among laboratories, and will facilitate and accelerate the development of medical countermeasures.
- It is particularly noteworthy that the NASA Space Radiation Element is reaching out to the Multidisciplinary European Low Dose Initiative (MELODI) platform coordinating low dose radiation risk research, and to other international agencies that are studying low dose radiation effects in an effort to fill the void generated by the cancelation of the Department of Energy (DOE) low dose radiation program. While NASA is working actively with NIAID and BARDA to integrate their relevant findings of radiation mitigator investigations to NASA programs, the committee notes its disappointment that the United States currently lacks a dedicated low dose radiation program with clear mechanistic orientation and aimed at the quantification and mitigation of human radiation risk on Earth. This void gives to the NASA Space Radiation Program Element special societal value, but also makes its overall design more challenging.
- Presentations during the SRP meeting focused on CNS risk demonstrated that mouse models detect marked radiation effects at selected endpoints and at doses of radiation well within the range expected during space travel. Such observations identify risk factors that may be of great relevance to the goals of the program. Given the acute nature

of concern they generate and the known strong dependence of CNS effects on the model system employed to study them, it will be important to focus the program on effects with direct relevance to humans. A possible strategy towards this goal will be to carry out with priority studies in non-human primates (NHP). The goal of such studies should be to document relevant radiation effects, and to define their dependence on radiation dose. Subsequent studies using small and medium-size animal models should then specifically address the mechanistic underpinnings of the relevant endpoints and explore means for their mitigation.

- The SRP strongly supports the ongoing efforts to standardize animal models and outcomes across studies, as well as the sharing of tissues/biological samples across studies. In addition, the SRP supports the efforts to conduct studies in large outbred populations of animals to be coordinated across groups examining CNS, Cancer, Degen and Acute Risks. This may require unique research solicitations and or funding strategies to accomplish.

Concerns exist about the use of terms such as dose-rate, very low dose-rate, etc. Instead of using this terminology in a qualitative manner, it will be more relevant to the goals of the Space Radiation Program Element to adapt their use to well-defined, realistic situations arising during space travel. In deep space travel for heavy ions (HZE) we are concerned the dose rate is extremely low and if calculated out the SRP suggests this dose is really by individual ions separated by significant time periods in any one site (cell) and should be considered discrete high dose rate events of small doses. Thus members of the SRP consider it unlikely that dose rate is an issue for HZE particle exposure of astronauts. It may be meaningful to test this fact once and for all. If true, the risk analysis models would be simplified and only have to think about dose reduction factors not dose rate reduction factors. At the very least the SRP suggests that specific expected dose rates or fluence per time unit be developed for the most important ions so that researchers understand better what this means with respect to their research.

- The Program should review funded NSCORs on a regular basis to ensure that they continue to cover relevant areas of investigation. The general feeling among SRP members is that NSCORs are a better approach than individual grants in resolving key issues addressed by the Program, as they allow in-depth mechanistic analysis of the selected scientific question(s). Moreover, they enable much-needed and promising interdisciplinary interactions. Most of the NSCORs to date have been organ-based for good reasons. But a lot of the data developed has suggested that there is overlap in both effects of a given radiation across organs that there are effects in one organ that affect another organ and mechanistic responses that are whole animal mediated. NASA might consider introducing a more directed NSCOR or two addressing a specific gap from the effect or mechanism point of view to encourage a multidisciplinary approach to issues such as inflammation, genetic instability, etc.
- The need for larger-animal studies has been mentioned above that might be organized as a hybrid-study run between NASA and selected outside groups. Given concerns regarding the reliability and reproducibility of some of the CNS work, and to leverage

existing studies, it is recommended that NASA consider funding mechanisms purposefully integrating a large numbers of groups within the research community. When planning such an endeavor, especially if the study has a biological countermeasure arm, this includes the Food and Drug Administration (FDA) animal study rules in the planning. These will make it necessary to have more than one species and larger animals than mice and rats. It is important therefore to consider at the outset that larger animals and different species will be needed and to evaluate that effects and mechanisms translate across species.

- Much of the current radiation-related work on cancer, neuroscience and cardiovascular systems, is often done in different labs using highly specialized, genetically modified murine models. These “sensitized” models are excellent for discovery work in terms of detecting subtle risks, and identifying early biological changes and specialized aspects of the underlying mechanisms. However, the pathways uncovered will consist of both common paradigms related to general radiation-induced biological changes, as well as unique mechanisms relevant only to the specific models used. In addition, much of the experimental work consists of different radiation exposure protocols, different age, sex and genetic backgrounds of animals, as well as different genetic mutants and analytical approaches. Ultimately, it will be the common fundamentals and common mechanisms that will be most useful in moving forward to translation to humans. Therefore in order to have the ability to identify the “common fundamental mechanisms”, and to compare the pathological, molecular and functional consequences across experiments, it will be important to identify some of the most useful models that will help to establish the key questions of realistic risk, common mechanisms, translatable biomarkers and eventually countermeasures. This can be arrived at by objectively reviewing the currently available data, examining standards established by external agencies (e.g. FDA), and identifying the key biological models and exposure protocols, so that the data can be compared across experiments, organs and standardized early and late time points (e.g., C57Bl6 mice WT is a commonly used murine background standard for many diseases, etc.).
- In order to collate future meta-data to identify robust genetic susceptibility loci, key gene expression pathways, microRNA levels and protein expression patterns secondary to high and low LET exposure, it is also important to ensure that standard analytical techniques are applied to all specimens destined for systems biology studies. These include the appropriate and standardized sample processing and archiving procedures, the appropriate extraction techniques, the deposition of the data in the appropriate databases with the appropriate format, as well as analytical programs that will permit eventual meta-analysis of the data to achieve adequate statistical power to detect the most robust and stable changes.
- Additional study of past, present and future astronauts is recommended, recognizing their options to agree or not, per NASA guidelines. The purpose of these studies will be to initiate personalized medicine approaches that are recognized to have high potential health benefits, and may also be useful for refining risk estimates for future NASA missions.

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- To maximize the opportunities of individualizing biological risks to radiation and other potential risks to space travel, and to examine individualized mitigation-strategies as outlined above, the ability to use human stem cells in well-defined “personalized” countermeasure strategies is particularly attractive for future prolonged space travel. Individualized storage of stem cells prior to prolonged space travel, in order to mediate potential repairs during space travel, or to mitigate diseases once returned to Earth, is an approach worth exploring. However, the technology of obtaining the best source of stem cells, the most cost-effective means of archival, the feasibility of a small portion for storage on board the spacecraft, and long term storage and retrieval on the ground will need to be considered and options evaluated at this stage. Given such potential for use of stem cells in future space travel, it is recommended to experiment with storage on the International Space Station (ISS).
 - Many of the studies presented with heavy ions in the cancer risk section either had a non-targeted effect (NTE) component or were aimed directly at looking at NTE effects at very low dose exposures. The SRP suggests NASA take a critical look at these studies as in many cases these may not be NTE effects. By definition NTE effects are in cells that have not been hit by radiation. In most types of studies NTE effects only travel 10 to 20 cells from the cell that is hit (some host factor type NTE effects travel throughout the body). In the case of HZE particles many of them have a core track and then side tracks that contain many delta rays that can travel significant distances. In essence it appears to the SRP that some studies have actually looked at mixed field effects of the core track of an ion and its lengthy side tracks of lower LET radiation such as delta rays. This is not the same as NTE effects but may be interesting and important nonetheless. NASA should determine what really constitutes an NTE study and make it clear in any further research announcements, but also entertain the same sort of technology that could separate core track effects from side track effects of the lower LET radiations produced.

II. Critique of Gaps and Tasks for the Risk of Radiation Carcinogenesis (Cancer Risk)

- A. *Have the proper Gaps been identified to mitigate the Risk?*
 - a. *Are all the Gaps relevant?*
 - b. *Are any Gaps missing?*
- B. *Have the gap targets for closure been stated in such a way that they are measureable and closeable?*
 - a. *Is the research strategy appropriate to close the Gaps?*
- C. *Have the proper Tasks been identified to fill the Gaps?*
 - a. *Are the Tasks relevant?*
 - b. *Are there any additional research areas or approaches that should be considered?*
 - c. *If a Task is completed, please comment on whether the findings contribute to addressing or closing the Gap.*
- D. *If a Gap has been closed, does the rationale for Gap closure provide the appropriate evidence to support the closure?*

Gaps and Tasks:

Cancer 01: How can experimental models of tumor development for the major tissues (lung, colon, stomach, breast, liver, and leukemias) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk projections?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends rewording the Gap Title to: *“How can experimental models of tumor development for the major tissues (lung, colon, stomach, breast, liver, and leukemias) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk **and clinical outcome** projections?”*

Tasks:

- A Novel Biological Countermeasure and Mitigator of High LET-Induced Cancer Progression
- Dose-rate effects of protons on the induction of genomic instability in vivo – Completed Task
- Duke NSCOR: Lung Cancer Risk From HZE Ions – PI: David Kirsch, M.D., Ph.D. – Duke University
- Effects of Intestinal Microflora on High-LET Radiation Mediated Toxicity and Genomic Instability – Completed Task
- Elucidating the Relationship Between the Effects of Various Radiation Qualities and Cancer Development Processes using Novel Flow-based Assays – Completed Task
- Epigenetic effects of radiation on epithelial cell self-renewal – Completed Task
- Harderian Gland Tumorigenesis: Low-Dose-, Low-Dose-Rate-, and LET-Response – PI: Eleanor Blakely, Ph.D. – Lawrence Berkeley National Laboratory
- HZE-induced mammary cancer development processes in murine and "humanized" models, and their influence on radiation quality functions – Completed Task
- NSCOR: Lung Cancer Pathogenesis and HZE Particle Exposure – Completed Task
- Mechanisms of Cell Survival Following Space Radiation-Induced Mitotic Catastrophe: Implications for Cancer Risk – Completed Task
- NSCOR: Mechanisms Underlying the Risk of HZE Particle-Induced Solid Tumor Development – PI: Ya Wang, Ph.D. – Emory University
- NSCOR: NASA Specialized Center of Research on Radiation Carcinogenesis – PI: Robert Ullrich, Ph.D. – University of Texas Medical Branch
- NSCOR: Risks Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation – PI: John Minna, Ph.D. – University of Texas Southwestern Medical Center
- NSCOR: Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects – Completed Task
- NSCOR: Space Radiation and Intestinal Tumorigenesis: Risk Assessment and Counter Measure Development – PI: Albert Fornace, Ph.D. – Georgetown University
- NSCOR: The contribution of non-targeted effects in HZE cancer risk – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
- The Relation Between Mutagenesis and Genomic Instability After Particle Exposure In Vivo – Completed Task
- Tissue-specific acute and late molecular surveillance of particle radiation effects –

Completed Task

- In vivo induction of chromosome instability and aberrant patterns of DNA methylation in hematopoietic stem/progenitor cells by heavy ions – PI: Kanokporn Rithidech, Ph.D. – State University New York at Stony Brook
- Characterization of the Tumor Spectrum Arising in HZE Ion Irradiated Outbred Mice – PI: Michael Weil, Ph.D. – Colorado State University
- Synergistic Effects of Bcl2, Cigarette Smoking and Space Radiation on Carcinogenesis – PI: Xingming Deng, Ph.D. – Emory University
- High LET Radiation Induced Carcinogenesis: Epigenetic Mechanisms in Mouse Models of Human Cancers-NNX13AK69G – PI: Janet Baulch, Ph.D. – University of California, Irvine
- 3D Tissue Models for Study of Intercellular Signaling Stimulated by High Energy Particles – Completed Task
- Targeting protein cross talk signaling as a biological predictor for space radiation cancer risk – PI: Mohan Natarajan, Ph.D. – University of Texas Health Science Center at San Antonio
- DNA Damage Responses Induced by HZE Particles In Human Cells – Completed Task
- Mouse models approach for intestinal tumorigenesis estimates by space radiation – Completed Task
- Histone Acetyltransferases and the Cellular Response to DNA Damage – Completed Task
- A role for homologous recombination in complex DSB repair after HZE particles – Completed Task
- NSCOR Radiation Leukemogenesis – Completed Task
- NSCOR: Mechanisms of HZE Damage and Repair in Human Epithelial Cells – Completed Task
- Fundamental Biological studies of protein phosphorylation profiles after HZE exposure – Completed Task
- Risk Assessment of Space Radiation-Enhanced Colon Tumorigenesis – Completed Task
- Risk Assessment of Space Radiation-Enhanced Colon Tumorigenesis--NNX08BA54G – Completed Task
- Mechanistic Study of the Risk of Low Doses of HZE Particles on Human Cell Pre-Malignant Transformation – PI: Minli Wang, Ph.D. – USRA
- A Systems Analysis of Progression-Phase Determinants of Radiation-Induced Carcinogenesis and its Modulation by Stem Cells – Completed Task
- High-LET Radiation, Reproductive Hormones and Chronic Inflammation: An Integrated Approach to Carcinogenesis Risk Estimate – PI: Kamal Datta, Ph.D. – Georgetown University
- HZE Radiation Effects on Malignant Progression in Human Epithelial Cells – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
- Impact of Age, Genetics Variants and High LET Track Structure on Mammary Cancer Risk Estimates – PI: Janice Pluth, Ph.D. – Lawrence Berkeley National Laboratory
- Mouse Glioma Models to Estimate Cancer Risks from HZE Particle Exposure – PI: Sandeep Burma, Ph.D. – University of Texas Southwestern Medical Center at Dallas
- The Role of the Bone Marrow Microenvironment in Space Radiation-Induced

Leukemogenesis – PI: Christopher Porada, Ph.D. – Wake Forest University School of Medicine

- Low Dose IR Activation of TGF-Beta 1-IGF-1-sCLU In Vivo: Mechanisms, Functions of a Changing Microenvironment – Completed Task
- Links Between Persistent DNA Damage, Genome Instability, and Aging – PI: William Dynan, Ph.D. – Emory University
- Mitochondrial-Derived Oxidants and Cellular Responses to Low Dose/Low LET Ionizing Radiation – Completed Task
- Systematic Identification of Genes and Signal Transduction Pathways Involved in Radio-Adaptive Response – Completed Task
- Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects- NNX11AK26G – Completed Task
- Contribution of GCR Exposure to Hematopoietic Stem Cell Dysfunction and Oncogenesis – PI: Stanton Gerson, M.D. – Case Western Reserve University
- Defining the role of miR-182 in HZE-Induced Tumorigenesis – PI: David Kirsch, M.D., Ph.D. – Duke University
- The Effect of High LET Radiation on Differentiation and Tumorigenesis in the Human Hematopoietic System: Modeling in vitro and in vivo for Risk Assessment – PI: Lubomir Smilenov, Ph.D. – Columbia University
- The Relation Between Mutagenesis and Genomic Instability After Particle Exposure In Vivo-NNX14AC97G – PI: Mitchell Turker, Ph.D. – Oregon Health and Science University
- HZE-induced skin carcinoma: an in-vivo-like multicellular epithelial model system for analysis of radiation quality effects and DSB repair processes – Completed Task
- Oxidative Stress and the Cancer Risk of Space Radiation – PI: Edward Azzam, Ph.D. – University of Medicine and Dentistry of New Jersey
- Exosomes and secretory factors as mediators of non-targeted effects of HZE particles – PI: William Dynan, Ph.D. – Emory University
- Induction of Hepatocellular Carcinoma by Space Radiation: A Systems Biology Study of Causative Mechanisms – PI: Mark Emmett, Ph.D. – The University of Texas Medical Branch
- Radiation-induced apoptosis avoidance and colon tumorigenesis: Epigenetic regulation in adult stem cells – PI: Nancy Turner, Ph.D. – Texas A&M University
- Space Radiation and Gastrointestinal Cancer: A Comprehensive Strategy for Risk Assessment and Model Development – PI: Albert Fornace, Ph.D. – Georgetown University
- NASA Specialized Center of Research on Carcinogenesis – PI: Michael Weil, Ph.D. – Colorado State University

Cancer 02: How can experimental models of tumor development for the other tissues (bladder, ovary, prostate, brain, uterus, esophagus, skin, etc.) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk projections?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends rewording the gap title to: “*How can experimental models of*

*tumor development for the other tissues (bladder, ovary, prostate, brain, uterus, esophagus, skin, etc.) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk **and clinical outcome** projections?”*

Tasks:

- Comparative Analysis of Charged Particle-Induced Autosomal Mutations in Murine Tissues and Cells – Completed Task
- DNA Damage Clusters in Human Cell Transformation Induced by Single or Multiple Space Radiation Ion Exposures—Wilson – Completed Task
- Effects of prolonged exposure to space radiation on carcinogenesis and neuroendocrine differentiation in human prostate models – Completed Task
- Harderian Gland Tumorigenesis: Low-Dose-, Low-Dose-Rate-, and LET-Response – PI: Eleanor Blakely, Ph.D. – Lawrence Berkeley National Laboratory
- HZE-induced skin carcinoma: an in-vivo-like multicellular epithelial model system for analysis of radiation quality effects and DSB repair processes – Completed Task
- Impact of Radiation Quality on Cancer Processes in 2D and 3D Esophageal Cell Models – Completed Task
- Integrated experimental and computational study of radiation induced matrix remodeling in a human skin equivalent – Completed Task
- Mechanisms of Cell Survival Following Space Radiation-Induced Mitotic Catastrophe: Implications for Cancer Risk – Completed Task
- NSCOR: Mechanisms Underlying the Risk of HZE Particle-Induced Solid Tumor Development – PI: Ya Wang, Ph.D. – Emory University
- miRNA profiling of radiation response: A systems biology approach to understanding regulation of proton and heavy ion dose effects – Completed Task
- Radiation and Gliomagenesis: A Sensitive Model System to Evaluate the Tumorigenic Potential of HZE Particles – Completed Task
- Structural Chromosome Aberrations Formed in Response to Changes in Proton Energy and Dose Rate – Completed Task
- Characterization of the Tumor Spectrum Arising in HZE Ion Irradiated Outbred Mice – PI: Michael Weil, Ph.D. – Colorado State University
- 3D Tissue Models for Study of Intercellular Signaling Stimulated by High Energy Particles – Completed Task
- Targeting protein cross talk signaling as a biological predictor for space radiation cancer risk – PI: Mohan Natarajan, Ph.D. – University of Texas Health Science Center at San Antonio
- Comparative Analysis of Charged Particle-Induced Autosomal Mutagenesis in Murine Tissue and Cells – PI: Amy Kronenberg, Ph.D. – Lawrence Berkeley National Laboratory
- Mechanism of Radiation-Induced Alteration of Astrocyte-Neuronal Coupling – Completed Task
- Functional Role of The Betaig-H3 Gene In High-Energy Heavy Ions-Induced Carcinogenesis – Completed Task
- High-LET Radiation, Reproductive Hormones and Chronic Inflammation: An Integrated Approach to Carcinogenesis Risk Estimate – PI: Kamal Datta, Ph.D. – Georgetown University

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- Mouse Glioma Models to Estimate Cancer Risks from HZE Particle Exposure – PI: Sandeep Burma, Ph.D. – University of Texas Southwestern Medical Center at Dallas
 - Defining the role of miR-182 in HZE-Induced Tumorigenesis – PI: David Kirsch, M.D., Ph.D. – Duke University
 - Charged Particle Effects on the Ovary – PI: Ulrike Luderer, M.D., Ph.D. – University of California, Irvine
 - The Relation Between Mutagenesis and Genomic Instability After Particle Exposure In Vivo-NNX14AC97G – PI: Mitchell Turker, Ph.D. – Oregon Health and Science University
 - Oxidative Stress and the Cancer Risk of Space Radiation – PI: Edward Azzam, Ph.D. – University of Medicine and Dentistry of New Jersey
 - E Exosomes and secretory factors as mediators of non-targeted effects of HZE particles – PI: William Dynan, Ph.D. – Emory University
 - Mechanisms Underlying Charged Particle-Induced Disruption of CNS Function – PI: Charles Limoli, Ph.D. – University of California, Irvine

Cancer 03: How can experimental models of carcinogenesis be applied to reduce the uncertainties in radiation quality effects from SPE’s and GCR, including effects on tumor spectrum, burden, latency and progression (e.g., tumor aggression and metastatic potential)?

- The SRP thinks this Gap is appropriate and relevant.

Tasks:

- A mechanistic investigation of space radiation-induced carcinogenesis - NNX12AB88G – Completed Task
- A Novel Biodosimetry Method – Completed Task
- A Novel Biological Countermeasure and Mitigator of High LET-Induced Cancer Progression – Completed Task
- Comparative Analysis of Charged Particle-Induced Autosomal Mutations in Murine Tissues and Cells – Completed Task
- Dependence of Radiation Quality on Charged Particle-induced Early and Late Damages in Chromosomes – PI: Honglu Wu, M.D., Ph.D. – NASA Johnson Space Center
- Dose rate effects on the mechanisms of space radiation induced delayed genomic instability – Completed Task
- Effects of Intestinal Microflora on High-LET Radiation Mediated Toxicity and Genomic Instability – Completed Task
- Effects of prolonged exposure to space radiation on carcinogenesis and neuroendocrine differentiation in human prostate models – Completed Task
- Elucidating the Relationship Between the Effects of Various Radiation Qualities and Cancer Development Processes using Novel Flow-based Assays – Completed Task
- Epigenetic effects of radiation on epithelial cell self-renewal – Completed Task
- Harderian Gland Tumorigenesis: Low-Dose-, Low-Dose-Rate-, and LET-Response – PI: Eleanor Blakely, Ph.D. – Lawrence Berkeley National Laboratory
- High energy proton dose-rate and mixed field effects on neoplastic transformation in vitro – Completed Task

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- HZE-induced mammary cancer development processes in murine and "humanized" models, and their influence on radiation quality functions – Completed Task
 - HZE-induced skin carcinoma: an in-vivo-like multicellular epithelial model system for analysis of radiation quality effects and DSB repair processes – Completed Task
 - Impact of Radiation Quality on Cancer Processes in 2D and 3D Esophageal Cell Models – Completed Task
 - Integrated experimental and computational study of radiation induced matrix remodeling in a human skin equivalent – Completed Task
 - NSCOR: Lung Cancer Pathogenesis and HZE Particle Exposure – Completed Task
 - Mechanisms for induction of bystander effects by high-energy particles in cells and tissues – Completed Task
 - Mechanisms of Cell Survival Following Space Radiation-Induced Mitotic Catastrophe: Implications for Cancer Risk – Completed Task
 - Mechanisms of the Repair of HZE Induced DNA Double-Strand Breaks in Human Cells – Completed Task
 - NSCOR: Mechanisms Underlying the Risk of HZE Particle-Induced Solid Tumor Development – PI: Ya Wang, Ph.D. – Emory University
 - Mitigating High Z Radiation Induced Genomic Instability by Non-Protein Thiols – Completed Task
 - NSCOR: NASA Specialized Center of Research on Radiation Carcinogenesis – PI: Robert Ullrich, Ph.D. – University of Texas Medical Branch
 - Radiation and Gliomagenesis: A Sensitive Model System to Evaluate the Tumorigenic Potential of HZE Particles – Completed Task
 - Radiation quality and the relationship between induced telomere dysfunction and mutagenesis – Completed Task
 - NSCOR: Risks Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation – PI: John Minna, Ph.D. – University of Texas Southwestern Medical Center
 - Role of high-LET radiation-induced mitotic catastrophe in mutagenesis: implication for carcinogenesis – Completed Task
 - NSCOR: Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects – Completed Task
 - NSCOR: Space Radiation and Intestinal Tumorigenesis: Risk Assessment and Counter Measure Development – PI: Albert Fornace, Ph.D. – Georgetown University
 - Space Radiation Effects on Genomic and Epigenetic Stability: Influence of Radiation Quality and Genetic Predisposition-NNX13AK70G – PI: Janet Baulch, Ph.D. – University of California, Irvine
 - Space Radiation Risk Assessment Project-Cucinotta – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
 - Telomeric proteins in the radiation/DNA damage response – Completed Task
 - NSCOR: The contribution of non-targeted effects in HZE cancer risk – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
 - The mechanism of excess relative risk on carcinogenesis induced by high-LET radiation – Completed Task
 - The Relation Between Mutagenesis and Genomic Instability After Particle Exposure In Vivo – Completed Task

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- The Role of Gap-Junction Communication and Oxidative Metabolism in the Biological Effects of Space Radiation – Completed Task
 - Tissue-specific acute and late molecular surveillance of particle radiation effects – Completed Task
 - High LET Radiation Induced Carcinogenesis: Epigenetic Mechanisms in Mouse Models of Human Cancers-NNX13AK69G – PI: Janet Baulch, Ph.D. – University of California, Irvine
 - 3D Tissue Models for Study of Intercellular Signaling Stimulated by High Energy Particles – Completed Task
 - Targeting protein cross talk signaling as a biological predictor for space radiation cancer risk – PI: Mohan Natarajan, Ph.D. – University of Texas Health Science Center at San Antonio
 - Comparative Analysis of Charged Particle-Induced Autosomal Mutagenesis in Murine Tissue and Cells – PI: Amy Kronenberg, Ph.D. – Lawrence Berkeley National Laboratory
 - DNA Damage Responses Induced by HZE Particles In Human Cells – Completed Task
 - Histone Acetyltransferases and the Cellular Response to DNA Damage – Completed Task
 - A role for homologous recombination in complex DSB repair after HZE particles – Completed Task
 - T-helper Cell Gene Expression and Function in Response to Low Dose and Acute Radiation – Completed Task
 - Radioprotectors and Tumors: Molecular Studies in Mice – Completed Task
 - Comparative Analysis of Fe-Induced Autosomal Mutations in Murine Tissue and Cell Lines – Completed Task
 - Heritable Genetic Changes in Cells Recovered From Irradiated 3D Tissue Constructs – Completed Task
 - Mechanisms of Human Skin Responses to Low Radiation Doses and Dose Rates – Completed Task
 - Mechanistic and Quantitative Studies of Bystander Responses in 3-D Human Tissues for Low-Dose Radiation Risk Estimation – Completed Task
 - The Contribution of Tissue Level Organization to Genomic Stability Following Low Dose/Low Dose Rate Gamma and Proton Irradiation – Completed Task
 - Mechanism of Radiation-Induced Alteration of Astrocyte-Neuronal Coupling – Completed Task
 - NSCOR Radiation Leukemogenesis – Completed Task
 - HZE Radiation: Modulation Of Genetic Effects By RNA Interference Of NHEJ – Completed Task
 - NSCOR: Mechanisms of HZE Damage and Repair in Human Epithelial Cells – Completed Task
 - Methods for Real Time Measurement of Dose and Charged Particle Spectrum – Completed Task
 - Early Detection of Inflammatory Response and the Subsequent Health Outcomes Due to High LET Particle Radiation: An Integrated Metabolomics Study – Completed Task
 - Fundamental Biological studies of protein phosphorylation profiles after HZE exposure – Completed Task

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- Mechanisms of the Repair of HZE Induced DNA Double-Strand Breaks in Human Cells - NNX12AH07G – Completed Task
 - Mechanistic Study of the Risk of Low Doses of HZE Particles on Human Cell Pre-Malignant Transformation – PI: Minli Wang, Ph.D. – USRA
 - A Systems Analysis of Progression-Phase Determinants of Radiation-Induced Carcinogenesis and its Modulation by Stem Cells – Completed Task
 - High-LET Radiation, Reproductive Hormones and Chronic Inflammation: An Integrated Approach to Carcinogenesis Risk Estimate – PI: Kamal Datta, Ph.D. – Georgetown University
 - Impact of Age, Genetics Variants and High LET Track Structure on Mammary Cancer Risk Estimates – PI: Janice Pluth, Ph.D. – Lawrence Berkeley National Laboratory
 - Mechanism of Clustered DNA Double-strand Break Repair in Response to HZE Particles in Human Cells – PI: Aroumougame Asaithamby, Ph.D. – University of Texas Southwestern Medical Center
 - Mouse Glioma Models to Estimate Cancer Risks from HZE Particle Exposure – PI: Sandeep Burma, Ph.D. – University of Texas Southwestern Medical Center at Dallas
 - Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects- NNX11AK26G – Completed Task
 - Contribution of GCR Exposure to Hematopoietic Stem Cell Dysfunction and Oncogenesis – PI: Stanton Gerson, M.D. – Case Western Reserve University
 - Defining the role of miR-182 in HZE-Induced Tumorigenesis – PI: David Kirsch, M.D., Ph.D. – Duke University
 - The Contribution of Delta Rays to the Chromosome Aberration Dose Response in Human Cells Irradiated with HZE Particles of Different Energy but the Same LET – PI: Bradford Loucas, M.D., Ph.D. – University of Texas Medical Branch, Galveston
 - The Relation Between Mutagenesis and Genomic Instability After Particle Exposure In Vivo-NNX14AC97G – PI: Mitchell Turker, Ph.D. – Oregon Health and Science University
 - Oxidative Stress and the Cancer Risk of Space Radiation – PI: Edward Azzam, Ph.D. – University of Medicine and Dentistry of New Jersey
 - Molecular characterization of transmissible chromosome aberrations produced by ions of intermediate and high atomic number – PI: Michael Cornforth, Ph.D. – University of Texas Medical Branch
 - Exosomes and secretory factors as mediators of non-targeted effects of HZE particles – PI: William Dynan, Ph.D. – Emory University
 - Induction of Hepatocellular Carcinoma by Space Radiation: A Systems Biology Study of Causative Mechanisms – PI: Mark Emmett, Ph.D. – The University of Texas Medical Branch
 - Space Radiation Risk Assessment Project – PI: Steven Blattnig, Ph.D. – NASA Langley Research Center
 - Space Radiation and Gastrointestinal Cancer: A Comprehensive Strategy for Risk Assessment and Model Development – PI: Albert Fornace, Ph.D. – Georgetown University
 - NASA Specialized Center of Research on Carcinogenesis – PI: Michael Weil, Ph.D. – Colorado State University

Cancer 04: How can models of cancer risk be applied to reduce the uncertainties in dose-rate dependence of risks from SPE's and GCR?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends changing the Gap Title to: *“How can experimental evidence be improved to determine if dose-rate dependence for HZE particles is a risk? If so, how can models of cancer risk be applied?”*

Task:

- A Novel Biodosimetry Method – Completed Task
- A Novel Biological Countermeasure and Mitigator of High LET-Induced Cancer Progression – Completed Task
- DNA Damage Clusters in Human Cell Transformation Induced by Single or Multiple Space Radiation Ion Exposures—Wilson – Completed Task
- Dose-Rate Effects and Components of Systems Governing Variations in Susceptibility for Carcinogenic and Acute Radiation Risks following Gamma-Ray, Proton, or HZE Irradiation – Completed Task
- Dose-rate effects of protons on the induction of genomic instability in vivo – Completed Task
- Effects of prolonged exposure to space radiation on carcinogenesis and neuroendocrine differentiation in human prostate models – Completed Task
- Harderian Gland Tumorigenesis: Low-Dose-, Low-Dose-Rate-, and LET-Response – PI: Eleanor Blakely, Ph.D. – Lawrence Berkeley National Laboratory
- NSCOR: Mechanisms Underlying the Risk of HZE Particle-Induced Solid Tumor Development – PI: Ya Wang, Ph.D. – Emory University
- NSCOR: NASA Specialized Center of Research on Radiation Carcinogenesis – PI: Robert Ullrich, Ph.D. – University of Texas Medical Branch
- NSCOR: Lung Cancer Pathogenesis and HZE Particle Exposure – Completed Task
- NSCOR: Risks Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation – PI: John Minna, Ph.D. – University of Texas Southwestern Medical Center
- NSCOR: Space Radiation and Intestinal Tumorigenesis: Risk Assessment and Counter Measure Development – PI: Albert Fornace, Ph.D. – Georgetown University
- Space Radiation Risk Assessment Project-Cucinotta – Completed Task
- Structural Chromosome Aberrations Formed in Response to Changes in Proton Energy and Dose Rate – Completed Task
- The mechanism of excess relative risk on carcinogenesis induced by high-LET radiation – Completed Task
- Tissue-specific acute and late molecular surveillance of particle radiation effects – Completed Task
- 3D Tissue Models for Study of Intercellular Signaling Stimulated by High Energy Particles – Completed Task
- Targeting protein cross talk signaling as a biological predictor for space radiation cancer risk – PI: Mohan Natarajan, Ph.D. – University of Texas Health Science Center at San Antonio
- T-helper Cell Gene Expression and Function in Response to Low Dose and Acute

Radiation – Completed Task

- Radioprotectors and Tumors: Molecular Studies in Mice – Completed Task
- Heritable Genetic Changes in Cells Recovered From Irradiated 3D Tissue Constructs – Completed Task
- Mechanisms of Human Skin Responses to Low Radiation Doses and Dose Rates – Completed Task
- Mechanistic and Quantitative Studies of Bystander Responses in 3-D Human Tissues for Low-Dose Radiation Risk Estimation – Completed Task
- The Contribution of Tissue Level Organization to Genomic Stability Following Low Dose/Low Dose Rate Gamma and Proton Irradiation – Completed Task
- NSCOR Radiation Leukemogenesis – Completed Task
- Mechanistic Study of the Risk of Low Doses of HZE Particles on Human Cell Pre-Malignant Transformation – PI: Minli Wang, Ph.D. – USRA
- A Systems Analysis of Progression-Phase Determinants of Radiation-Induced Carcinogenesis and its Modulation by Stem Cells – Completed Task
- High-LET Radiation, Reproductive Hormones and Chronic Inflammation: An Integrated Approach to Carcinogenesis Risk Estimate – PI: Kamal Datta, Ph.D. – Georgetown University
- Mechanism of Clustered DNA Double-strand Break Repair in Response to HZE Particles in Human Cells – PI: Aroumougame Asaithamby, Ph.D. – University of Texas Southwestern Medical Center
- Mouse Glioma Models to Estimate Cancer Risks from HZE Particle Exposure – PI: Sandeep Burma, Ph.D. – University of Texas Southwestern Medical Center at Dallas
- The Contribution of Delta Rays to the Chromosome Aberration Dose Response in Human Cells Irradiated with HZE Particles of Different Energy but the Same LET – PI: Bradford Loucas, Ph.D. – University of Texas Medical Branch, Galveston
- Oxidative Stress and the Cancer Risk of Space Radiation – PI: Edward Azzam, Ph.D. – University of Medicine and Dentistry of New Jersey
- Exosomes and secretory factors as mediators of non-targeted effects of HZE particles – PI: William Dynan, Ph.D. – Emory University
- Space Radiation Risk Assessment Project – PI: Steven Blattnig, Ph.D. – NASA Langley Research Center
- Space Radiation and Gastrointestinal Cancer: A Comprehensive Strategy for Risk Assessment and Model Development – PI: Albert Fornace, Ph.D. – Georgetown University
- NASA Specialized Center of Research on Carcinogenesis – PI: Michael Weil, Ph.D. – Colorado State University

Cancer 05: How can models of cancer risk be applied to reduce the uncertainties in individual radiation sensitivity including genetic and epigenetic factors from SPE and GCR?

- The SRP thinks this Gap is appropriate and relevant.

Tasks:

- A Novel Biological Countermeasure and Mitigator of High LET-Induced Cancer

Progression – Completed Task

- Dependence of Radiation Quality on Charged Particle-induced Early and Late Damages in Chromosomes – PI: Honglu Wu, M.D., Ph.D. – NASA Johnson Space Center
- Effects of Intestinal Microflora on High-LET Radiation Mediated Toxicity and Genomic Instability – Completed Task
- Harderian Gland Tumorigenesis: Low-Dose-, Low-Dose-Rate-, and LET-Response – PI: Eleanor Blakely, Ph.D. – Lawrence Berkeley National Laboratory
- NSCOR: Lung Cancer Pathogenesis and HZE Particle Exposure – Completed Task
- miRNA profiling of radiation response: A systems biology approach to understanding regulation of proton and heavy ion dose effects – Completed Task
- NSCOR: Risks Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation – PI: John Minna, Ph.D. – University of Texas Southwestern Medical Center
- Space Radiation Effects on Genomic and Epigenetic Stability: Influence of Radiation Quality and Genetic Predisposition-NNX13AK70G – PI: Janet Baulch, Ph.D. – University of California, Irvine
- Space Radiation Risk Assessment Project-Cucinotta – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
- NSCOR: The contribution of non-targeted effects in HZE cancer risk – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
- In vivo induction of chromosome instability and aberrant patterns of DNA methylation in hematopoietic stem/progenitor cells by heavy ions – PI: Kanokporn Rithidech, Ph.D. – State University New York at Stony Brook
- Characterization of the Tumor Spectrum Arising in HZE Ion Irradiated Outbred Mice – PI: Michael Weil, Ph.D. – Colorado State University
- High LET Radiation Induced Carcinogenesis: Epigenetic Mechanisms in Mouse Models of Human Cancers-NNX13AK69G – PI: Janet Baulch, Ph.D. – University of California, Irvine
- NSCOR: Mechanisms of HZE Damage and Repair in Human Epithelial Cells – Completed Task
- Impact of Individual Susceptibility and Previous Radiation Risk for Astronauts – Completed Task
- High-LET Radiation, Reproductive Hormones and Chronic Inflammation: An Integrated Approach to Carcinogenesis Risk Estimate – PI: Kamal Datta, Ph.D. – Georgetown University
- Impact of Age, Genetics Variants and High LET Track Structure on Mammary Cancer Risk Estimates – PI: Janice Pluth, Ph.D. – Lawrence Berkeley National Laboratory
- Mechanism of Clustered DNA Double-strand Break Repair in Response to HZE Particles in Human Cells – PI: Aroumougame Asaithamby, Ph.D. – University of Texas Southwestern Medical Center
- Mouse Glioma Models to Estimate Cancer Risks from HZE Particle Exposure – PI: Sandeep Burma, Ph.D. – University of Texas Southwestern Medical Center at Dallas
- The Role of the Bone Marrow Microenvironment in Space Radiation-Induced Leukemogenesis – PI: Christopher Porada, Ph.D. – Wake Forest University School of Medicine
- Patterns of Energy Deposition by HZE Particles in Cellular Targets – Completed Task

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- Systems Biology Model of Interactions Between Tissue Growth Factors and DNA Damage Pathways: Low Dose Response and Cross-Talk in TGFbeta and ATM Signaling – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
 - Mitochondrial-Derived Oxidants and Cellular Responses to Low Dose/Low LET Ionizing Radiation – Completed Task
 - Contribution of GCR Exposure to Hematopoietic Stem Cell Dysfunction and Oncogenesis – PI: Stanton Gerson, Ph.D. – Case Western Reserve University
 - Defining the role of miR-182 in HZE-Induced Tumorigenesis – PI: David Kirsch, M.D., Ph.D. – Duke University
 - Oxidative Stress and the Cancer Risk of Space Radiation – PI: Edward Azzam, Ph.D. – University of Medicine and Dentistry of New Jersey
 - Space Radiation Risk Assessment Project – PI: Steven Blattnig, Ph.D. – NASA Langley Research Center
 - Mechanisms Underlying Charged Particle-Induced Disruption of CNS Function – PI: Charles Limoli, Ph.D. – University of California, Irvine
 - Space Radiation and Gastrointestinal Cancer: A Comprehensive Strategy for Risk Assessment and Model Development – PI: Albert Fornace, Ph.D. – Georgetown University
 - NASA Specialized Center of Research on Carcinogenesis – PI: Michael Weil, Ph.D. – Colorado State University
 - Individual Genetic Susceptibility – Completed Task

Cancer 06: How can models of cancer risk be applied to reduce the uncertainties in the age and sex dependence of cancer risks from SPE's and GCR?

- The SRP thinks this Gap is appropriate and relevant.

Tasks:

- A Novel Biological Countermeasure and Mitigator of High LET-Induced Cancer Progression – Completed Task
- Effects of Intestinal Microflora on High-LET Radiation Mediated Toxicity and Genomic Instability – Completed Task
- HZE-induced mammary cancer development processes in murine and "humanized" models, and their influence on radiation quality functions – Completed Task
- NSCOR: Risks Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation – PI: John Minna, Ph.D. – University of Texas Southwestern Medical Center
- NSCOR: Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects – Completed Task
- Space Radiation Risk Assessment Project-Cucinotta – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
- NSCOR: The contribution of non-targeted effects in HZE cancer risk – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
- Characterization of the Tumor Spectrum Arising in HZE Ion Irradiated Outbred Mice – PI: Michael Weil, Ph.D. – Colorado State University
- NSCOR: Mechanisms of HZE Damage and Repair in Human Epithelial Cells – Completed Task

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- High-LET Radiation, Reproductive Hormones and Chronic Inflammation: An Integrated Approach to Carcinogenesis Risk Estimate – PI: Kamal Datta, Ph.D. – Georgetown University
 - HZE Radiation Effects on Malignant Progression in Human Epithelial Cells – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
 - Impact of Age, Genetics Variants and High LET Track Structure on Mammary Cancer Risk Estimates – PI: Janice Pluth, Ph.D. – Lawrence Berkeley National Laboratory
 - The Role of the Bone Marrow Microenvironment in Space Radiation-Induced Leukemogenesis – PI: Christopher Porada, Ph.D. – Wake Forest University School of Medicine
 - Mouse Glioma Models to Estimate Cancer Risks from HZE Particle Exposure – PI: Sandeep Burma, Ph.D. – University of Texas Southwestern Medical Center at Dallas
 - Patterns of Energy Deposition by HZE Particles in Cellular Targets – Completed Task
 - Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects- NNX11AK26G – Completed Task
 - Oxidative Stress and the Cancer Risk of Space Radiation – PI: Edward Azzam, Ph.D. – University of Medicine and Dentistry of New Jersey
 - Space Radiation Risk Assessment Project – PI: Steven Blattnig, Ph.D. – NASA Langley Research Center
 - Space Radiation and Gastrointestinal Cancer: A Comprehensive Strategy for Risk Assessment and Model Development – PI: Albert Fornace, Ph.D. – Georgetown University
 - NASA Specialized Center of Research on Carcinogenesis – PI: Michael Weil, Ph.D. – Colorado State University

Cancer 07: How can systems biology approaches be used to integrate research on the molecular, cellular, and tissue mechanisms of radiation damage to improve the prediction of the risk of cancer and to evaluate the effectiveness of CM's? How can epidemiology data and scaling factors support this approach?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends spelling out the countermeasures (CM) instead of using the abbreviation in the Gap Title.

Tasks:

- A Novel Biological Countermeasure and Mitigator of High LET-Induced Cancer Progression – Completed Task
- Duke NSCOR: Lung Cancer Risk From HZE Ions – PI: David Kirsch, Ph.D. – Duke University
- Effects of prolonged exposure to space radiation on carcinogenesis and neuroendocrine differentiation in human prostate models – Completed Task
- Elucidating the Relationship Between the Effects of Various Radiation Qualities and Cancer Development Processes using Novel Flow-based Assays – Completed Task
- Epigenetic effects of radiation on epithelial cell self-renewal – Completed Task
- Integrated experimental and computational study of radiation induced matrix remodeling in a human skin equivalent – Completed Task

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- NSCOR: Mechanisms Underlying the Risk of HZE Particle-Induced Solid Tumor Development – PI: Ya Wang, Ph.D. – Emory University
 - NSCOR: NASA Specialized Center of Research on Radiation Carcinogenesis – PI: Robert Ullrich, Ph.D. – University of Texas Medical Branch
 - NSCOR: Risks Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation – PI: John Minna, Ph.D. – University of Texas Southwestern Medical Center
 - NSCOR: Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects – Completed Task
 - Space Radiation Risk Assessment Project-Cucinotta – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
 - NSCOR: The contribution of non-targeted effects in HZE cancer risk – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
 - 3D Tissue Models for Study of Intercellular Signaling Stimulated by High Energy Particles – Completed Task
 - Computational Modeling Of Chromosome Aberrations Produced By HZE Particles – Completed Task
 - NSCOR: Mechanisms of HZE Damage and Repair in Human Epithelial Cells – Completed Task
 - Mechanistic Study of the Risk of Low Doses of HZE Particles on Human Cell Pre-Malignant Transformation – PI: Minli Wang, Ph.D. – USRA
 - A Systems Analysis of Progression-Phase Determinants of Radiation-Induced Carcinogenesis and its Modulation by Stem Cells – Completed Task
 - High-LET Radiation, Reproductive Hormones and Chronic Inflammation: An Integrated Approach to Carcinogenesis Risk Estimate – PI: Kamal Datta, Ph.D. – Georgetown University
 - HZE Radiation Effects on Malignant Progression in Human Epithelial Cells – PI: Mary Barcellos-Hoff, Ph.D. – University of California, San Francisco
 - Mouse Glioma Models to Estimate Cancer Risks from HZE Particle Exposure – PI: Sandeep Burma, Ph.D. – University of Texas Southwestern Medical Center at Dallas
 - Low Dose IR Activation of TGF-Beta 1-IGF-1-sCLU In Vivo: Mechanisms, Functions of a Changing Microenvironment – Completed Task
 - Systems Biology Model of Interactions Between Tissue Growth Factors and DNA Damage Pathways: Low Dose Response and Cross-Talk in TGFbeta and ATM Signaling – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
 - Solid Tumor Risk Estimation: Incorporating Intercellular Interaction Effects- NNX11AK26G – Completed Task
 - Charged Particle Effects on the Ovary – PI: Ulrike Luderer, M.D., Ph.D. – University of California, Irvine
 - Oxidative Stress and the Cancer Risk of Space Radiation – PI: Edward Azzam, Ph.D. – University of Medicine and Dentistry of New Jersey
 - Molecular characterization of transmissible chromosome aberrations produced by ions of intermediate and high atomic number – PI: Michael Cornforth, Ph.D. – University of Texas Medical Branch
 - Exosomes and secretory factors as mediators of non-targeted effects of HZE particles – PI: William Dynan, Ph.D. – Emory University

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- Induction of Hepatocellular Carcinoma by Space Radiation: A Systems Biology Study of Causative Mechanisms – PI: Mark Emmett, Ph.D. – The University of Texas Medical Branch
 - Radiation-induced apoptosis avoidance and colon tumorigenesis: Epigenetic regulation in adult stem cells – PI: Nancy Turner, Ph.D. – Texas A&M University
 - Space Radiation Risk Assessment Project – PI: Steven Blattnig, Ph.D. – NASA Langley Research Center
 - Space Radiation and Gastrointestinal Cancer: A Comprehensive Strategy for Risk Assessment and Model Development – PI: Albert Fornace, Ph.D. – Georgetown University
 - NASA Specialized Center of Research on Carcinogenesis – PI: Michael Weil, Ph.D. – Colorado State University

Cancer 08: What biological countermeasures should be used to reduce SPE and GCR cancer risks? What side effects should be tolerated vs. mission risks?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends rewording the gap title to: “*What ~~biological~~ biomedical countermeasures should be used to reduce SPE and GCR cancer risks? What side effects should be tolerated vs. mission risks?*”

Tasks:

- A Novel Biological Countermeasure and Mitigator of High LET-Induced Cancer Progression – Completed Task
- NSCOR: Mechanisms Underlying the Risk of HZE Particle-Induced Solid Tumor Development – PI: Ya Wang, Ph.D. – Emory University
- Mitigating High Z Radiation Induced Genomic Instability by Non-Protein Thiols – Completed Task
- Mitochondrial-Derived Oxidants and Cellular Responses to Low Dose/Low LET Ionizing Radiation – Completed Task
- NSCOR: NASA Specialized Center of Research on Radiation Carcinogenesis – PI: Robert Ullrich, Ph.D. – University of Texas Medical Branch
- NSCOR: Space Radiation and Intestinal Tumorigenesis: Risk Assessment and Counter Measure Development – PI: Albert Fornace, Ph.D. – Georgetown University
- T-helper Cell Gene Expression and Function in Response to Low Dose and Acute Radiation – Completed Task
- Radioprotectors and Tumors: Molecular Studies in Mice – Completed Task
- Heritable Genetic Changes in Cells Recovered From Irradiated 3D Tissue Constructs – Completed Task
- Mechanisms of Human Skin Responses to Low Radiation Doses and Dose Rates – Completed Task
- Mechanistic and Quantitative Studies of Bystander Responses in 3-D Human Tissues for Low-Dose Radiation Risk Estimation – Completed Task
- The Contribution of Tissue Level Organization to Genomic Stability Following Low Dose/Low Dose Rate Gamma and Proton Irradiation – Completed Task
- Fundamental Biological studies of protein phosphorylation profiles after HZE exposure –

Completed Task

- Risk Assessment of Space Radiation-Enhanced Colon Tumorigenesis--NNX08BA54G – Completed Task

Cancer 09: Are there significant synergistic effects from other spaceflight factors (e.g. altered gravity (μ -gravity), stress, altered immune function, altered circadian rhythms, depressed nutritional status, or other) that modify the carcinogenic risk from space radiation?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends rewording the Gap Title to: “*Are there significant synergistic interactive effects from other spaceflight factors (e.g., altered gravity (microgravity), stress, altered immune function, altered circadian rhythms, depressed nutritional status, or other) that modify the carcinogenic risk from space radiation?*”

No current or planned tasks

Cancer 10: Are space validation experiments needed for verifying knowledge of carcinogenic or other risks prior to long-term deep space missions, and if so what experiments should be undertaken?

- The SRP thinks this Gap is appropriate and relevant.
- Under this Gap it may be useful to consider what research is needed to send sorted specific human adult stem cells into space (say aboard ISS for long periods of time) and if this should be started soon to elucidate: 1) Can they be preserved in space and then recovered alive for use?; 2) What level of shielding would be needed to completely shield say a pint of stem cells (to Earth background level)?; and 3) What effect would space radiation have at a lower shielding threshold?

No current or planned tasks

Cancer 11: What are the most effective shielding approaches to mitigate cancer risks?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends rewording the Gap Title to: “*What are the most effective shielding approaches to mitigate cancer risks with emphasis on the type and quantity of secondary radiations produced by the shielding and considering the LET and Z’s of the particles that ultimately reach the target?*”

Tasks:

- Measurements and Transport Phase 2 Physics Project – PI: John Norbury, Ph.D. – NASA Langley Research Center
- Quantum Multiple Scattering Model of Heavy Ion Fragmentation (QMSFRG) – Completed Task
- Space Radiation Risk Assessment Project-Cucinotta – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
- Update of the Nuclear Fragmentation Cross Section Code NUCFRG2 – Completed Task
- Fast Neutron Dosimeter for the Space Environment – Completed Task

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- Molecular and cellular effects of heavy ion fragmentation due to shielding – Completed Task
 - Spectroscopic Dosimeter – Completed Task
 - Integrated Radiation Analysis and Design Tools – PI: Chris Sandridge, Ph.D. – NASA Langley Research Center

Cancer 12: What quantitative models, numerical methods, and experimental data are needed to accurately describe the primary space radiation environment and transport through spacecraft materials and tissue to evaluate dose composition in critical organs for mission relevant radiation environments (ISS, Free-space, Lunar, or Mars)?

- The SRP thinks this Gap is appropriate and relevant.

Tasks:

- Measurements and Transport Phase 2 Physics Project – PI: John Norbury, Ph.D. – NASA Langley Research Center
- Quantum Multiple Scattering Model of Heavy Ion Fragmentation (QMSFRG) – Completed Task
- Space Radiation Risk Assessment Project-Cucinotta – PI: Francis Cucinotta, Ph.D. – University of Nevada, Las Vegas
- Update of the Nuclear Fragmentation Cross Section Code NUCFRG2 – Completed Task
- Integrated Radiation Analysis and Design Tools – PI: Chris Sandridge, Ph.D. – NASA Langley Research Center

Cancer 13: What are the most effective approaches to integrate radiation shielding analysis codes with collaborative engineering design environments used by spacecraft and planetary habitat design efforts?

- The SRP thinks this Gap is appropriate and relevant.

Tasks:

- Integrated Radiation Analysis and Design Tools – PI: Chris Sandridge, Ph.D. – NASA Langley Research Center

Cancer 14: What biodosimetry methods are required for exploration missions and how can biomarker approaches be used for outcome prediction and surveillance?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends rewording the gap title to: “*What biodosimetry methods are required for exploration missions and how can biomarker, including imaging, approaches be used for outcome prediction and surveillance?*”

Tasks:

- A Novel Biodosimetry Method – Completed Task
- miRNA profiling of radiation response: A systems biology approach to understanding regulation of proton and heavy ion dose effects – Completed Task
- Analysis of Clastogenic Factors in Gamma-Exposed Animals – PI: Honglu Wu, M.D., Ph.D. – NASA Johnson Space Center

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- Chromatid Painting for Chromosomal Inversion Detection – Completed Task
 - Cytogenetic Study Of Heavy Ion-Induced Chromosomal Damage In Human Cells – Completed Task
 - NEXGEN Approaches to Chromatid Painting – Completed Task
 - Dose-Rate Effects and Components of Systems Governing Variations in Susceptibility for Carcinogenic and Acute Radiation Risks following Gamma-Ray, Proton, or HZE Irradiation – Completed Task

Cancer 15: Given that the majority of astronauts are never smokers, are there research approaches that can elucidate the potential confounding effects of tobacco use inherent in population-based epidemiology data on space radiation cancer risk estimates?

- The SRP thinks this Gap is appropriate and relevant.
- The SRP recommends rewording the gap title to: “*Given that the majority of astronauts are never smokers, are there research approaches that can elucidate the potential confounding effects of traditional risk factors (e.g., tobacco smoke, alcohol, environmental pollutants, etc.) inherent in population-based epidemiology data on space radiation cancer risk estimates?*”

Tasks:

- Synergistic Effects of Bcl2, Cigarette Smoking and Space Radiation on Carcinogenesis – PI: Xingming Deng, Ph.D. – Emory University

III. Discussion on the strengths and weaknesses of the IRP and identify remedies for the weaknesses, including answering these questions:

- A. Are the Risks addressed in a comprehensive manner?
- The SRP thinks the Risks are addressed in a comprehensive manner and that the Space Radiation Element is doing a good job at trying to alleviate the Risks.
- B. Are there areas of integration across HRP disciplines that are not addressed that would better address the Cancer Risk?
- Although the Space Radiation Element demonstrated integration with some of the HRP disciplines, the SRP thinks there needs to be even more collaboration with the immune and nutrition disciplines, as well as exercise (Human Health Countermeasures (HHC) Element).

IV. Evaluation of the progress on the Cancer Risk Research Plan since the 2014 SRP meeting

The SRP is very pleased with the progress of the Cancer Risk research plan since the 2014 SRP meeting. The Cancer Risk research plan is very well developed and organized and continuous to generate valuable and relevant knowledge. The SRP also thinks the Space Radiation Element has been very responsive to previous SRP comments on the Cancer Risk.

V. Additional Comments regarding the Cancer Risk Research Plan

- Whole genome analysis by DNA sequencing for determining existing genetic risks for various health consequences may help in selection for individual in-flight risk mitigation strategies and post-flight surveillance based on medical and molecular characteristics. Given the potential for personalized cancer surveillance and care in the new era of molecular medicine, the ability for early diagnosis and molecular-based treatment may reduce the risk of death from cancer by enhancing cures and/or making it a chronic disease.
- Given that many cancers are curable and that screening and risk-reduction procedures may reduce mortality, the improved and improving outcomes for people following the diagnosis of cancer should be taken into account when calculating mortality for all hazards to the astronauts.

VI. Additional Comments regarding the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (Acute Risk) Status Review

- The current needs include more awareness of emerging areas: expand work in immunology, coagulopathies, endothelial cells as potential target cells, inflammation as playing a role in the acute response, and vascular changes. The endothelial cells in arterioles are one of the most sensitive cells to radiation known. Since they are present in every organ and may be the determining factor of response at low dose, it is very important that vascular effects be separated from cardiac effects.

VII. Additional Comments regarding the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (CNS Risk) Status Review

- The SRP is pleased with the significant advances in describing the effects of space radiation on the CNS that were summarized at the SRP review meeting.
- There was concern by the fact that CNS studies are mostly correlative and lack a basis for mechanistic understanding. Also the endpoints measured are frequently qualitative and the results obtained may be relevant only in the model system used to generate them. Given these limitations, emphasis on non-human primates (NHP) is warranted to identify effects relevant to human space travel. Quantitative endpoints should also be used whenever possible in carefully selected and appropriate model systems. Behavioral effects are very difficult to reproduce across species. This approach will benefit from new biology linking CNS effects to macromolecular interactions. Efforts should be made to discourage experiments “trying” to find effects at very low radiation doses, before relevance of the effect, the model system, and the radiation dose studied have been determined to be relevant to human space travel. NASA will need a comprehensive analysis of CNS risk.

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- Routine imaging of astronauts with existing technologies such as magnetic resonance imaging (MRI) and positron emission tomography (PET) can be used to generate a database to draw from in future behavioral radiation health programs.
 - There are strong mechanistic components in most components of the Space Radiation Program Element. This is very important as correlative studies rarely help resolve scientific questions and cannot help in the development of educated countermeasures. Along similar lines, the CNS component of the Program needs to define relevant behavioral endpoints first and begin then with the mechanistic analysis of the underlying mechanisms. These studies: 1) will need to emphasize reproducibility of the observed effects and their clear connection to the radiation insult, 2) will need to use outbred mice to avoid genetically tainted conclusions, and 3) will need to show relevance to human space travel.
 - For astronauts who experienced relatively longer overall times in flight, conduct the newer neuroimaging and behavioral studies as a baseline to define what, if any, is the risk of CNS lesions or dysfunction.
 - It will become important to examine disease mechanisms that link the various observations, focusing on the spatial and temporal relationship between the findings, the role of systemic versus brain-based effects, the role of specific cell types (neurons, glia, endothelial cells, etc.) and the biological mechanism that links space radiation exposure to these findings.
 - Long-term strategies will be required to determine the significance of the findings from rodent studies to the human CNS, including examination of potential biomarkers from the rodents studies in human samples (although this may be complicated by the fact that these may need to be determined in cerebral spinal fluid and not blood) and confirmation/extension studies in non-human primates (as suggested by the 2012 Ad-Hoc Panel on CNS Research).
 - For those in sleep and four-person 45/60 day confinement studies, conduct neuroimaging and other biomarker tests along with behavioral tests to establish what changes are present without the presence of radiation. This will help determine what changes, if any, are attributable to radiation per se.
 - It will be critical to identify biomarkers (brain, blood and imaging) relevant to the CNS findings in animal models and cross-reference this data to existing databases in order to identify biomarkers that could be validated in non-human primate and human studies. Given that isolation of cerebrospinal fluid (CSF) from astronauts may prove difficult, and considering the significant recent advances in brain imaging, it is recommended that NASA should consider integrating brain imaging (MRI, PET) into these studies with the corresponding and relevant expertise.
 - More specific integration of the Behavioral Health and Performance Element with these efforts is recommended. This will help in directing the overall research

program, and in efforts examining synergistic effects of other physiological or space flight factors relevant to astronauts. Similarly, given the confirmed effects of physical exercise on CNS functioning and the ongoing efforts to utilize physical exercise as a countermeasure for astronauts, it is recommended that physical exercise be examined as a modifying factor for the effects of space radiation on the CNS.

VIII. Additional Comments regarding the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure (Degen Risk) Status Review

- Overall, there are interesting emerging data on cardiovascular degenerative risks. However, replication of data across models and standardization of models will be important to ensure accurate estimate of risk and understanding of biological mechanisms.
- Opportunities of Stem Cell Reprogramming as Models of Individualized Risk and Countermeasure Assessment
One way to cross validate biomarkers and move forward with personalized therapy is the ability to reprogram human stem cells into different specialized cells (e.g., neurons, myocytes, bone cells, etc.) and develop mini-organoids incorporating different cell types constituting an organ (e.g., neurons + astrocytes + oligo in brain, myocytes + fibroblasts + vascular in heart, etc.). These organoids would contain the unique genetic background of the individuals, and can be potential platforms for evaluating individualized radiation risk and countermeasure effectiveness, subject to validation. Planning and incorporating this type of consideration into future plans will be useful as a translational platform, and also relevant for therapeutic rescue (see below).
- Distinct Prioritization for Both Cardiac and Vascular Components of Risk:
It is conceptually useful to identify specifically the cardiac and vascular components of radiation risk in the cardiovascular system because of distinctions in underlying biology and functional implications. For comprehensive cardiovascular evaluation, distinct delineation of the cardiac component (e.g., myocyte susceptibility, radiation biology, released biomarkers, acute and chronic effects and counter measures) secondary to radiation low and high LET exposure, and appropriate specific cardiac functional evaluation (biomarker, imaging or physiology) should be considered separately from a mechanistic point of view from the vascular components (e.g., biomarkers such as natriuretic peptides and high sensitivity troponin are more cardiac specific, vs. adhesion molecules and platelet/coagulation markers are more vascular specific).

On the other hand, vascular evaluation, particularly with a focus on endothelial function, is important not only for promotion of atherosclerosis in the heart, but also for organ perfusion and function at remote sites (e.g., brain, gut, kidney, etc.) at the microvascular level. Vascular aging is an important emerging concept both at the

macro- and microvascular level, and radiation exposure with potential activation of inflammatory response leading to acute injury and chronic remodeling are important parameters to consider, with implications again on biomarker, imaging and physiological tools for translational assessment for vascular consequences of radiation exposure.

- Consideration of Common Mechanistic Models of Radiation Induced Biological Changes

It will be useful to develop a common mechanistic framework to consider multiple tissue processes secondary to radiation exposure relevant to space flight. This type of framework will allow cross-referencing information across different tissues, different mechanisms, mapping of biomarkers, and mitigation strategies. For example, following relevant exposure, there can be genomic instability and oxidative modifications, activating senescence programs. The latter will in turn lead to immune activation (both pro- and anti-inflammatory), changes in vascular perturbation, and potentially leading to tissue injury.

- Cross Validation of Potential Biomarker Candidates to Reflect Radiation Risks

Systems biology and discovery science can provide a multitude of potential biomarker candidates and pathway indicators. However, many of these biomarkers will only have impact and relevance if they can be validated in another cohort of relevant animal models. These will also need to be validated in human population samples, particularly where outcome phenotypes are already available.

IX. 2015 Space Radiation SRP Research Plan Review: Statement of Task for the Risk of Radiation Carcinogenesis

The 2015 Space Radiation Standing Review Panel (SRP) is chartered by the Human Research Program (HRP) Chief Scientist. The purpose of the SRP is to review the Risk of Radiation Carcinogenesis section of the current version of the HRP's Integrated Research Plan (IRP) which is located on the Human Research Roadmap (HRR) website (<http://humanresearchroadmap.nasa.gov/>). Your report, addressing each of the questions in the charge below and any addendum questions, will be provided to the HRP Chief Scientist and will also be made available on the HRR website.

The 2015 Space Radiation SRP is charged (to the fullest extent practicable) to:

1. Based on the information provided in the current version of the HRP's IRP, evaluate the ability of the IRP to satisfactorily make progress in mitigating the Risk by answering the following questions:
 - A. Have the proper Gaps been identified to mitigate the Risk?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Have the gap targets for closure been stated in such a way that they are measurable and closeable?
 - i) Is the research strategy appropriate to close the Gaps?
 - C. Have the proper Tasks been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are there any additional research areas or approaches that should be considered?
 - iii) If a Task is completed, please comment on whether the findings contribute to addressing or closing the Gap.
 - D. If a Gap has been closed, does the rationale for Gap closure provide the appropriate evidence to support the closure?
2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including, but not limited to, answering these questions:
 - A. Is the Risk addressed in a comprehensive manner?
 - B. Are there areas of integration across HRP disciplines that are not addressed that would better address the Risk?
 - C. Other
3. Based on the updates provided by the Element, please evaluate the progress in the research plan since the last SRP meeting.
4. Please comment on any important issues that are not covered in #1, #2, or #3 above, that the SRP would like to bring to the attention of the HRP Chief Scientist and/or the Element.

Additional Information Regarding This Review:

1. Expect to receive review materials at least four weeks prior to the meeting.
2. Attend a meeting in Houston, TX on December 8 - 9, 2015.
 - A. Discuss the 2015 Space Radiation SRP Statement of Task and address questions about the SRP process.
 - B. Receive presentations from the HRP Chief Scientist (or his designee), the Space Radiation Program Element (SRPE), and participate in a question and answer session, and briefing.
3. Prepare a draft final report (approximately one month after the meeting) that contains a detailed evaluation of the current IRP specifically addressing items #1, #2, and #3 of the SRP charge. The draft final report will be sent to the HRP Chief Scientist and he will forward it to the appropriate Element for their review. The SRPE and the HRP Chief Scientist will review the draft final report and identify any misunderstandings or errors of fact and then provide official feedback to the SRP within two weeks of receipt of the draft report. If any misunderstandings or errors of fact are identified, the SRP will be requested to address them and finalize the 2015 SRP Final Report as quickly as possible. The 2015 SRP Final Report will be submitted to the HRP Chief Scientist and copies will be provided to the SRPE and also made available to the other HRP Elements. The 2015 SRP Final Report will be made available on the HRR website (<http://humanresearchroadmap.nasa.gov/>).

X. 2015 Space Radiation SRP Status Review: Statement of Task for the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs), the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure, and the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure

The 2015 Space Human Factors Engineering (SHFE) Standing Review Panel (SRP) will participate in a Status Review that will occur via a site visit with the Human Research Program (HRP) Chief Scientist (or designee) and members of the Space Human Factors and Habitability (SHFH) Element. The purpose of this review is for the SRP to:

1. Receive an update by the HRP Chief Scientist (or designee) on the status of NASA's current and future exploration plans and the impact these will have on the HRP.
2. Receive an update on any changes within the HRP since the 2014 SRP meeting.
3. Receive an update by the Element or Project Scientist(s) since the 2014 SRP meeting.
4. Participate in a discussion with the HRP Chief Scientist (or designee) and the Element regarding possible topics to be addressed at the next SRP meeting

The 2015 SHFE SRP will produce a report/comments from this status review within 30 days of the 2015 update. These comments will be submitted to the HRP Chief Scientist and copies will be provided to the SHFH Element and also made available to the other HRP Elements. The 2015 SRP Final Report will be made available on the Human Research Roadmap public website (<http://humanresearchroadmap.nasa.gov/>).

XI. 2015 Space Radiation Standing Review Panel Roster

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