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Center for Space Radiation Research

National Space Biomedical Research Institute

Request for Applications

NSBRI-RFA-13-02

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Proposals Due: DECEMBER 20, 2013

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Center for Space Radiation Research

Executive Summary

This National Space Biomedical Research Institute (NSBRI) Request for Applications (RFA) solicits for proposals to establish a **Center for Space Radiation Research (CSRR)**. The CSRR will represent the principal focus of NSBRI's Radiation Effects (RE) Team and be a critical component of radiation research for the Human Research Program (HRP) of the National Aeronautics and Space Administration (NASA).

The CSRR will address the acute and degenerative tissue effects on living systems following exposures modeling space radiation beyond low Earth orbit (LEO). For the purposes of this RFA, acute health effects are defined as those that initially manifest within 4-72 hours and typically persist for 2-8 weeks following a high dose exposure to ionizing radiation that occurs over a short time period, such as during a solar particle event (SPE). With respect to this solicitation, degenerative tissue effects are defined as those that manifest within months to years following exposure to ionizing space radiation. Protons from SPEs, in combination with ionized nuclei that constitute galactic cosmic radiation (GCR), elicit the main radiation health risks in interplanetary space.

Acute radiation syndrome (ARS) and degenerative tissue effects due to radiation exposure have the potential to adversely impact long-duration human space exploration missions. Degenerative tissue diseases may occur in the cardiac, circulatory, digestive, ocular, and other systems. NASA considers the most serious degenerative tissue and health risks to be radiation effects on the cardiovascular and circulatory systems that occur on a similar timescale to cancer. Early degenerative tissue effects may however be detectable in a time period of months, in specific tissues or organs, following exposure to space radiation. Research is needed in this area, since the dose thresholds giving rise to associated physiological endpoints and the extent to which space radiation eventually leads to degenerative diseases are poorly understood. In particular, the highest priority is to establish whether health risks exist below threshold radiation does occurring near NASA's permissible exposure limits (PELs).

The CSRR will longitudinally characterize the acute and degenerative tissue effects of space-like radiation on living systems by combining the more established methodology of observing physiological endpoints with biomolecular read-outs, obtained via a systems biology approach. CSRR investigators will employ a combination of low linear energy transfer (LET) beams producing SPE-like proton radiation and high-LET heavy-ion exposures to accurately model the space environment beyond LEO. Radiation countermeasures that are commercially available or currently being developed for terrestrial applications will also be tested by CSRR investigators for efficacy to protect against the observed acute and degenerative tissue effects of space-like radiation.

The CSRR will contribute significantly to NASA's path to risk reduction for the acute radiation risk, as well as specifically target several important degenerative gaps pertaining to the effects of space radiation on the cardiovascular and circulatory systems, by implementing the following **three research goals**:

- **Detailed physiological and biomolecular characterization of acute and degenerative tissue responses to space-like radiation doses that are mission relevant for future human spaceflight outside of LEO;**
- **Determination of relative biological effects (RBEs) as quantitative inputs to methods and models that calculate equivalent acute and degenerative tissue responses in humans following exposures to space radiation; and**
- **Testing the efficacy of established and experimental radiological countermeasures in appropriate animal models using relevant intermediate as well as late physiological endpoints and effects, e.g. inflammatory responses.**

The acute radiation studies, outcomes, and deliverables should be implemented at the level of the whole organism. The degenerative tissue responses should be focused on the structure, function and pathology of the cardiovascular and circulatory systems following exposure to mixed modality GCR-like and SPE-like radiation.

Following analysis and annotation, the biomolecular data obtained by the CSRR should be deposited into a suitable publically accessible database such as GenBank (maintained by National Center For Biotechnology Information; http://www.ncbi.nlm.nih.gov/genbank/) or geneLAB (being developed by NASA; http://spacebiosciences.arc.nasa.gov/story/bioinformatics-space), and linked to the physiological metadata. NSBRI anticipates that these correlated physiological and biomolecular datasets will establish a basis for future studies focused on developing radiation specific biomarkers and molecular assays.

NSBRI intends to fund a single CSRR program grant with a total budget, including beam time and indirect costs, not to exceed $2 million per year, with a completion date of no later than May 2017. Up to 20% of the budget can be allocated for acute radiation studies and no less than 80% of the budget allocated to pursue radiation research relevant to the manifestation of degenerative cardiovascular and circulatory system tissue effects following radiation exposures.

Applications may be submitted as a single comprehensive proposal addressing both the acute and the degenerative tissue effects research opportunities. NSBRI will also consider separate focused proposals that address only the acute radiation effects or the degenerative tissue effects components of the CSRR, within the budget guidelines detailed above. The Institute will then work to integrate the research projects into one coherent program. Collaborations among institutions and other entities are highly encouraged in order to comprehensively address the important new radiation research to be performed by the CSRR.

Applications are to be submitted using NSPIRES, (http://nspires.nasaprs.com). The deadline for application submittal is 5 P.M. Central Time on December 20, 2013. Researchers intending to submit a full proposal are required to submit a Notice of Intent by 5 P.M. Central Time on September 13, 2013.

The National Space Biomedical Research Institute

Mission and Vision

NSBRI was established through an open competition by NASA in 1997, and was awarded a 20-year cooperative agreement. The Institute's mission is to lead a national effort to conduct the integrated, critical path, biomedical research necessary to support the long-term human presence, development, and exploration of space. The terrestrial component of NSBRI's mission is to enhance life on Earth by applying the resulting advances in human knowledge and technology.

NSBRI's vision is to be a world leader in translational space biomedical research, and is committed to achieving its mission using innovative science, technology, career development, and management strategies - having high impact for all stakeholders. The Institute is focused on developing safe and effective countermeasures and technologies that substantially reduce significant health risks associated with human space travel. These discoveries not only ensure crew health, but they also improve life on Earth.

NSBRI is achieving its mission while inspiring the next generation of space life scientists by engaging a diverse, open community of outstanding scientists, engineers, clinicians, and educators to collaborate on peer-reviewed projects in integrated teams, and by using the resources available through leading institutions. The Institute strives to be the focal point of, and a major resource for, NASA-sponsored space biomedical research and career development in the United States. Through international cooperation and collaboration, NSBRI also aims to serve as a leading space biomedical institute among space-faring nations.

Strategic Goals

NSBRI has a published strategic plan (http://www.nsbri.org/default/About/NSBRI_strategic_plan.pdf) and the Institute has a strong track record of adapting to change and in leading new initiatives in high-priority areas. Additional details describing NSBRI's strategic goals are available in Appendix A: NSBRI: Organization and Operating Mechanisms.

Science and Technology Teams

The current NSBRI scientific research program consists of more than 45 science and technology projects organized into seven research teams: Cardiovascular Alterations, Human Factors and Performance, Musculoskeletal Alterations, Neurobehavioral and Psychosocial Factors, Radiation Effects, Sensorimotor Adaptation, and Smart Medical Systems and Technology. Additional details describing the focus and tasking for each of the seven research teams is provided in Appendix A: NSBRI Organization and Operating Mechanisms.

Leadership, Governance, and Oversight

NSBRI is governed by a consortium of 12 institutions as detailed in Appendix A: NSBRI – Organization and Operating Mechanisms. The Institute's Headquarters are located in Houston, Texas. Consortium membership is not a requirement for research program participation.

NSBRI Radiation Effects Team

The NSBRI RE Team, (http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Radiation-Effects/) focuses on the development of a scientifically based integrated approach to understanding and mitigating the acute risks associated with radiation exposure to astronauts. Acute risks are of particular concern

during interplanetary transit and extravehicular activities (EVAs) on the lunar, asteroid, or Martian surfaces because of the rapid onset of SPEs. The RE Team is working on multiple projects assessing the impact to crew health following exposure to SPEs, quantifying these risks, and developing methods to prevent and treat ARS. These effects include utilizing multiple animal models to characterize the response of the immune, hematologic, gastrointestinal, and epidermal systems to ionizing radiation. Advanced dosimetry methods and technologies are also being developed and refined to more accurately quantify the acute radiation risk and test methods to protect astronauts.

The RE Team is providing countermeasures and other deliverables consistent with human health and performance standards and is aligned with the NASA HRP Integrated Research Plan (IRP), HRP goals, and Design Reference Missions (DRMs). Deliverables provided include risk assessments, methodologies, and recommendations for radiation mitigation in support of long-duration exploration missions. The NSBRI Center of Acute Radiation Research (CARR) is implementing these objectives. Investigators are encouraged to review summaries of the research currently funded by the NASA Space Radiation Program Element as well as the NSBRI RE Team by accessing the NASA Task Book (https://taskbook.nasaprs.com) and performing an advanced search by checking "Radiation Health."

Scientific Problem

The National Council on Radiation Protection and Measurement (NCRP) Report 153 published in 2006 states in part: "Current space radiation guidelines pertain only to missions in LEO and are not considered relevant for missions beyond LEO. The acceptable levels of risk for space exploration beyond LEO have not been defined at this time and need to be dealt with before sending manned missions to colonize the moon or to deep space, such as a mission to Mars."

This same report also describes the pernicious radiation environment found outside of LEO. Most ionizing particles found in interplanetary space are from the solar wind, which produces a fluence of low-LET radiation. Unpredictable and intermittent SPEs can produce large plasma clouds containing highly energetic protons and relatively few heavy ions. High-LET GCR ions originate from outside our solar system and contain mostly highly energetic protons and alpha particles with a small component of high atomic number and high energy, (HZE) nuclei moving at relativistic speeds and energies. HZE ions are so penetrating that shielding can only partially reduce intravehicular doses. For current space missions in LEO, shielding provided by the Earth's magnetic field attenuates the major effects of SPE and GCR radiation. The risks of space radiation will however become much more onerous as future spaceflight missions to a near Earth object (NEO) or Mars requires extended transit beyond the protection of the Earth's magnetosphere.

The unpredictable nature of SPEs has the potential to cause a rapid deterioration of the intravehicular and extravehicular radiation environments. Astronauts on future long duration space missions outside of LEO could be exposed to multiple SPEs of unpredictable magnitude and dose that may exacerbate biological effects from the concurrent protracted GCR radiation exposure. Ground-based research on model organisms seeking to accurately mimic the space radiation environment should therefore appropriately combine exposures from both proton and heavy-ion sources.

There are currently no biophysical models that can forecast the degenerative tissue risks for the range of particles and energies of ionizing radiation found in space. The dose response and dose-rate modifiers for specific effects are still unknown and there is a significant lack of appropriate epidemiological data. Moreover, the high-LET radiation found in the GCR spectrum can directly or indirectly damage biomolecules (e.g., proteins, DNA, lipids), as well as organelles and cellular structures. The resultant radiation-induced increase in oxidative stress levels has been shown to exacerbate some degenerative tissue changes that are normally associated with aging (e.g., cardiovascular disease and cataract formation) and alter tissue microenvironments (e.g., bone). In addition, it is thought that certain aspects of spaceflight (e.g., microgravity) as well as the artificial and confined environment may also accentuate degenerative tissue responses. No studies to date have properly assessed the possibility of synergistic effects between high-LET radiation and the space environment.

There is a need to identify relevant mechanisms and intermediate, progressive physiological indicators of degenerative tissue effects, and any adaptive responses, that are specific to a protracted, low-dose exposure to GCR and concurrent SPE radiation. Little, if any, research has been performed to correlate observed genetic and epigenetic damage associated with degenerative radiation-induced tissue effects at the low doses expected for space exploration missions. It therefore remains to be seen if experiments utilizing new and more powerful –omics technologies (e.g., genomics, transcriptomics, proteomics, and metabolomics) that probe genomic instability and delayed mutagenesis, when coupled with careful phenotypic observations, can help in more precisely quantifying the risks of space radiation induced diseases.

Additional information regarding the scientific background can be found in Appendix B: Background on the Scientific Problem, as well as in NCRP report number 153 and the 2008 National Research Council (NRC) report "Managing Space Radiation Risk in the New Era of Space Exploration".

Research Opportunities

The goals of the CSRR are as follows:

(1) Detailed physiological and biomolecular characterization of acute and degenerative tissue responses to space-like radiation doses that are mission relevant for future human spaceflight outside of LEO;

(2) Determination of RBEs as quantitative inputs to methods and models that calculate equivalent acute and degenerative tissue responses in humans following exposures to space radiation; and

(3) Testing the efficacy of established and experimental radiological countermeasures in appropriate animal models using relevant intermediate as well as late physiological endpoints and effects, e.g. inflammatory responses.

Correlated phenotype-genotype datasets will be deposited into a mineable, annotated publically accessible database such as GenBank or geneLAB. This work will lay the foundation for future validation of one or more biomarkers or biomarker panels exhibiting sensitivity and specificity to different types

and levels of space-like radiation. Each of these research goals is described in more detail below in the context of both the low dose acute and degenerative tissue effects scopes of work.

Research Goals

Goal 1: Detailed physiological and biomolecular characterization of acute and degenerative tissue responses to space-like radiation doses that are mission relevant for future human spaceflight outside of LEO.

Low Dose Acute Radiation Effects

Applicants should utilize low-dose SPE-like radiation exposures (0.2 – 2.0 Gy skin dose) to investigate acute physiological responses and measure concomitant bimolecular responses in suitable animal models. These experiments should be carefully designed to observe less pronounced physiological and biomolecular acute radiation responses, than those already reported at higher doses.

Degenerative Tissue Effects Of Radiation

To investigate the degenerative tissue effects of radiation on the cardiovascular and circulatory system, physiological endpoints should be obtained in multiple animal models. The progression of degenerative cardiovascular and circulatory diseases should be longitudinally monitored over time courses representing the human equivalent of several years. Animals should be used that emulate the current age range of astronaut crewmembers (i.e., typically 40 – 60 human years).

Investigators studying the degenerative tissue effects of radiation on cardiovascular and circulatory systems have typically utilized endpoints such as atherosclerosis and cardiomyopathy. Based on current epidemiological data, definitive physiological endpoints for the cardiovascular and circulatory systems are not yet well established for early degenerative tissue effects that may be detected several months after radiation exposure. Newly observed responses to space-like radiation that manifest at early time-points should be considered as putative intermediate cardiovascular or circulatory system physiological endpoints. Such intermediate physiological events can be used as early indicators of disease, thereby potentially conferring prognostic utility.

The CSRR should aim to couple the more traditional intermediate and late physiological endpoint observations (e.g., atherosclerosis and cardiomyopathy) that are now well-accepted and validated in radiobiology research, with –omics data collected via a systems biology approach. These –omics datasets and physiological metadata should be overlaid, analyzed, and displayed in a way that allows for phenotype to be associated with genotype.

In order to efficiently and thoroughly characterize the biomolecular effects of space-like ionizing radiation, it will be important and necessary for investigators to employ an integrated –omics approach. This will involve the collection of data from biological samples at multiple levels of the central dogma (i.e. DNA, RNA, and protein) – and potentially beyond (i.e. bacteriome or metagenome, epigenome, and metabalome). Tissues, biofluids and biomolecules must be carefully archived in biorepositories to ensure that other investigators can request, acquire and conduct future experiments with these bio-specimens.

The radiobiology studies must also be fully integrated with radiation physics. Key radiation parameters such as particle energy, ion species, lineal energy, etc. must be carefully captured for all experiments and

correlated with physiological and biomolecular data.

Goal 2: Determination of RBEs as quantitative inputs to methods and models that calculate equivalent acute and degenerative tissue responses in humans following exposures to space radiation; and

Low Dose Acute Radiation Effects

The CSRR will improve biodosimetry techniques by scaling low radiation doses across the multiple animal species utilized during the course of this NSBRI program grant. Combined physiological and biomolecular data collected from model organism studies will be analyzed to determine RBEs. This RBE data will be used to further inform and improve the veracity of NASA's radiation risk models, e.g. the acute radiation risk and baryon transport code (BRYNTRN) organ dose projection, usually referred to as the ARRBOD model. These RBE data will therefore assist in calibrating dose thresholds for the occurrence of acute radiation effects in humans, to within known and reasonable confidence intervals, and better assessing risk for human spaceflight outside of LEO.

Degenerative Tissue Effects of Radiation

An appropriate combination of physiological observations and biomolecular readouts embodying the degenerative tissue effects of ionizing radiation on the cardiovascular and circulatory systems should be used to calculate RBEs. Such RBE data should be obtained for GCR particles, as well as mixed modality GCR plus SPE radiation. The RBE data should be amenable for downstream analysis using suitable existing or newly developed methods or models that translate animal measurements to equivalent health effects expected in astronaut crewmembers.

Goal 3: Testing the efficacy of established and experimental radiological countermeasures in appropriate animal models using relevant intermediate as well as late physiological endpoints and effects, e.g. inflammatory responses.

Low Dose Acute Radiation Effects

Pharmaceutical or biopharmaceutical radiological countermeasures, including anti-emetics, anti-inflammatories, antioxidants, and other drugs are expected to provide risk reduction for SPE radiation delivered at low-dose and low dose-rate. Existing candidate countermeasures, or those in development, (particularly those on the path to clinical approval by the FDA) may be administered to animal models prior to, or following acute exposure(s) to space-like ionizing radiation. Physiological responses should again be closely tracked, to determine any temporal changes in intermediate and late endpoints. Any observed changes in the timing of physiological endpoints will offer important insights into the efficacy of tested radiological countermeasures.

Degenerative Tissue Effects of Radiation

Currently, a paucity of validated pharmaceutical countermeasures exist that can be deployed in response to space radiation exposures. Moreover, the effectiveness of these pharmaceutical countermeasures at low to moderate total radiation dose-rates, and particularly at time-points of months or years following initial exposure, remains unclear. The additive effects of the relentless, but more predictable GCR exposure, as well as multiple SPE exposures during long-duration missions may exacerbate degenerative tissue effects and influence the effectiveness of pharmacological countermeasures. Countermeasures for long-duration space exploration missions that mitigate the degenerative tissue effects of radiation must preserve

astronaut health, have minimal toxicity, and must not compromise immune system responses to future health challenges.

Following administration of countermeasures, the intermediate and late physiological endpoints that delineate the progression of degenerative cardiovascular and circulatory system diseases should be closely tracked. Any observed changes in the timing of these physiological endpoints will offer important insights into the efficacy of tested radiological countermeasures.

Enabling Future Biomarker and Molecular Assay Research

This applied program will provide the combination of scientific data and rigorous, validated methods that may eventually permit the future discovery and validation of biomarkers that are specific and sensitive signatures of space-like radiation. These biomarkers may subsequently lead to the development of molecular assays that can be used to measure the quality and quantity of space radiation absorbed by astronaut crewmembers.

With carefully correlated physiological endpoint and biomolecular data in hand it is probable that future research efforts can succeed in pinpointing discrete biomarkers or biomarker panels that are specific to dose, dose-rate, or radiation modality. These radiation biomarkers or "radiomarkers" may exist as somatic DNA lesions, post-translational modifications to proteins or altered levels of protein expression, changes in messenger RNA (mRNA) or non-coding RNA (ncRNA) concentrations, unique epigenetic motifs, or altered metabolite concentrations.

In other fields of biomedical research, following sufficient testing and validation, biomarker measurements have graduated to become broadly adopted molecular assays, and eventually molecular diagnostics. Such molecular assays potentially represent a paradigm shift for radiobiologists, as they theoretically permit precise "early time" biomolecular read-outs that are organ specific or whole body signatures of the effects of space-like radiation.

Mapping to the NASA HRP Integrated Research Plan

These acute and degenerative tissue effects of radiation studies will address critical gaps detailed in the IRP – Revision D, (http://humanresearchroadmap.nasa.gov/evidence/IRP%20Rev%20D.pdf), as updated by NASA's HRP. Specifically, the IRP states in part: "Recently, several epidemiological studies, including results from the atomic bomb survivors and nuclear reactor workers, have identified an increased risk of stroke and coronary heart disease (CHD) for low-LET radiation at doses comparable to those of a Mars mission, or a lunar mission incurring a large SPE. Because the risk of heart disease is a recent finding, preliminary studies in these areas are seeking to establish possible distinctions, in mechanisms for this risk, between protons, HZE nuclei and gamma rays."

In addition to this cardiovascular linkage, this work to elucidate the acute and degenerative tissue responses to space radiation at fundamental physiological and biomolecular levels will likely have enumerable and possibly unanticipated important touch-points to existing work in the areas of neurobehavioral and psychosocial factors, musculoskeletal alterations, and sensorimotor adaptation. These touch points are the subject of degenerative gap 7 (http://humanresearchroadmap.nasa.gov/Gaps/?i=383), i.e. "Are there significant synergistic effects

from other spaceflight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify the degenerative risk from space radiation?"

The work of the CSRR will address the acute radiation risk, as well as specifically target several important degenerative gaps pertaining to the effects of space radiation on the cardiovascular and circulatory systems, that are detailed in the relevant sections below. Accordingly this RFA addresses the associated set of research and technology gaps listed in Appendix C: Acute and Degenerative Tissue Radiation Specific Gaps.

The research of the CSRR will also update and significantly add to the existing body of scientific knowledge that is currently detailed in two NASA evidence reports, namely:

- "Risk of Acute Radiation Syndromes Due to Solar Particle Events, (http://humanresearchroadmap.nasa.gov/evidence/reports/ARS.pdf); and
- "Risk of Degenerative Tissue or Other Health Effects from Radiation Exposure", (http://humanresearchroadmap.nasa.gov/evidence/reports/Degen.pdf).

Research proposals should address either the low-dose acute radiation effects focused opportunity or the degenerative tissue effects of radiation focused opportunity, or both focus areas, as described below. Successful applicants will join the CSRR as part of NSBRI's effort to mitigate the risks associated with the acute and degenerative tissue effects of radiation that face astronauts as they embark upon long-duration space exploration missions.

Low-Dose Acute Radiation Effects

Exposure to a SPE radiation dose continues to pose a critical and acute health risk to astronaut crews by enhancing the negative effects of damaged tissues and can have a serious impact on all biomedical aspects of space exploration. NSBRI has accepted the leadership role in researching the multi-system and detailed biomolecular responses in crewmembers following an acute exposure to SPE radiation.

Important considerations impacting future exploration class space missions are the short and longer-term health effects of space radiation on crewmembers. Many unanswered questions still remain regarding the impact of acute radiation exposures on various sensitive and vulnerable internal organs, viewed at both a gross physiological or phenotypic level, as well as through the more granular prism of supporting biomolecular data. Given genetic variability, uncertainties exist in individual physiological and biomolecular responses regarding the thresholds and dependency on dose-rates, (especially near the threshold dose), following a full body exposure to low-dose SPE radiation.

Proposals responsive to this RFA should address all of the areas described below:

- Employing realistic models of nominal and maximal SPE fluence rate, and using appropriate SPE-like surrogate radiation species, quantify the dose-rate dependence, RBE values, and time to on-set for the following acute radiation effects that can potentially affect mission operations: depletion of the blood forming organs (BFOs), hematopoietic perturbations, skin injury, immune system decrements, and underlying concomitant biomolecular (i.e. DNA, RNA, protein, metabolites) alterations.
- Hematopoietic endpoints must include white blood cell, red blood cell, lymphocyte, neutrophil, and platelet counts.

- Research teams must also simulate the combination of exposure to microgravity, (i.e., via unloading experiments) and space radiation on depletion of the BFOs, hematopoietic cell loss, skin injury, immune functions, and underlying biomolecular alterations.
- Proposals should use low SPE-like doses (i.e. 0.2 Gy - 2.0 Gy skin dose; no more than 1.0 Gy deep dose) using the appropriate mammalian animal models. Doses should be progressively titrated to lower values over the range of 2.0 Gy – 0.2 Gy, as a key aspect of the experimental schema.
- The combined physiological and biomolecular datasets should be analyzed to generate RBEs. Such RBE values must be of high veracity and suitable for further refining NASA's radiation models, e.g. ARRBOD, used to estimate equivalent doses that will elicit acute radiation effects in human crew members.
- Radiobiology studies must be fully integrated with radiation physics. Key radiation parameters such as particle energy, ion species, and lineal energy should be captured for all experiments and correlated with physiological and biomolecular data.
- Existing countermeasures, as well as those in the late stages of clinical development, should be tested for efficacy in mitigating the acute effects of SPE-like radiation. This testing should involve administering countermeasures following exposure to ionizing radiation and subsequent monitoring of (presumably) revised times to onset for the manifestation of physiological endpoints and accompanying biomolecular read-outs.

Proposals should also describe in detail which concomitant –omics data will be captured, along with physiological (especially hematopoietic) endpoints. In this regard, careful consideration should be given to characterizing DNA/RNA damage and observing novel genetic variants as a result of SPE-like radiation, as well as altered proteinaceous content (i.e. changed protein expression levels, altered amino acid sequence, the occurrence of post-translational modifications, atypical secondary or tertiary protein structure) and metabolite levels.

Degenerative Tissue Effects of Radiation

Models of the space environment outside of LEO have predicted that astronaut crews can receive a total body dose of approximately 1-2 mSv per day in interplanetary space and approximately 0.5 - 1 mSv each day on the surface of Mars, due to GCR radiation. These doses will increase as a result of each SPE encountered throughout the course of the mission. Future long-duration missions outside of LEO could encounter large SPE doses and a total mission dose in excess of 1.0 Sv.

There is only a small probability that radiation from SPEs will reach high enough doses to cause degenerative tissue effects if appropriate and effective operational procedures and radiation shielding are in place. However, it remains unclear whether low-dose (< 0.5 Gy) exposures influence the same biological pathways that have been shown to be involved in disease progression following moderate to high-dose SPE radiation exposures. Likewise, very little information is available on the role of individual susceptibilities and the possible synergistic effects from GCR when combined with other space flight factors. It will be essential to obtain this knowledge to successfully mitigate degenerative tissue risks for astronauts on missions outside of LEO.

Proposals should target the degenerative tissue effects that can deleteriously perturb astronaut health during and after the mission. Proposers should consider realistic mission scenarios for the space radiation environment that account for:

- The accumulated GCR dose at specific time points (e.g., during transit to Mars or NEO, over the period of the surface stay, and during subsequent return to Earth) and how moderate to large SPEs (e.g. such as those events that occurred in August 1972 or September 1989) can affect repair mechanisms initiated in response to the relentless GCR radiation.
- Multiple SPEs (such as those observed in August, September and October 1989), combined with accumulated GCR dose at specific time points (e.g., during transit to Mars or NEO, over the period of a surface stay, and during subsequent return to Earth).
- Crew vulnerability to SPEs because of reduced vehicle shielding during interplanetary transits.
- Habitat and indigenous shielding during a lunar, Mars, or NEO surface stay.

Proposals should describe in detail how the planned research studies to examine the degenerative tissue effects of radiation will address the degenerative gaps, (see Appendix C) in the context of NASA's DRMs.

Cardiovascular and Circulatory System Degenerative Risks

Life span studies of atomic bomb survivors who received high dose-rate, moderate doses of radiation (<2.0 Gy) when 40 years old or less, have shown a significant dose-response relationship for developing hypertension, stroke, and heart attack. The development of radiation-related health effects has been recorded though continuous longitudinal health studies. Respondents to this RFA should address all of the following tasks:

- Quantify and characterize dose and dose-rate dependent intermediate and late physiological endpoints to assess radiation induced cardiovascular and circulatory system risks using appropriate animal models and radiation modalities that simulate the interplanetary medium. This task should include establishing dose thresholds for a progressive sequence of cardiovascular and circulatory system health effects that may lead to serious conditions including atherosclerosis and cardiomyopathy.
- In order to accurately quantify and tease apart the individual contributions of GCR and SPE radiation to degenerative tissue effects, investigators should employ two different radiation modalities as follows: (1) GCR-like; and (2) GCR-like plus SPE radiation.
- In parallel with characterizing the intermediate and late physiological endpoints, obtain, analyze, overlay, and integrate relevant cardiovascular and circulatory system biomolecular profiles (DNA, RNA, protein, metabolite, metagenome, etc.) for doses, dose-rates, and time-points germane to long-duration exploration space missions.
- Radiobiology studies must be fully integrated with radiation physics. Key radiation parameters such as particle energy, ion species, and lineal energy should be captured for all experiments and correlated with physiological and biomolecular data.
- Initial quantification, followed by careful verification and validation of RBEs for both radiation modalities, viz. (1) GCR-like; and (2) GCR-like plus SPE-like radiation. These RBE values must be accurate inputs to models capable of inferring radiation doses that would generate observable degenerative tissue effects in human crewmembers.

- Using an appropriate set of intermediate and late physiological read-outs, assess the potential role of standard-of-care or novel mitigators of degenerative radiation injury on cardiovascular and circulatory system diseases.

In order to be considered fully responsive to this RFA, proposals must target significant progress, leading to gap closure, of the cardiovascular and circulatory system elements embedded within Degenerative Gaps 1 through 6, as prescribed below:

- Degen – 1: How can tissue specific risk models be developed for the major degenerative tissue risks, including heart, circulatory, endocrine, digestive, lens and other tissue systems in order to estimate GCR and SPE risks for degenerative diseases?
- Degen – 2: What are the mechanisms of degenerative tissues risks in the heart, circulatory, endocrine, digestive, lens and other tissue systems? What surrogate endpoints do they suggest?
- Degen – 3: What are the progression rates and latency periods for degenerative risks, and how do progression rates depend on age, gender, radiation type, or other physiological or environmental factors?
- Degen – 4: How does individual susceptibility including hereditary pre-disposition alter degenerative tissue risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?
- Degen – 5: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?
- Degen – 6: What are the most effective biomedical or dietary countermeasures to degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CMs additive, synergistic, or antagonistic to other Risks?

Implementation of Research

Ground-Based Proton and GCR Radiation Simulations

Research proposals are expected to utilize beams of charged particles available at research and clinical heavy-ion accelerators capable of producing mixed-energy SPE-like dose distributions. Proposers must submit documentation detailing access, cost, animal model utilization, and support of the facility physics and beam scientist(s) with proposals. Hospital-based Clinical Proton Therapy Centers may also have sufficient capabilities to generate SPE-like radiation. Guarantee of access, capability of producing mono-energetic and mixed energy SPE-like dose distributions, and animal support capabilities must be submitted with supporting documentation from the center's science and beam physics staff.

The NASA Space Radiation Laboratory at Brookhaven (NSRL) must be used to provide the heavy ion radiation exposures required to model GCR exposures. Jointly managed by the U.S. Department of Energy's Office of Science and NASA's Johnson Space Center, the NSRL facility employs beams of heavy ions extracted from Brookhaven's Booster accelerator, the preeminent facility in the United States for performing radiobiology studies. NSRL also features its own beam line dedicated to radiobiology research, as well as providing state-of-the-art specimen-preparation areas. Information regarding beam ion species, energy, planning, and execution of experiments at NSRL can be found at:
http://www.bnl.gov/medical/NASA/CAD/NSRL_Beam_Information_Guide.asp

Teams applying for the low dose acute radiation effects focused research opportunity, the degenerative tissue effects of radiation focused research opportunity, or both research opportunities should place emphasis on maximizing CSRR resources and sharing beam time access. Awards will support research that takes into account the impact on multi-system toxicity due to SPEs with differing energy profiles (e.g., soft versus hard SPE spectra) when added to the more predictable flux of GCR particles. Merit will be placed on those proposals targeted at understanding if and how the unique SPE dose distribution can change the dose limits for internal BFOs. Respondents to this RFA should also propose plans for determining if and how other spaceflight environment stressors, (e.g. microgravity) can alter dose-toxicity profiles, including the effect on biomolecules, especially DNA, RNA, proteins, and metabolites.

Use of Model Organisms

Radiobiology studies that are responsive to this solicitation should utilize mammalian model organisms that are susceptible to ionizing radiation and develop the relevant intermediate and late endpoints via mechanisms that are physiologically and pathologically similar to humans. Animal experiments employing an integrated "systems biology" approach are likely to generate highly informative data. Researchers should use the model system(s) most appropriate for their research goal(s) and are encouraged to take full advantage of functionally characterized transgenic and mutant species as well as comparative biology approaches (e.g., oxidative stress to mimic radiation effects) that enhance the research scope. Model organisms (animals), as well as possible countermeasure strategies, should permit surveillance of the low dose acute and degenerative tissue effects of space-like radiation, and may be distinct from those employed to study cancer and central nervous system (CNS) radiation risks.

Proposals responding to the degenerative tissue effects opportunity must address the health risks using model organisms and meaningful intermediate and late surrogate linked phenotypic and biomolecular endpoints. These findings in model organisms should be used to generate RBEs as inputs to appropriate radiation models that are capable of calculating the equivalent biomedical effects expected to occur in humans following exposure to SPEs when overlaid on the solar cycle modulated flux of GCR radiation. Experiments involving multiple model organisms will likely be necessary for full analysis of observed physiological and biomolecular effects, the efficacy of countermeasure agent(s), and the calculation of RBE's - facilitating extrapolation to a response in humans and, by extension, to astronaut crews. As part of the proposal submission process, assurance of compliance with applicable federal regulations regarding animal care and use is required.

Investigators should also thoughtfully develop and implement comparative genomics strategies to examine the effects of ionizing radiation on homologous genes and the same or similar biological pathways in a plurality of model organisms and living systems, with the goal of ultimately translating the key findings to humans. In particular, it is anticipated that the genomes of organisms may be affected inhomogenously by space radiation, and in fact that radiation induced genetic "hot spots" may be observed. These genetic "hot spots," if conserved across organisms, will form a starting point for deeper experimental probing and offer exciting possible opportunities for diagnostic and therapeutic interventions.

Synergistic Elements of the Research Plan

Proposers must include a Research Plan containing the following synergistic elements:

a) An integrated strategy to conduct experiments at laboratories or facilities that can generate protons of relevant SPE-like doses and energy distributions.
b) A clear strategy, including timelines, to utilize Brookhaven National Laboratory for simulating GCR radiation.
c) A comprehensive plan to share biological samples (including DNA, RNA, proteinaceous samples and metabolites) among all CSRR team members, and safely archive bio-specimens for future use.
d) A comprehensive strategy to integrate with other areas/proposer(s) that are undertaking research that have touch-points with space radiation.
e) How the proposed studies could synergistically link space radiation research with initiatives currently being undertaken by other U.S. research institutes that are also conducting radiation research (e.g., enhancement of radiation therapy, treatment of radiation related injuries, interfacing radiation countermeasures with clinical oncology). In particular merit will be given to proposals that leverage existing or future terrestrial radiobiology programs that are supported by other government agencies, foundations or funding entities.
f) A description of how promising radiological countermeasures being developed by companies supported by the Biomedical Advanced Research and Development Authority (BARDA) will be leveraged.
g) Details of how and where the –omics biomolecular data generated as a result of CSRR research activities will be deposited and made available to other researchers in a timely fashion, and how this data will be tangibly linked to the physiological metadata.

Structure of the Center for Space Radiation Research (CSRR)

The CSRR will be comprised of a team of investigators who have complementary interdisciplinary skills and work in a coordinated, team-spirited fashion, to solve a highly focused and inter-related set of radiation research questions. The CSRR will constitute the major program occurring within NSBRI's RE Team. Each proposing team must identify a Principal Investigator (PI) with demonstrated scientific area expertise in radiobiology or a closely related field, also possessing administrative leadership qualities, and who, if their proposal is selected, will be capable of serving as the CSRR Director.

The proposal should detail a coherent management structure architected to accomplish the goals of the CSRR and be consistent with the research goals of NSBRI's RE team. The qualifications, roles, and responsibilities of Co-Investigators (Co-Is) and key personnel must be clearly defined in the proposal, and may not be substituted or removed without the approval of NSBRI leadership. The expertise of key personnel should match the areas of emphasis detailed in this RFA. The home laboratories of CSRR team members may be geographically contiguous or dispersed, provided that CSRR team members have strong operating mechanisms for communicating, coordinating, and working productively together.

CSRR Mission and Milestones

The CSRR is being established to advance fundamental and applied knowledge in radiobiological and biomedical sciences and technology, with the ultimate goal of enabling safer human spaceflight and long-duration exploration missions. The CSRR team will utilize a multidisciplinary research strategy spanning expertise in biology, physics, immunology, medicine, and the rapidly emerging –omics disciplines, to

accurately model and characterize at physiological and molecular levels how organ systems are perturbed by, and respond to, simulated space radiation.

CSRR Director and Associate Director

The Principal Investigator awarded this program grant will be appointed as the Director of the CSRR and will act as the primary point of contact between the CSRR team and NSBRI. The CSRR Director may recommend one of her/his Co-Investigators to be appointed as CSRR Associate Director, and this nomination should be initially provided to the NSBRI Associate Director.

Radiation Effects Program Manager

The Radiation Effects Program Manager, (REPM) will be a scientist identified within the NSBRI Science Office who will act as the "tactical", or day-to-day point of contact between the CSRR team and NSBRI headquarters. The CSRR Director and Associate Director are requested and required to coordinate scheduling and utilization of NSRL resources through the REPM. CSRR investigators will work with the REPM to ensure models, experiment dosimetry, beam energies, and ion spectra are programmatically relevant to both NSBRI's and NASA's missions.

Radiation Effects Team Leadership

The Director and Associate Director of the CSRR will serve as the Team Leader and Associate Team Leader, respectively, for the RE Team. Team Leaders and Associate Team Leaders play a pivotal role in leading the NSBRI research teams, guiding the Institute's programs and helping to ensure the ultimate success of the Institute. Team leadership is guided by the Institute's strategic plan and by NASA's HRP needs and requirements, and play an important role in facilitating productive interactions between NASA investigators and those in the biomedical community at large. Team leadership is charged with adding value to their teams by enabling appropriate inter- and intra-team synergies to advance the mission of NSBRI and its partnership with NASA.

Each Principal Investigator must sign a written agreement and a commitment to carry out these team leadership responsibilities in the event that their proposal is selected and funded.

Key Personnel

The management structure must be minimal and consistent with financial and programmatic accountability, and should not impose onerous costs or processes on the investigators or the Institute. Procedures to allocate resources and adjudicate differences of opinion need to be clearly defined and agreed upon by all participants.

Roles and Responsibilities

In order to achieve the research goals of the CSRR, the roles and responsibilities of the CSRR Director, Associate Director, Co-Investigators, and research leads must be clearly defined. The proposal must include a description of these roles and responsibilities and interactions between partnering institutions. A description of the processes for the transfer of resources and other partnering agreements between the participating institutions must be included in the proposal.

Interactions Between Investigators, University Partners, NSBRI, and NASA

Beam access, biological sample sharing (including the sharing of nucleic acids, proteins, metabolites, and biofluids) and data sharing arrangements among Co-Investigators and research groups, (at the same institution and between different institutions) is required and must be clearly explained. Evidence of appropriate approvals from each institution must be included in the proposal. The proposal must

indicate how the CSRR will maintain awareness of NSBRI's and NASA's needs in the technical areas described in this RFA and maintain communication with the appropriate team leads, discipline leads, and managers at both NSBRI and NASA.

Institutional Expertise

The participating institutions must have committed personnel and facilities to accommodate the research needs of the CSRR. There should be a plan for coordination of research activities, resources, and sample storage and sharing**.** The participating institutions must have faculty with the expertise to undertake this multidisciplinary CSRR project. The proposal should outline how the complementary expertise of the faculty will result in a team effort that will address the research needs of the CSRR and generate high quality outcomes.

Radiation Beam Time

Research proposals are expected to utilize beams of charged protons and other appropriate ionizing species that will simulate SPEs that are available at research and clinical proton accelerators. Proposals should detail: ionized species, energies, dose, dose rate, and estimated hours of annual beam time. Investigators should note their preference of radiation facilities to conduct their studies. A separate budget providing estimated beam costs should also be submitted. NSRL must be used to provide the heavy ion radiation exposures required to model GCR radiation.

CSRR Scientific Advisory Committee

NSBRI will establish a Scientific Advisory Committee (SAC) to assist and support the CSRR Director, CSRR Associate Director, and NSBRI headquarters management to ensure that:

- The internal activities and external interactions of the CSRR are coordinated.
- Funds are allocated and used to properly fulfill the objectives of the CSRR.
- Advice on productivity and effectiveness of the CSRR is provided to the CSRR Director.
- Appropriate interactions take place to ensure information exchange and technology transfer among scientists, engineers, and administrators, as well as with other public and private institutions deemed important to the team's research goals.

The CSRR SAC will include members with appropriate scientific, operational, and management expertise. The composition of this committee will be at the discretion of the NSBRI Director. The committee will meet annually to evaluate the progress of the CSRR.

Program Management Information

Type of Award

The mechanism for funding the CSRR will be via a single program grant or two discrete research opportunity grants, with funding allocations to participating investigators based on the submitted budget. Once the awards are made, NSBRI may elect to fund participating institutions directly. Budgets will then be required from each participating institution within 30 days of the award selection.

The CSRR Director and Associate Director, with the advice and consent of the NSBRI Science Office and SAC, may make changes to this budget. CSRR research grants will be funded by NSBRI one year at a time. The funding is to last for a maximum of three years and the total of indirect and direct costs comprising the entire work of the CSRR may not exceed $2 million per year. The CSRR Director and Associate Director are expected to work closely with the appropriate technical and management

representatives from NSBRI and NASA in order to assure continued success and programmatic relevance. NSBRI will conduct yearly reviews of CSRR progress, as described below.

Program Productivity

As a vital measure of productivity, results from CSRR research should be submitted to peer-reviewed journals as the work progresses. Only those published papers that acknowledge NSBRI support and identify the CSRR grant, as a funding source will be considered as resulting from research of the CSRR and used to evaluate its productivity. Another especially critical aspect of program productivity that the CSRR must closely track and report on is the reduction of the acute and degenerative tissue radiation risks, and how the research is quantitatively and qualitatively closing the gaps associated with these important risks.

CSRR Quarterly Report to NSBRI

Every three months the CSRR Director and Associate Director will provide an update on research findings and the progress made toward the specific aims described in the proposal to the NSBRI Science Office. The reporting will be done via webinar and may include discipline scientists from NASA's Space Program Radiation Element, (SPRE) and the NASA JSC Radiation Health Office.

CSRR Annual Review

The CSRR Director, Associate Director, Co-Investigators, and selected team members (by agreement with NSBRI management) will attend an annual review at the NSBRI Consolidated Research Facility, (CRF) in Houston, Texas. The CSRR team will present an overview of their progress and discuss appropriate revisions to the CSRR scientific plans with the SAC and NSBRI management. Additional external and internal scientific experts may be invited to participate in the evaluation of CSRR research progress.

The review is intended to be both scientific and programmatic, and to provide an open exchange of opinions without the constraints and visibility of public presentations at a formal meeting or workshop. The review purpose is to enable NSBRI, the SAC, and the participating scientists to arrive at a clear assessment of progress and make recommendations, if needed, to the CSRR Director and Associate Director.

CSRR Annual Report

The CSRR Director shall provide a written annual report to NSBRI before the anniversary of the start of each one year of increment annual funding, detailing progress including a list of scientific publications, presentations at scientific meetings, and personnel actions. This information will consist primarily of:

- An abstract;
- A bibliographic list of scientific publications, presentations at scientific meetings, patents, patent applications, and invention disclosures;
- Copies of publications;
- A description of progress, including a comparison with the originally proposed work schedule; and
- A description of how progress is reducing the acute and degenerative tissue radiation risks and quantitatively and qualitatively closing associated gaps.

The annual report must include information on each research project conducted by the CSRR team members. It must also include the following information for the entire CSRR:

- A report on interactions and collaborations with groups outside of CSRR;
- A plan for the next 12 months;
- Status information on the CSRR management and financial conditions, itemized for each team; and
- Details of any personnel changes and partnerships.

Annual Investigator Meetings

All scientific participants in the CSRR are required to attend and present current research results at the NASA HRP Investigators' Workshop and the NASA Space Radiation Investigators' Workshops which are both held annually. The CSRR Director and Associate Director are also required to submit abstracts for presentation and attend the annual meeting of the Radiation Research Society.

Final Report

A final report must be provided to the NSBRI Director and Associate Director at the end of the funding period. The report should include a detailed listing of all peer reviewed publications, patents, patent applications, invention disclosures, and:

- A summary of CSRR team research activities;
- A statement of each specific research objective;
- Significance of the work;
- Background;
- Overall progress made during the grant period;
- Narrative discussion of technical approaches, including problems encountered;
- Accomplishments related to the various approaches;
- Appendix with bibliography and copies of all publications, presentations made at scientific conferences, patents, patent applications and reports;
- Any publications or other public materials containing data; and
- A description of how the acute and degenerative tissue radiation risks have been reduced and a detailed quantitative and qualitative account of associated gap closure.

Required Travel

Proposals must include travel funds for the following:

- Experiments to be performed at charged particle beam accelerators;
- NASA's Annual Space Radiation Investigators' Workshop;
- The annual NASA HRP Investigators' Workshop;
- The annual CSRR review; and
- Presentations at the annual meetings of relevant professional societies.

Availability of Funds for Award

NSBRI's obligation to make awards is contingent upon the availability of the appropriated funds from which payment can be made and the receipt of proposals that are deemed acceptable for award under this solicitation.

Award Information

Selected proposals will be funded as research grants in one-year increments for activities lasting until no later than May 2017. The anticipated start date for proposals selected in response to this RFA is no earlier than March 2014. The funding duration will depend on proposal requirements, review panel recommendations, and continuing progress of the activity. All proposals will be evaluated for overall merit by an independent peer-review panel, and also assessed by the NSBRI Science Office for relevance and proposed cost.

The total annual cost (direct and indirect costs) cannot exceed $2 million. NSBRI reserves the right to return proposals, without review, that exceed $2 million per year.

NSBRI will make funding allocations in one-year increments based on the submitted budget, available funds and project review. All NSBRI award recipients will be reimbursed on expenses incurred in the performance period. NSBRI may withhold payment of any expenditure that appears questionable, or for which additional information or support is required. Annual renewals are contingent on meeting all NSBRI Investigator Requirements including NASA-NSBRI customer-supplier agreements where appropriate.

NSBRI may, in certain cases, elect to fund only a portion of a proposed effort. In this case, the applicant will be given the opportunity to accept or decline such partial funding. The initial selection will be announced no earlier than February 2014 and the grant awarded in a reasonable timeframe thereafter.

Submission Dates and Times

Solicitation Announcement Identifier: **NSBRI-RFA-13-02**
Notices of Intent Due: **September 13, 2013**
Proposals Due: **December 20, 2013**
Estimated Selection Announcement: **February 2014**

NSBRI Contacts

Selection Official: NSBRI Director

Additional NSBRI Team and Research Emphases information is available from:

Jeff Chancellor
Scientist
National Space Biomedical Research Institute
Bioscience Research Collaborative
6500 Main St., Suite 910
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Fax: 713-798-7413
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Additional information on the proposal submission process is available from: **NSPIRES**
Phone: 202-479-9376, Monday through Friday, 8 a.m. to 6 p.m. Eastern Time.
Email: nspires-help@nasaprs.com
Frequently Asked Questions: Available through the Proposal Online Help site at http://nspires.nasaprs.com/external/help.do.
Tutorials of NSPIRES: Available at http://nspires.nasaprs.com/tutorials/index.html.

Appendices

Appendix A: NSBRI: Organization & Operating Mechanisms

NSBRI Strategic Plan

The NSBRI strategic plan lays out the following aspirational, high-level goals:

- Lead a national biomedical research effort to support human space exploration.
- Enhance life on Earth through advances made in space biomedical science and technology.
- Provide a comprehensive education program in space biomedical science and technology.
- Expand partnerships in space biomedical science, technology and education.
- Broaden capabilities as a national science and education resource.

For more information on NSBRI's strategic plan, please visit:
http://www.nsbri.org/default/About/NSBRI_strategic_plan.pdf

NSBRI's Science and Technology Teams

The seven NSBRI scientific research teams are focused and tasked as follows:

1. *Cardiovascular Alterations* – Determining the effect of long-duration spaceflight on the heart and blood vessels and researching ways to reduce the risks and to improve pre-flight detection and management of cardiovascular diseases. Team information, including research goals and priorities can be accessed at: http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Cardiovascular-Alterations/

2. *Human Factors and Performance* – Reducing performance errors and mitigating habitability, environmental and behavioral factors that pose significant risks to mission success. Team information, including research goals and priorities can be accessed at: http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Human-Factors-and-Performance/

3. *Musculoskeletal Alterations* – Understanding and mitigating bone and muscle loss during spaceflight. Team information, including research goals and priorities can be accessed at: http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Musculoskeletal-Alterations/

4. *Neurobehavioral and Psychosocial Factors* – Investigating methods and tools to predict, prevent, detect and mitigate neurocognitive and psychosocial decrements in the space environment. Team information, including research goals and priorities can be accessed at: http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Neurobehavioral-and-Psychosocial-Factors/

5. *Radiation Effects* - Determining the risks of space radiation with an emphasis on acute effects, and mitigating these effects through countermeasure testing. Team information, including research goals and priorities can be accessed at: http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Radiation-Effects/

6. *Sensorimotor Adaptation* – Addressing the problems of disorientation, vestibular-autonomic responses, and changes in vision, proprioception, cognition, balance and motor control that may lead to impaired performance and compromised mission success. Team information, including research goals and priorities can be accessed at: http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Sensorimotor-Adaptation-Team/

7. *Smart Medical Systems and Technology* – Developing new methods of noninvasive medical monitoring, diagnosis and therapy using small, low-power instrumentation for use on space missions. Of particular interest to the team at present are approaches and technologies that can non-invasively assess intracranial pressure. Team information, including research goals and priorities can be accessed at: http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Smart-Medical-Systems-and-Technology/

Each of the seven research teams has a portfolio of complementary projects focused on the NASA HRP Risks and Gaps. Team management and integration amongst members and other NSBRI teams is the responsibility of team leadership. A Team Leader, assisted by an Associate Team Leader, heads each research team. Team Leaders play a pivotal role in guiding the Institute's science and technology program and in the ultimate success of the Institute. Their expertise and "hands-on" approach to research management adds considerable value across both projects and NSBRI teams. The seven Team Leaders are guided by the IRP (http://humanresearchroadmap.nasa.gov) which is the cornerstone for developing each team's integrated strategic research plan. Strong, effective and knowledgeable team leadership, in close partnership with senior management at NSBRI headquarters, collectively constitutes the keys to accomplishing the Institute's mission.

NSBRI Leadership, Governance and Oversight

NSBRI is governed by the following consortium of twelve prestigious institutions: Baylor College of Medicine, Brookhaven National Laboratory, Harvard Medical School, The Johns Hopkins University, Massachusetts Institute of Technology, Morehouse School of Medicine, Mount Sinai School of Medicine, Rice University, Texas A&M University, the University of Arkansas for Medical Sciences, the University of Pennsylvania Health System, and the University of Washington.

An External Advisory Council (EAC) is responsible for advising Institute management. A Board of Directors (comprised of, but not limited to, representatives from the senior management of the 12 NSBRI Consortium member institutions) advises the Institute concerning program strategy, tactical implementation, and effectiveness.

NSBRI also has a User Panel of former and current astronauts and flight surgeons responsible for ensuring that the research program is focused squarely on astronaut health, safety, and performance. The User Panel advises the EAC and NSBRI senior management on the operational relevance of science and technology projects.

An Industry Forum of representatives drawn from space and biomedical-related industries advises and assists NSBRI concerning Earth based applications for Institute research.

The Institute coordinates research activities with NASA through several committees and working groups including a joint NASA/NSBRI Steering Committee.

In addition to its research program, NSBRI has developed a robust career development and outreach program that takes advantage of the Institute's core research activities.

Appendix B: Background on the Scientific Problem

In 2006, the NRCP issued Report 153, entitled "Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit." The report contains a comprehensive summary of the current evidence for radiation-induced health risks and makes recommendations on areas requiring future experimentation. Specifically, NCRP Report 153 mentions, "Current space radiation guidelines pertain only to missions in LEO and are not considered relevant for missions beyond LEO. The acceptable levels of risk for space exploration beyond LEO have not been defined at this time and need to be dealt with before sending manned missions to colonize the moon or to deep space, such as a mission to Mars." The Council's report also emphasizes the need for identifying and validating biomarkers that can reliably detect adverse effects, improving radiation biodosimetry by providing accurate estimates of cumulative radiation doses, and identifying increased personal risks for individual astronauts due to genetic predisposition to the effects of space radiation.

Subsequently in 2008, the National Research Council released a report entitled "Managing Space Radiation Risk in the New Era of Space Exploration." The committee that authored this report found that the "lack of knowledge about the biological effects of, and responses to, space radiation is the single most important factor limiting the prediction of radiation risk associated with human space exploration."

The environment outside of LEO contains several types of radiation. Most of the ionizing particles found in interplanetary space are from the solar wind, which produces a constant flux of low-LET radiation. Unpredictable and intermittent SPEs can produce large plasma clouds containing highly energetic protons and (relatively few) heavy ions. GCR ions originate from outside our solar system and contain mostly highly energetic protons and alpha particles with a small component of HZE nuclei moving at relativistic speeds and energies. Astronauts traveling on a protracted voyage to Mars, or some other destination outside of LEO, may be exposed to SPE radiation events, overlaid on a more predictable flux of GCR exposure. Accordingly, and importantly, ground-based research on model organisms seeking to accurately mimic the space radiation environment should appropriately concatenate or combine exposures to both proton and HZE sources.

For current space missions in LEO, the shielding provided by the Earth's magnetic field attenuates the major effects of SPE and GCR exposures. However, the risks of space radiation will become much more onerous as future spaceflight missions to a NEO or Mars requires extended transit beyond the protection of the Earth's magnetosphere. The unpredictable nature of SPEs has the potential of causing a rapid deterioration of the intravehicular and extravehicular radiation environments. Exposure to charged particles representing a wide array of atomic numbers, energies, dose rates, and resulting secondary radiation cascades can induce health effects that are associated with both SPE and GCR exposures.

Solar Particle Event Radiation

SPEs largely consist of low-LET protons with energies ranging up to 1 GeV/n. SPE dose-rates are variable over the course of an event and range from 0-100 mGy/hr inside a space vehicle and 0-500 mGy/hr for an astronaut exposed during EVA on missions outside of LEO. SPE dose rates can also vary several-fold between tissue sites because of the variable energy spectra of the protons and nuclei. SPE radiation and the synergistic effects of spaceflight can place the crew at significant risk for prodromal effects, skin injury, hematological changes, and immune system dysfunction. A very low risk of mortality exists as a

result of a major solar event or the combined effect of multiple SPEs and accumulated GCR exposure over the course of exploration class missions to Mars, the Moon or an asteroid.

Exploration missions outside of LEO will include interplanetary transits and reduced shielding protection may leave astronaut crews more vulnerable to the effects of a SPE. It remains unclear how a moderate to large magnitude SPE, when combined with relentless GCR exposure as well as multiple prior or subsequent SPEs, will affect the health and performance of intravehicular activity (IVA) astronaut crews during interplanetary transits. To underscore the stochastic nature of SPEs, a recent paper, (Zeitlin *et al*., *Science*, 340, 1080-1084, 2013) reported that five SPE events were recorded during the 2011–2012 transit of the Mars Science Laboratory spacecraft (containing the Curiosity rover) from Earth to Mars. These recent data clearly illustrates that crewmembers may well be exposed to multiple SPEs during long duration space exploration missions outside of LEO.

Galactic Cosmic Ray Radiation

GCR nuclei originate from outside our solar system and are high-LET relativistic particles, possessing sufficient energies to penetrate any shielding technology used on current mission vehicles. The GCR spectrum consists of about 87% hydrogen ions (protons) and 12% helium ions (alpha particles), with the remaining 1-2% being heavier HZE nuclei with charges ranging from Z=3 (lithium) to ~ Z=28 (nickel). Ions heavier than nickel, such as iron, are also present, and are biologically harmful as no reasonable amount of spacecraft material can shield them. The fluence of the ionized nuclei that make up the GCR is inversely proportional to the solar cycle and decreases by a factor of two during solar maximum.

HZE particles have very high energies, sufficient to penetrate many centimeters of biological tissue or other organic or inorganic materials. In addition, the HZE nuclei are highly-charged, and therefore, very densely ionizing. As a consequence, even though the flux of HZE particles is relatively low, these particles have significant deleterious biological effects. The large ionization power of HZE ions makes them a major health threat contribution to astronauts during interplanetary missions and constitutes one of the most important barriers impeding plans for interplanetary travel by crewed spacecraft.

Further details describing the health risk from space radiation can be found within the NCRP report number 153 entitled "Information Need to Make Radiation Protection Recommendations for Space Missions Beyond Low Earth Orbit", and the 2008 National Research Council (NRC) report entitled "Managing Space Radiation Risk in the New Era of Space Exploration." In addition, a 2012 report published by the European Community's THESEUS Consortium entitled "Toward Human Exploration of Space: a European Strategy – Cluster 3: Space Radiation - Report," provides additional information regarding the effects of space radiation on humans and radiation dosimetry, (http://www.esf.org/fileadmin/Public_documents/Publications/Cluster3_web.pdf).

Space Radiation Dosimetry and Modeling

The GCR fluence rate and spectrum outside of LEO have been generally characterized due to measurements made by unmanned space craft such as the Mars Science Laboratory spacecraft, and will vary slowly over the course of the solar cycle. Recent evidence has demonstrated that the absorbed dose and dose equivalent from incident particles can be predicted in advance of an exploration class space mission.

When compared to GCR exposures, SPE radiation has a unique dose distribution with respect to whole body irradiation, resulting in skin doses 5-10 times higher than seen in the internal organs. The potential toxicity profiles from SPE-like dose distributions still remain poorly understood. This is despite the existence of a large body of literature describing the effects from the anticipated absorbed dose range to the BFOs. Calculation of the radiation exposures to astronauts in a detailed and realistic way is challenging because of complexity of the radiation environment, the shielding effects of the vehicle and/or space suit, and human anatomy. In some cases, approximations have allowed simpler and faster calculations to be performed, but such approximations typically come at the cost of reduced accuracy and increased uncertainty in predicted doses. Approximations may include a simplified treatment of the particle trajectories such as assuming charged particles travel only in straight lines by neglecting lateral deflections caused by elastic Coulomb scattering, using simplified computational human models (i.e. so-called "phantoms"), and estimating organ and tissue doses based on depth-dose curves in homogeneous human phantoms.

The uncertainty with dose toxicity and the complex variation in SPE spectra likely to be encountered in future exploration missions emphasizes the need for models that are capable of identifying particle energy and species on an event-by-event basis. This knowledge will provide a more complete characterization of SPE radiation fields, and further reduce uncertainties in dose determination. Additionally, integrating microdosimetry measurements with radiobiology studies will prove essential to reducing the uncertainties in dose projections during mission planning, spaceflights, and post-flight research on astronaut health.

Degenerative Tissue Effects of Radiation

To address the non-cancerous, late effects of radiation, the authors of NCRP Report 153 recommended that experiments be conducted using protracted or extended exposure times and low dose-rates of protons, heavy ions, and neutrons in energy ranges that are relevant to the space radiation environment outside of LEO. Specifically, the authors of the report recommended that analyses be conducted to study the effects of protracted radiation exposures on the lens, whole-body vasculature, gastrointestinal tract, gonadal cell populations, hematopoietic and immune systems, and fertility.

With respect to the different qualities of space radiation that may be encountered, the high LET radiation found in the GCR spectrum can directly or indirectly damage biomolecules (e.g., proteins, DNA, lipids), as well as organelles and cellular structures. The resultant radiation-induced increase in oxidative stress levels has been shown to exacerbate some degenerative tissue changes that are normally associated with aging (e.g., cardiovascular disease and cataract formation). In addition, it is thought that certain aspects of spaceflight (e.g., microgravity) as well as the artificial and confined environment etc., may also accentuate such degenerative tissue responses. No studies to date have properly assessed the possibility of synergism between high LET radiation and the space environment, (http://humanresearchroadmap.nasa.gov/Evidence/reports/Degen.pdf)

Epidemiological studies on the atomic-bomb survivors in Japan, radiotherapy patients, and occupationally exposed workers have characterized the association between moderate to high doses of low-LET radiation and the long-term development of degenerative tissue effects, such as heart disease, cataracts, immunological changes, and premature aging. These findings are supported by laboratory studies using animal models. However, the risks for these same effects occurring after low dose-rate or

HZE nuclei exposures are much more difficult to assess due to the multifactorial nature of the diseases and their long latency periods. Furthermore, there is only a small probability that low-LET radiation from SPEs will reach high enough doses to cause degenerative tissue effects if proper operational procedures and radiation shielding are in place. However, it remains unclear whether low-dose (< 0.5 Gy) exposures influence the same biological mechanisms that have been shown to be involved in disease progression following moderate to high-dose SPE radiation exposures. Likewise, as with high-LET radiation, very little information is available regarding the role of individual susceptibilities and the possible synergistic effects with other space flight factors. It will be essential to obtain this knowledge to successfully mitigate degenerative tissue risks for astronauts during missions outside of LEO.

Currently, there are no biophysical models that can forecast the degenerative tissue risks for the range of particles and energies of ionizing radiation found in space. The dose response and dose-rate modifiers for specific effects are still unknown and there is a significant lack of appropriate epidemiological data. Although some of the modifiers have been elucidated with respect to cancer models, the response for degenerative diseases may be different due to their non-stochastic nature. As a result, computer models for degenerative tissue risks have not been developed since relevant biological data and observations are needed to inform a computer model in order to assess risk.

NCRP Report 153 also directly addressed the utility of genomic and proteomic studies to elucidate the effects of space radiation on living systems. Specifically, the authors of this report stated, "It has been suggested that genetic screening of individuals for evidence of radiosensitive genes may become an important future criteria for selection of candidates for missions beyond LEO." This report went on to explain, "The study of space radiation effects on various tissues of the body has revealed a previously unappreciated role for low-dose tissue remodeling involving stromal cell populations as well as cytoskeletal rearrangements in individual cells. These epigenetic effects involve changes in protein expression independent of the rapidly expanding work on direct radiation effects on gene expression. What is clear is that a different complement of genes and phosphorylated proteins is activated by exposure to low doses of conventional radiations, compared to the complement activated by higher doses of radiation. The ultimate medical consequences of perturbations in both genetic and epigenetic endpoints is however completely unknown. The radiosensitivity of tissue-specific stem cells and endothelial cells remains a concern."

Much of the genetic evidence referenced in NRCP Report 153 is highly germane to the acute and degenerative tissue effects of space radiation. The linkage between DNA lesions, including point mutations, insertions and deletions, as well intra- and inter-chromosomal rearrangements and carcinogenesis is well established. What is far less clear is if genetic mutations are also implicated in early (acute) or late (degenerative) radiation effects such as cardiovascular and circulatory system decrements. To date there has been little research relating DNA genetic and epigenetic damage to degenerative radiation-induced tissue effects at the relatively low doses associated with the space environment found outside of LEO.

Cytogenetic data unequivocally reveals that space radiation exposure produces significant damage to cells. Indeed, post-flight chromosomal breaks were first observed using the Giemsa staining technique in the Gemini and Apollo Astronauts during the 1960s and early 1970s. This work showed that chromosome break yields were two-fold higher in the Apollo Astronauts compared to the Gemini

Astronauts, suggesting for the first time a link between dose and flight duration. Interestingly, the Apollo and Gemini data also showed some inter-individual differences. In hindsight these findings are not surprising given the known heterogeneous responses to radiation following even standardized irradiation protocols. Age, gender, immune status, and ethnicity are all factors that affect responses to ionizing radiation, but there are also many others that are especially germane to the space environment such as microgravity and stress.

The ISS was launched in 1998, allowing the collection of additional biomolecular data that further informed the response of the human body to space radiation. Additional conclusions were able to be drawn about the fate of the chromosomal aberrations at time-points long after flight and between two flights; this included the very intriguing observation that the yield of chromosomal aberrations decreases some years after a first flight but without reaching the unirradiated values. Moreover, a second flight apparently does not proportionately increase the yield of aberrations, suggesting a non-additive or even an infra-additive effect – again raising the possibility of a radio-adaptive response in crewmembers (i.e. so called "radiation hormesis").

In 2008, using multicolor fluorescence in-situ hybridization, (FISH), Cucinotta *et al.* vividly showed complex chromosomal aberrations in lymphocyte cells involving three or more chromosomes, observed post mission in ISS astronauts. This work was highly significant as it tangibly and dramatically demonstrated that gross biomolecular damage at the fundamental DNA level is definitely occurring within ISS crewmembers as a result of exposure to space radiation.

Notwithstanding this impressive body of scientific endeavor, our knowledge of the basic mechanisms specific to low-dose radiation, to sequential doses of low does radiation, and any adaptive response is still lacking. Experiments utilizing new and more powerful –omics technologies (e.g., genomics, transcriptomics, proteomics) that probe genomic instability and delayed mutagenesis, when coupled with careful phenotypic observations, may help in quantifying the risks of potential space radiation induced diseases and progressing this field.

Appendix C: Acute and Degenerative Tissue Radiation Specific Gaps

The following Acute and Degenerative Tissue Gaps have been developed and are maintained by NASA's HRP, and may be reviewed on-line by navigating to: http://humanresearchroadmap.nasa.gov/

Acute - 1: Determine the dose response for acute effects induced by SPE-like radiation, including synergistic effects arising from other spaceflight factors (microgravity, stress, immune status, bone loss, etc.) that modify and/or enhance the biological response.

Acute - 2: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict acute radiation risks in astronauts? How can human epidemiology data best support these procedures or models?

Acute - 4: What are the probabilities of hereditary, fertility, and sterility effects from space radiation?

Acute - 5: What are the optimal SPE alert and dosimetry technologies? (Closed. Technology maturation transferred to Advanced Exploration Systems).

Acute - 6: What are the most effective shielding approaches to mitigate acute radiation risks, how do we know, and implement? (Closed. Transferred to Operations)

Acute - 7: What are the most effective biomedical or dietary countermeasures to mitigate acute radiation risks?

Acute - 8: How can probabilistic risk assessment be applied to SPE risk evaluations for EVA, and combined EVA+IVA exposures?

Degen – 1: How can tissue specific risk models be developed for the major degenerative tissue risks, including heart, circulatory, endocrine, digestive, lens and other tissue systems in order to estimate GCR and SPE risks for degenerative diseases?

Degen – 2: What are the mechanisms of degenerative tissues risks in the heart, circulatory, endocrine, digestive, lens and other tissue systems? What surrogate endpoints do they suggest?

Degen – 3: What are the progression rates and latency periods for degenerative risks, and how do progression rates depend on age, gender, radiation type, or other physiological or environmental factors?

Degen – 4: How does individual susceptibility including hereditary pre-disposition alter degenerative tissue risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?

Degen – 5: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?

Degen – 6: What are the most effective biomedical or dietary countermeasures to degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CMs additive, synergistic, or antagonistic to other Risks?

Degen – 7: Are their significant synergistic effects from other spaceflight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify the degenerative risk from space radiation?

Degen - 8: Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation circulatory disease risk estimates?

Appendix D: Eligibility Information

Eligibility of Applicants

All categories of U.S. entities, including private, public and nonprofit organizations, are eligible to submit proposals in response to this RFA. Principal Investigators may collaborate with universities, Federal Government laboratories, the private sector, and state and local government laboratories. In all such arrangements, the applying entity is expected to be responsible for administering the project according to the management approach presented in the proposal.

Guidelines for International Participation

NASA's policy is to conduct research with non-U.S. organizations on a cooperative, no exchange-of-funds basis. Although Co-Investigators or collaborators employed by non-U.S. organizations may be identified as part of a proposal submitted by a U.S. organization, NSBRI funding through this RFA may not be used to support research efforts by non-U.S. organizations at any level. The direct purchase of supplies and/or services that do not constitute research from non-U.S. sources by U.S. award recipients is, however, permitted.

Please see NASA FAR Supplement Part 1835.016-70 for additional information on international participation, which can be referenced at:
http://www.hq.nasa.gov/office/procurement/regs/1835.htm#35_016-70.

Also please see NASA Policy Directive 1360.2B, Initiation and Development of International Cooperation in Space and Aeronautics Programs, which is located at:
http://nodis3.gsfc.nasa.gov/displayDir.cfm?Internal_ID=N_PD_1360_002B_&page_name=main

Export Control Guidelines Applicable to Proposals Including Foreign Participation

Proposals including foreign participation must include a section discussing compliance with U.S. export laws and regulations, e.g., 22 CFR Parts 120-130 and 15 CFR Parts 730-774, as applicable to the circumstances surrounding the particular foreign participation. The discussion must describe in detail the proposed foreign participation and is to include, but not be limited to, whether or not the foreign participation may require the prospective investigator to obtain the prior approval of the Department of State or the Department of Commerce via a technical assistance agreement or an export license, or whether a license exemption/exception may apply. If prior approvals via licenses are necessary, Principal Investigators should discuss whether the license has been applied for or, if not, the projected timing of the application and any implications for the schedule. Information regarding U.S. export regulations is available by navigating to the following website: http://www.bis.doc.gov/.

Cost Sharing or Matching

NSBRI awards require a cost-sharing arrangement with all non-government entities consisting of an augmentation of at least 10% of the total annual NSBRI award. This contribution should not be identified in the submitted project budget but will be requested at the time the institutional award is made.

Appendix E: Proposal and Submission Information

Principal Investigators and their organizations must be registered with NSPIRES. An authorized representative of the applicant's organization must submit each proposal. All team members listed on the proposal must be registered with NSPIRES.

Source of Application Materials

Except where specifically stated otherwise in this RFA, applicants must prepare proposals in accordance with the "Instructions for Responding to NASA Research Announcements," NASA Federal Acquisition Regulations (FAR) Supplement (NFS), Part 1852.235-72. These instructions hereafter referred to as the *NASA FAR Supplement Provision*, can be referenced here:
http://www.hq.nasa.gov/office/procurement/regs/5228-41.htm#52_235-72

All information needed to submit an electronic proposal in response to this solicitation is contained in this RFA and in the companion document entitled "Guidebook for Proposers Responding to a NASA Research Announcement (NRA)" (hereafter referred to as the *Guidebook for Proposers*) that is located at: http://www.hq.nasa.gov/office/procurement/nraguidebook/.

Proposals that do not conform to these standards will be declared noncompliant and declined without review.

Proposal submission questions received will be answered and published in a Frequently Asked Questions (FAQ) document. This FAQ will be posted on the NSPIRES solicitation download site alongside this RFA, and will be updated periodically between submission release and the proposal due date.

Content and Form of Proposal Submission

1. NSPRIRES Proposal Data System

a. NSPIRES Registration

This RFA requires that the proposer register key data concerning their intended submission with the NASA Solicitation and Proposal Integrated Review and Evaluation System (NSPIRES) located at http://nspires.nasaprs.com. Potential Applicants are urged to access this site well in advance of the proposal due date(s) of interest to familiarize themselves with its structure and enter the requested identifier information. It is especially important to note that every individual named on the proposal's Cover Page (see further below) must be registered in NSPIRES and that such individuals must perform this registration themselves; that is, no one may register a second party, even the Principal Investigator of a proposal in which that person is committed to participate. This data site is secure, and all information entered is strictly for NSBRI use only.

Before beginning an online application, the Principal Investigator must ensure that the Organization to which the Principal Investigator belongs is registered with NSPIRES through an Authorized Organizational Representative (AOR). Every organization that intends to submit a proposal in response to this RFA, including educational institutions, industry, nonprofit institutions, NASA Centers, and other

U.S. Government agencies, must be registered in NSPIRES prior to submitting a proposal. Such registration must be performed by an organization's electronic business point-of-contact (EBPOC) in the Central Contractor Registry (CCR).

NSPIRES help topics may be accessed through the NSPIRES on-line help site at http://nspires.nasaprs.com/external/help.do. For any questions that cannot be resolved with the available on-line help menus, requests for assistance may be directed by email to nspires-help@nasaprs.com or by telephone to 202-479-9376, Monday through Friday, 8 a.m. to 6 p.m. Eastern Time.

1. Electronic Submission

Proposals must be submitted electronically, and all proposers are required to use NSPIRES. NSBRI proposals must be submitted electronically by one of the officials at the Principal Investigator's organization who is authorized to make such a submission. It is strongly recommended that the PI work closely with his/her Organization to ensure the proposal is submitted by the due date and time listed in this solicitation. Proposals will not be accepted after the listed due date and time.

NSPIRES accepts fully electronic proposals through a combination of data-based information (e.g., the electronic Cover Page and its associated forms) and an uploaded PDF file that contains the body of the proposal. The NSPIRES system will provide a list of all elements that make up an electronic proposal, and the system will conduct an element check to identify any item(s) that is (are) apparently missing or incomplete. Note that a failed element check will not preclude submission, but rather it will serve as a warning that a proposal may be incomplete. Proposers are particularly encouraged to begin their submission process early.

Requests for assistance in accessing and/or using NSPIRES may be directed by email to nspires-help@nasaprs.com or by telephone to 202-479-9376, Monday through Friday, 8 a.m. to 6 p.m. Eastern Time. Frequently Asked Questions (FAQs) may be accessed through the Proposal Online Help site at: http://nspires.nasaprs.com/external/help.do.

Tutorials of NSPIRES are available at: http://nspires.nasaprs.com/tutorials/index.html.

2. Notice of Intent to Propose

To facilitate planning for the review process, Applicants are requested to submit a Notice of Intent, (NOI) through NSPIRES by following the online instructions. Notices of Intent must be electronically submitted by September 13, 5:00 p.m. Central Time, through the NSPIRES website (http://nspires.nasaprs.com).

To create an NOI:

1. Log in to NSPIRES;
2. Select the "Proposals/NOIs" link;
3. Select the "Create NOI" link; Select Research Solicitation for a NSBRI Center For Space Radiation Research (CSRR).

Please refer to the NSPIRES tutorial at http://nspires.nasaprs.com/tutorials/index.html for on-line help. All information entered will remain private until the electronic submission is completed. Please note that Notices of Intent are requested, and required, for submission.

3. Proposal Format and Submission Process

Proposals must be completed and electronically submitted by December 20, 2013, 5:00 pm Central Time to be considered for funding. The same web address used for NOIs will serve as the entry point for proposal development. All proposals must meet the requirements for responding to an RFA.

The NSPIRES system will guide proposers through submission of all required proposal information. To create a proposal:

1. Log in to NSPIRES;
2. Select the "Proposals/NOIs" link;
3. Select the "Create Proposal" link
4. Select "Create a proposal from your list of submitted NOIs".

Please note that the Proposal Summary, Business Data, Budget, and Proposal Team are required Cover Page Elements for a proposal. The proposal summary should be between 200-300 words and understandable by the layman reader.

To ensure proper proposal transmission, please provide only one PDF attachment upload ordered as follows:

- Research Certifications (3.a. below);
- Scientific/Technical/Management Section (3.b. below);
- References and Citations *(see Guidebook for Proposers and NASA FAR Supplement Provision);*
- Personnel Biographical Sketches, (3.c. below)
- Facilities and Equipment *(see Guidebook for Proposers and NASA FAR Supplement Provision)*; Budget Justification of Proposed Costs *(see Guidebook for Proposers and NASA FAR Supplement Provision)*; Letters of Collaboration/Support *(see Guidebook for Proposers and NASA FAR Supplement Provision)*; and
- Appendices/Reprints (3.d below)

The PDF upload must not be password protected or locked in any way. As a courtesy, the NSPIRES system performs a "check" of the proposal components upon submission. Multiple programs for proposal submission use NSPIRES and only the components outlined in this solicitation are required for compliance. Warnings referring to proposal components not mentioned above or requesting proposal components be uploaded separately (such as budget justification) can be ignored.

The following supersedes the information provided in the Guidebook for Proposers and is required in addition to the NASA FAR Supplement Provision:

a) Research Certifications

For proposals employing human subjects and/or animals, NSBRI requires assurance of compliance with human subjects and/or animal care and use provisions within 90 days of notice of award.

Policies for the protection of human subjects in NASA-sponsored research projects are described in the NASA Policy Directive (NPD) 7100.8E "Protection of Human Research Subjects" (http://nodis.hq.nasa.gov/displayDir.cfm?Internal_ID=N_PD_7100_008E_&page_name=main).

Animal use and care requirements are described in Title 14 of the NASA Code of Federal Regulations (CFR) 1232 (14 C.F.R. part 1232) (http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title14/14cfr1232_main_02.tpl).

NSBRI utilizes just-in-time practices for approval of the use of human subjects or animals. For proposals employing human subjects and/or animals, assurance of compliance with human subjects and/or animal care and use provisions is required within 90 days of notice of award. Please select "pending" or "approved" for the IRB/IACUC question on the Proposal Cover Page. If the IRB/IACUC certification is already approved at proposal submission, attach a copy of the certification as part of the proposal upload and select "approved." Otherwise, select "pending."

After award, a statement must be provided to NSBRI from the Applicant institution which identifies the selected proposal by name and which certifies that the proposed work will meet all Federal and local requirements for human subjects and/or animal care and use. This includes relevant documentation of Institutional Review Board (IRB) approval and/or approval by the Institutional Animal Care and Use Committee (IACUC). NSBRI will require current IRB and IACUC certification prior to each year's award.

b) Scientific/Technical/Management Section (Project Description)

The length of the project description of the proposal cannot exceed 40 pages using standard 12-point font and one inch margins. Referenced figures and tables must be included in the 40 pages of the project description; however figure captions can use a 10-point font. The proposal should contain sufficient detail to enable reviewers to make informed judgments about the overall merit of the proposed research and about the probability that the investigators will be able to accomplish their stated objectives with current resources and the resources requested. The hypotheses and specific aims of the proposed research must be clearly stated. Proposals that exceed the 40-page limit for the project description will be declined without review.

Each proposal must specify a single Principal Investigator (who if the proposal is selected will become the CSRR Director) who is responsible for carrying out the proposed project and coordinating the work of other personnel involved in the project. The roles and responsibilities of the proposed CSRR Associate Director (if applicable), Research leads, and other key personnel in the CSRR - and the proportion of each individual's time to be devoted to the proposed research activity must be clearly defined. The proposal must clearly and unambiguously state whether these key personnel have reviewed the proposal and endorsed their participation. The CSRR Director is strongly encouraged to identify only the most critically important personnel to aid in the execution of their proposals.

NOTE: Cited literature and all other proposal sections are not considered part of the 40-page project description. Reviewers are not required to consider information presented as appendices or to view and/or consider Web links in their evaluation of the proposal.

c) Personnel Biographical Sketches

The CSRR Director is responsible for direct supervision of the work and must participate in the conduct of the research regardless of whether or not compensation is received under the award. A short biographical sketch (similar to the NIH BioSketch format) of the Director that includes his or her current position, title, and educational background, a list of principal publications, and a description of any exceptional qualifications must be included. The research and professional experience of the Associate Director, (if applicable), Research Leads and other Key Personnel must also be described.

CVs should be organized to conclude with present position, and chronologically list previous employment, experience, and honors.

CVs should include present membership on any Federal Government public advisory committees. CVs should list, in chronological order, the titles, all authors, and complete references to all publications during the past three years. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. Omit social security numbers and other personal items that do not merit consideration in evaluation of the proposal. Provide similar biographical information for other senior professional personnel who will be directly associated with the project.

Provide the names and titles of any other scientists and technical personnel associated substantially with the project in an advisory capacity. Universities should list the approximate number of students or other assistants, with information as to their level of academic attainment. Any special industry-university cooperative arrangements should be described. Other support over the last five years, including currently active support, should be stated and a brief explanation of potential overlap described.

d) Appendices / Reprints

Appendices and Reprints, if any, do not count toward the project description page limit, and are to be included following all other sections of the proposal (reviewers are not required to consider information presented in appendices).

Appendix F: Proposal Review Information

The following supersedes the information provided in the Guidebook for Proposers and is in addition to the NASA FAR Supplement Provision.

Proposal Intrinsic Scientific and/or Technical Merit

To be responsive to this research solicitation, proposed studies should be hypothesis-driven and lead to new knowledge within accepted scientific standards. Purely phenomenological approaches with no significant mechanistic basis or likely gain in scientific knowledge are not acceptable. Experimental studies not directly relevant to improved interpretation of experiments already conducted with radiation emulating SPEs and GCRs will not be funded.

Proposers are required to provide evidence for expertise in radiation and biomolecular research, either by reference to the CSRR members' work or by the inclusion of active collaborators who are expert in radiation research. Proposals should take into account the impact of gender, age, nutrition, stress, genetic predisposition, or sensitivity to other factors of importance in managing space radiation risks. For relevant and compliant proposals, the primary criterion for an award will be scientific merit.

All of the following criteria will be used in determining the merit of CSRR proposals (significance and approach are the most important and weigh more than innovation, investigators, and environment):

- **Significance:** Does this study address a research emphasis stated in this solicitation? Does the study test one or more significant hypothesis or produce data that would enable one or more significant hypothesis to be generated? If the study is non-hypothesis driven, are the data produced needed to understand or reduce the risk addressed by the research emphases? If the task will produce a software model or tool, how will it serve to better quantify or mitigate a radiation risk? If the aims of the application are achieved, how well will the product(s) address the research emphases? If the aims of the application are achieved, how will scientific knowledge or technology advance?
- **Approach**: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Is the proposed approach likely to yield the desired results? Does the applicant acknowledge potential problem areas and consider alternative tactics?
- **Innovation**: Does the project employ appropriate novel concepts, approaches, or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?
- **Risk Mitigation:** For aspects of a study quantifying risks to crew health or performance; does the research adequately improve the understanding of the adverse consequences, the probability of its occurrence, or the timeframe in which the risk must be addressed? For aspects of a study developing countermeasures, will the proposed countermeasure(s) reduce one or more risks to crew health or performance reduce the impact of one or more risks, or reduce the resources required to mitigate it? For aspects of a study developing technology, will the research product(s) reduce the risk to crew health or performance, reduce its impact or better define it, and is the technology feasible within the confines of the operational environment?

- **Investigators:** Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the Principal Investigator and any co-investigators? Is the evidence of the investigators' productivity satisfactory?
- **Environment**: Does the scientific environment in which the work will be performed contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support? Additionally, is there evidence of leveraging of complementary or closely related radiobiology research being funded by other U.S. Government agencies or funding entities.

Proposal Review and Selection Processes

1. Compliance Review

All proposals must comply with the general requirements of the RFA as described in this solicitation, the Guidebook for Proposers, and the NASA FAR Supplement Provision. Upon receipt, proposals will be reviewed for compliance with these requirements including:

a) The proposal project description must be no more than 40 pages in length, and should be titled and numbered as its own section.
b) Indication of appropriate Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC) certification status for all proposals using human or animal test subjects.
c) Submission of an appropriate and justified budget for a funding period not exceeding that described in the RFA.
d) A description of how the research aims map to the identified IRP risks and gaps as described in Appendix C.
e) Submission of all other appropriate information as required by this RFA.

Note: At NSBRI's discretion, non-compliant proposals will be withdrawn from the review process and declined without further review. Compliant proposals submitted in response to this RFA will undergo an intrinsic scientific or technical merit review. Only those proposals most highly rated in the merit review process will undergo additional reviews for program balance and cost.

2. Scientific and Programmatic Reviews

Proposals passing compliance review will undergo peer-review for scientific merit. This will be performed by a panel of scientific or technical subject matter experts. The number and diversity of experts required will be determined by the response to this RFA and by the variety of disciplines represented in the proposals relevant to the research emphases described in this RFA. The merit review panel will assign a score from 0-100 based upon the intrinsic scientific or technical merit of the proposal. This score will reflect the consensus of the panel.

Following peer review, proposals are reviewed by the NSBRI EAC for programmatic balance, scientific merit, and cost. Programmatic balance includes an evaluation of how the proposed work may help achieve an appropriate balance of scientific and technical tasks in alignment with the HRP IRP and the NSBRI mission. Evaluation of the cost of a proposed effort includes consideration of the reasonableness of the proposed cost.

In accordance with the NIH policy that NSBRI has adopted, all applications will also be assessed with respect to:

- Adequacy of plans to include males and females, members of minority groups, and their subgroups, as appropriate for the scientific goals of the research;
- Plans for the recruitment and retention of subjects;
- Reasonableness of the proposed budget and duration in relation to the proposed research; and
- Adequacy of the proposed protection for humans, animals or the environment to the extent they may be adversely affected by the project proposed in the application.

A set of selection recommendations will be developed by the NSBRI EAC based on merit, programmatic balance and costs.

3. Selection

The NSBRI Director makes the final selection.

4. **Award Notices**

At the end of the selection process, each proposing organization and Principal Investigator will receive notification of selection or non-selection. The selection letters will include a statement indicating that the selected organization's business office will be contacted by NSBRI, and a reminder that any costs incurred by the investigator in anticipation of an award are at their own risk. Notification will be made by a letter signed by the selecting official. Selection notification will also include proposal reviews generated during the peer-review process. NSBRI reserves the right to offer selection of only a portion of a proposal. In these instances, the organization/investigator will be given the opportunity to accept or decline the offer. NSBRI provides debriefings to those investigators who request one.

Appendix G: Important Definitions

Acute Radiation Effects:
ARS is also known as radiation sickness or radiation toxicity. ARS effects initially manifest within 4 - 72 hours, and typically persist for two to eight weeks or longer following a high dose exposure to ionizing radiation that occurs over a short time period, such as a SPE.

There are three acute radiation syndromes, namely the bone marrow syndrome (or hematologic syndrome), the gastrointestinal (GI) syndrome, and the cardiovascular (CV)/central nervous system (CNS) syndrome.

- The bone marrow syndrome is characterized by anorexia (lack of appetite), fever, and malaise. There is a drop in all blood cell counts for several weeks. The primary cause of death is infection and hemorrhage. The chance of survival decreases with increasing dose of radiation.
- The GI syndrome is more severe. It includes severe diarrhea, fever, dehydration, and imbalance in the electrolytes (sodium, potassium, etc.). Death is due to infection, dehydration and electrolyte imbalance and usually occurs within two weeks of exposure.
- The CV/CNS syndrome is the most severe. There is initially extreme nervousness; confusion; severe nausea, vomiting, and watery diarrhea; burning sensations of the skin; and loss of consciousness. After the latent period, five to six hours after exposure, there is return of watery diarrhea, convulsions, and coma and death typically comes within three days of exposure.

Degenerative Tissue Effects of Radiation:
A group of pathologies that can occur in several organ systems and tissues, typically manifesting within months or years following exposure to ionizing radiation. The mechanisms and the magnitude of influence of radiation leading to degenerative diseases are currently not well characterized. Moreover, degenerative disease risks are difficult to assess because multiple factors, including radiation, are believed to play a role in the etiology of the diseases.

The major degenerative conditions of concern to NASA and astronaut crewmembers that could potentially result from space radiation exposure are detailed below:

- Degenerative changes in the heart and vasculature (e.g., atherosclerosis and cardiomyopathy).
- Cataract formation.
- Other diseases that are related to aging, including digestive and respiratory disease.
- Other aging effects, including premature senescence and endocrine and immune system dysfunction.

SPE like radiation:
Fluence/energy distributions and dose rates similar to both nominal and worst case historical SPEs (extraordinarily large SPEs were recorded in November 1960, August 1972, and October 1989). Deep, BFO dose should be no greater than 1.5 Gy. The NASA Radiation Health Office (RHO) has established a high dose rate of 50 cGy/min and a low dose rate of 50 cGy/hr for NSBRI CSRR research.

Low-dose SPE-like exposure:
For the CSRR, a low dose, SPE-like exposure will be defined as a skin dose ranging from 0.2 Gy - 2.0 Gy with no more than a 1.0 Gy deep dose to the BFOs.

Spaceflight environment stressors:
These include, but are not limited to: stress/fatigue, immune system suppression, bone loss, environmental factors (artificial atmosphere, microgravity, etc.).

Hard (versus Soft) SPE spectra:
SPEs where the flux distribution of proton energies is predominately >100 MeV. Sometimes referred to as an Energetic SPE.

Appropriate models:
It is important to note that current research within NSBRI has identified outcomes unique to non-homogeneous exposures, such as prolonged cytopenia, vascular injury and hemorrhage/disseminated intravascular coagulation. Since these observations were made through the use of pig and ferret models, i.e., non-rodent models - for *in vivo* investigations care should be taken to choose the most appropriate "higher" organism(s) that are as genetically and physiologically similar to humans, as possible.

Appendix H: Center of Acute Radiation Research Results and Selected Publications

In 2008, the NSBRI CARR was established to expand the understanding of specific scientific and biological challenges associated with the high doses inherent in the radiation environment during SPEs, better define the risks, and develop and evaluate countermeasures to protect astronauts. The collaborative structure was designed to engage a broad spectrum of high caliber radiobiologists, physicists, research scientists, space life science students, in a concerted effort to understand the underlying mechanisms and develop effective mitigation strategies.

The CARR research provides a critical point of integration across NSBRI and NASA's HRP organization, providing a partnership focused on the overarching importance of radiation in mediating or contributing to practically all space-related health issues. The work of the CARR Team is an important evaluation of the acute effects that might affect mission success by compromising astronaut function - including nausea, vomiting, and fatigue.

The CARR Team is utilizing multiple animal model systems as surrogate endpoints that are representative of human radiation risks to study the multi-organ effects that can be instigated by a localized exposure and spread to multiple organ systems with debilitating consequences. Current CARR research into the acute effects following a SPE exposure, use the following biological endpoints:

- Vomiting (and/or retching) and white blood cell counts in ferrets;
- White blood cell counts, fatigue, and immune system parameters in mice; and
- Skin injury, white blood cell counts, and immune system changes in pigs.

In addition, the effects of combined exposure to simulated hypogravity and SPE-like radiation on blood cell counts and immune functions (with respect to both the innate immune system and the acquired immune system) are being evaluated in mice.

In the CARR studies, selected drugs are being evaluated in the animal model systems to determine their effectiveness in prevention and/or mitigation of the specific ARS symptoms. The dose response relationships measured for these endpoints will be compared mathematically with published results for human subjects to determine RBEs. The predictive value of these animal models for biodosimetry and for intervention studies to evaluate FDA-approved drugs that can be used for prevention and/or mitigation of the ARS symptoms is also being investigated.

The results from the CARR studies will provide critical quantitative biological data for the NASA Probabilistic Risk Assessment (PRA) tool to identify or categorize risks. Once the ARS specific risk has been identified as significant and requiring mitigation, a step-by-step approach will provide validated medical countermeasures for the management of potential ARS symptoms during a SPE.

Knowledge is a large part of the CARR contribution to the success of the NASA HRP. Some of the major CARR deliverables have been:

- Significant decreases in white blood cell counts were observed in immune and hematopoietic cells in the mouse and ferret models following SPE irradiation at doses of 25 cGy to 50 cGy, up to 2 Gy, using both low and high dose rates.
- Wound-healing problems were observed in the pig models following full body exposures at SPE-like skin doses. At increasing doses of radiation, skin becomes more sensitive to touch and researchers observed blistering, burns, and epithelial dysfunction.
- In the skin studies, it was observed that doses of radiation primarily to the skin have adverse effects that would not *a priori* have been expected in internal organs (e.g., heart, lungs, and white blood cells in the circulating blood, spleen, and bone marrow).
- Modern radiation oncology approaches utilizing computed tomography [CT] based Monte Carlo dosimetry have been incorporated and provide enhanced capabilities for the prediction of the biological effects of SPE radiation to the Human Space Program.
- Critical understanding about the adverse health effects of inhomogeneous doses of interventional and therapeutic radiation.
- Knowledge about the effects of countermeasures to prevent or treat the expected acute biological effects of exposure to SPE radiation.
- RBE values for the effects of SPE proton radiation compared to a standard reference radiation have been determined for multiple biological endpoints.

Selected Peer Reviewed Scientific Publications

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Appendix I: Human Research Program Integrated Research Plan

In order to identify and make publicly know the biomedical and health risks of spaceflight and the research and technology gaps that must be answered to reduce those risks, NASA, in partnership with the NSBRI, has developed the HRP IRP. The IRP documents what activities are necessary to fill identified knowledge gaps, when those activities will be accomplished, where they will be accomplished (e.g., utilizing ground analogs, research laboratories, or the International Space Station) who will accomplish them, and what the expected product will be. The IRP is based on a strategy that incorporates evidence-based standards to deliverables approach. Evidence drives the standards and risks, risks drive the gaps, and gaps drive the activities required to produce the products or deliverables.

The IRP is based in part on current or past recommendations from internal NASA experts, advisory committees representing the United States science community, task forces, and published reports in the area of radiation effects. This includes the National Research Council (NRC) Space Studies Board's "A Strategy for Research in Space Biology and Medicine in the New Century," the NCRP Report No. 153, and the National Academy of Sciences (NAS) Institute of Medicine (IOM) "Bioastronautics Roadmap: A Risk Reduction Strategy for Human Exploration of Space."

The ultimate goal of the IRP is to protect the health and safety of spaceflight crews by allowing NASA to better define and focus the research that is required for development and validation of operational health care "deliverables" for the assessment and mitigation of spaceflight changes and of appropriate habitation and medical care systems.

In the area of radiation effects, the current IRP identifies four risks:

- Carcinogenesis
- Acute and Late Effects in the Central Nervous System
- Degenerative Tissue Damage
- Acute Radiation Syndrome.

Appendix J: NASA's Design Reference Missions

MARS
Short Stay:
Outbound: 217 days
Surface Stay: 30 days
Return: 403 days
Total Mission Time: 650 days

Long Stay:
Outbound: 210 days
Surface Stay: 496 days
Return: 210 days
Total Mission Time: 916 days

Near Earth Object (NEO)
Stays of 14, 30, 90, 180, and 365 days are possible