National Aeronautics and Space Administration
Johnson Space Center
Human Exploration and Operations Mission Directorate
Human Research Program
Houston, TX 77058

Human Exploration Research Opportunities (HERO)
Appendix F

NNJ14ZSA001N-NSCOR

NASA Specialized Centers of Research (NSCORs) for Ground-Based Studies Assessing Cancer Risks from Space Radiation and the Impact of Individual Susceptibility

NASA Space Radiation Program Element

Step-1 Response Period:	**May 15, 2015 – June 22, 2015**
Step-1 Proposals Due:	**June 22, 2015, 5 PM Eastern Time**
Step-1 Notification of Status:	**July 1, 2015**
Step-2 Response Period:	**July 1, 2015 – September 10, 2015**
Step-2 Proposals Due:	**September 10, 2015; 5 PM Eastern Time**
Step-2 Selection Announcement:	**December 2015**

NASA Specialized Centers of Research (NSCORs)
for Ground-Based Studies Assessing Cancer Risks from Space Radiation and the Impact of Individual Susceptibility

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NASA Specialized Centers of Research (NSCORs)
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Proposals that do not conform to the standards outlined in this solicitation will be declared noncompliant and declined without review. You must read and understand this solicitation in its entirety to prepare a competitive proposal. Key requirements are identified here:

- For Step-1 and Step-2 proposals: You and your organization must be registered with NSPIRES. Your proposal must be submitted by an authorized representative of your organization. All team members listed on the proposal must be registered with NSPIRES (Section IV.B.1).
- For Step-1 and invited Step-2 proposals: Your hypothesis and specific aims must address the research emphases in this solicitation, and must be clearly outlined in the project description of your proposal (Section I.G).
- For Step-2 proposals: Investigators submitting a proposal in response to this solicitation, and whose most recent submission that included similar specific aims to any NASA or National Space Biomedical Research Institute (NSBRI) sponsored research announcement was not accepted, must address prior review comments (2 pages maximum, Section IV.B.3.c).
- For Step-2 proposals: Proposals must identify Integrated Research Plan risks and gaps addressed by the research (Section I.E).
- For Step-2 proposals: The length of the project description of the proposal cannot exceed 30 pages using standard (12 point) type (Section IV.B.3.f).
- For Step-2 proposals: Proposers (minimally the Primary Investigator) currently funded by or who have received funding within the last four (4) years from any NASA funding source must provide specifics (5 pages maximum) to the productivity of your NASA-funded research in a section separate from the project description (Section IV.B.3.d).
- For Step-2 proposals: If using vertebrate animals, your proposal must meet requirements of the Vertebrate Animal Scientific Review section of this solicitation (Sections IV.B.3.e and Appendix B).
- For Step-2 proposals: Your proposal must meet requirements of the Compliance Review section of this solicitation (Section V.C.1).
- For Step-2 proposals: A thorough statistical section must be included which includes a power analysis for the estimate of sample size and the comparison of males and females unless compelling evidence is provided that shows that no gender differences are expected.
- NASA HRP has established a policy concerning the sharing of software produced through grants (Section III.E).
- Step-1 and Step-2 selection decision information can be accessed after the selection announcement date listed in this solicitation. After logging in, the PI selects the "Proposals" link, the "Submitted Proposals/NOIs" link, and then clicks on the proposal submitted to the solicitation identified above. The document(s) provided by NASA will be displayed under the heading "PI Information Package" located at the bottom of the "View Proposal" page.

I. Funding Opportunity Description

A. Introduction

This National Aeronautics and Space Administration (NASA) Research Announcement (NRA) solicits proposals for NASA Specialized Centers of Research (NSCOR) in support of the Human Research Program (HRP) Space Radiation Program Element (SRPE). **An NSCOR consists of a team of investigators who have complementary skills and who work together to answer a closely focused set of research questions with the goal of achieving overall research progress that is greater than the sum of the progress achievable by each project individually.** The home laboratories of NSCOR team members may be geographically contiguous or dispersed, as long as the team members have a mechanism for working together. The research will be conducted using the NASA Space Radiation Laboratory (NSRL), a ground-based irradiation facility at Brookhaven National Laboratory, in Upton, NY. Proposals received outside the stated research emphasis specific to this solicitation (Section I.G), will be considered non-responsive and will be returned without review. NASA reserves the right to act in the best interests of the Federal Government in the matter of acceptance and evaluation of all proposals.

It is anticipated that there will be one or two NSCOR awards. All proposals will be evaluated for overall scientific and technical merit by independent peer review panels. The review will also consider the management approach, the integration of the separate projects into the NSCOR, and the likelihood that the total will yield research results that are superior to the results that could be obtained by each project individually. Relevance to NASA's programmatic needs and goals will be evaluated separately by NASA. The government's obligation to make awards is contingent upon the availability of appropriated funds from which payment for award purposes can be made, and the receipt of proposals that the government determines are acceptable for award under this NRA.

Each award will be funded as a research grant. Selected proposals will be funded in one year increments for activities lasting up to five years for NSCORs. The funding duration will depend on proposal requirements, review panel recommendations, and continuing progress of the activity. An NSCOR award will have an average cost between $1,500,000 - $1,800,000 per year (total annual cost) for up to 5 years. NASA does not provide separate funding for direct and indirect costs; thus, the amount of the award requested is the total of all costs submitted in the proposed budget. (For Award Information, see Section II.) It is estimated that selections will be announced by December 2015 and grants awarded shortly thereafter.

Within NASA, HRP is responsible for research and development activities associated with astronaut health and performance. The SRPE is charged by HRP to understand the effects of radiation on the health, safety and performance of astronauts, both during and after their missions. The major goal of NASA's space radiation research is to enable human exploration of space with acceptable risks from space radiation. Space radiation is distinct from common terrestrial forms of radiation (X-rays and gamma rays) because it is comprised of high-energy protons and HZE particles, along with the secondary radiation produced in shielding and tissue. Because there are no human epidemiological data for these radiation types, risk estimation must

also be derived from a mechanistic understanding based on radiation physics, and on molecular, cellular, tissue, and organismal radiation biology related to cancer, cardiovascular, and central nervous system (CNS) risks of concern to NASA.

Accordingly, research to be supported will seek to: reduce the uncertainties in risk predictions for cancer and/or other late degenerative diseases; provide the necessary data and knowledge to establish significance of risks and to develop risk projection models for the CNS and cardiovascular disease; and significantly advance the understanding of mechanisms of biological damage that underlies radiation health risks. This research is also expected to provide a substantial contribution to the scientific knowledge base required for future development of biological countermeasures to mitigate these risks as appropriate and to aid in identification of key biomarkers for monitoring disease processes. While flight studies are recognized as a possible component in the future validation of radiation risk predictions, the scientific evidence is largely expected to be acquired on the ground utilizing irradiation facilities to simulate the space environment.

Scientists working in rapidly developing areas of life sciences not necessarily associated with the study of radiobiology should consider the contributions that their field of study can make and to propose relevant investigations. However, investigators new to radiobiology research are encouraged to consult or collaborate with radiobiology experts in order to develop realistic experimental plans. A comprehensive web site providing a broad range of information on space radiation topics may be profitably consulted at http://three.usra.edu. The background information presented here and the list of references are intended to provide further useful starting points for such scientists as well as for expert radiobiology researchers not necessarily familiar with the unique aspects of space radiation. Furthermore, NASA scientists are available to assist investigators wishing to enter this field of research.

It is important that the prospective investigator read the relevant section(s) carefully, as some of the programmatic emphases are different from those appearing in previous NRAs. In addition, this NRA includes guidelines for preparing and submitting proposals electronically and defines the administrative policies governing the program and investigators.

Proposals solicited through this NRA will use a two-step proposal process. Only Step-1 proposals determined to be relevant with respect to the Research Emphases outlined in Section I.G. of this NRA will be invited to submit full Step-2 proposals. Step-2 proposals must be compliant with respect to Section V.C.1 of this NRA or they may be declined without review.

Proposals must be submitted electronically. All proposers, team members, and their institution's authorized officials must be registered before proposal submission with NSPIRES as described under section IV.B.

Proposals are due as outlined in Section IV.C.

B. NSCOR Goals and Objectives

NSCORs were established by NASA to advance knowledge in biological and biomedical sciences and technology with the ultimate application of this knowledge to enable human space flight and long-term planetary missions as well as to include a strong educational and training component to expand the pool of research scientists trained to meet future human exploration challenges. An NSCOR differs from a set of independent projects in that suitable mechanisms are defined to engage the contributing projects in a synergistic manner, so that the total output of the NSCOR is greater than the sum of the parts: each project needs to contribute to all other projects, and each project needs to benefit in demonstrable ways from the contributions of all other projects. This NSCOR solicitation seeks:

- To expand our understanding of specific scientific challenges associated with biological and biomedical sciences related to space radiation risks;
- To provide substantial long-term funding to the research community in a manner that encourages the development of a stable base upon which problem-solving strategies can be built for the benefit of NASA and the public;
- To involve a broad spectrum of research scientists, technologists, and high caliber students in the activities of the NSCOR;
- To support the educational goals of NASA and the United States in the area of biomedical and radiation sciences in general and space radiation risk in particular; and
- To facilitate the rapid transfer of knowledge gained that is consistent with NASA missions.

C. Ground-Based Simulations

Research proposals are required to utilize beams of charged particles available at the NASA Space Radiation Laboratory (NSRL). This NSCOR does not request proposals for flight research.

The NSRL is an irradiation facility capable of supplying particles from protons to gold with primary energies in the range of 50-2500 MeV for protons and 50-1100 MeV/n for HZE (High charge Z and energy E) particles. NASA plans to operate the NSRL for approximately 900 hours per year; selection of beam species and energies for experimental periods will be made by NASA officials in consultation with scientists proposing experiments for these beams. Activities at the NSRL are a joint effort of BNL's Collider-Accelerator Department, providing accelerated particle beams, and the Biosciences Department, providing experimental area support, animal care, and cell and biology laboratories. The NSRL includes irradiation stations, beam controls, and laboratory facilities required for most radiobiological investigations. In addition, the newly available station at the Tandem Van de Graaff Radiobiology Laboratory can be used to irradiate cell cultures with lower energy particle beams than those available at NSRL for comparative studies of beams of similar Linear Energy Transfer (LET) values but with much lower velocities. This facility contains a fully equipped cell culture laboratory. A description of the BNL Tandem facilities can be found at the following: http://www.bnl.gov/tandem/ and http://three.usra.edu/articles/FinalThieberger032912.pdf.

At the NSRL, rectangular beam spots are normally provided, with dimensions up to 20 x 20 cm^2 and center-to-edge uniformity between 1% and 5% (depending on energy, with lower energy (<600 MeV/n) beams being less uniform than high energy beams). A second "large-beam" configuration provides beams of 60 x 60 cm^2 area with center-to-edge uniformity between 5% and 10%. In the 20 x 20 cm^2 beam, dose rates have been measured up to 15 Gy/min, and for low fluence studies fluence-rates as low as 100 and 2000 particles per cm^2 per spill for HZE particles and protons, respectively are possible. Dose-rates are generally lower for the large-beam with a maximum doses-rate of about 0.5 Gy/min. Coordination of beam use by investigators with the NASA Space Radiation Element and BNL is actively encouraged. In particular, the dosimetry group in BNL's Collider-Accelerator Department is available for investigators requiring their assistance.

The Galactic Cosmic Ray (GCR) Simulator Project at the NSRL will generate an accelerator-based spectrum of ions and energies that closely approximate those that are known to make up the shielded GCR environment in space. These upgrades will enhance our ability to simulate the primary and secondary environment with a mixed field, high-energy capability planned for completion in late 2016. The energy of the final beam line will be upgraded to deliver beams at 1.5 GeV/n, to better represent the energies in the natural GCR. Reference fields will be defined to include the rapid switching of ions such as, protons, He, O, Si and Fe over multiple energies with the possible usage of well-designed absorbers. This will allow GCR species to be simulated with high precision in major energy (or LET) bins. Energy is expected to range from 50-1500 MeV/n with LET ranging between 0.25 - 1,000 keV/μm. To simulate organ exposures within a shielded spacecraft geometry, emphasis will be placed on delivering the majority of the dose from protons (50-60%) and alpha particles (10-20%) with heavier ions (Z > 3) and secondary particles contributing the remainder of the total dose. An intermediate field capability will be developed to validate final beam selection, including number of species and energies, as well as operational parameters. An initial description of field characterization can be found on the THREE website (http://three.usra.edu/#section=main) at the following link: http://three.usra.edu/articles/Slaba_gcrsim_HRP2015_THREE.pdf. More detailed descriptions of the field characteristics will be made available on the NSRL website as the upgrades progress. Ultimately mixed field studies must inform risk model predictions, biomarker discovery and validation, and countermeasure identification and validation across all risk areas.

The following Table lists examples of the spectrum of Energy, LET and Range for beams available at NSRL. Additional sequential fields beyond Proton/Fe (e.g., Proton/O or Proton/Si) as well as usage of the Solar Particle Event (SPE) simulator in combination with heavier ions are available, however proposed irradiation schemes, species and dose rates, must be confirmed with the NSRL prior to submission. In addition, the GCR Event-based Risk Model (GERMCode) developed by NASA is available for estimating LET, range, and nuclear fragmentation of NSRL beams in proposed biological models. For access to the GERMCode please visit http://spaceradiation.usra.edu/irModels/.

Table: Examples of the spectrum of Energy, LET and Range for beams available at NSRL

Beam*	**Energy, MeV/n**	**LET, keV/µm**	**Range in Water, cm**
protons	50-2500	1.2 - 0.20	2 to >100
^{4}He	50- 1000	5 – 0.9	2 to >100
^{16}O	50- 1000	80 – 14	0.5 – 80
^{20}Ne	70-1000	96 – 22	0.45 – 65
^{28}Si	93-1000	151 – 44	0.66 – 46
^{35}Cl	500-1000	80 – 64	14 – 40
^{48}Ti	150-1000	265-108	1.5 – 32
^{56}Fe	50-1000	832 – 150	0.2 – 27
Sequential Field (H/Fe)	1000/1000	0.2/150	See above
Sequential Field (H/Si)	1000/300	0.2/69	>100 / 7
GCR Simulator (up to 6-12 species)	50- 1500	Various	Various
Solar Particle Event	30-180	See above	See above
Tandem Low Energy Beams	E<7 MeV/n for B, C, Si, and Fe ions	Various	Various

User facilities have been developed at BNL for radiation biology research, including cell cultures and small animals. These include the shielding cave containing the beam, the biological experiment stations at NSRL, and long-term laboratory space and animal facilities in the Brookhaven Biosciences Department. A 10-ft long optical bench for sample exposures is available in the cave, as well as beam handling, sample changing, and dosimetry instrumentation. The biological experiment station contains areas for cell culture equipped with laminar flow hoods and incubators, a short-term animal holding facility, and an area for physics/run-control use. In addition, laboratory space and access to animal facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care are available in the Biosciences Department, subject to standard use charges. BNL also has on-site housing accommodation for users (dormitory and apartment-style units).

Proposers selected for award through this NASA Research Announcement (NRA) must meet BNL requirements for experiment scheduling in order to gain access to beams and irradiation facilities. Specific guidance on how to apply for NSRL beam time and BNL resources can be found at http://www.bnl.gov/nsrl/facility-users/. Use of the Brookhaven facilities requires a separate beam time application that is reviewed by a BNL-appointed panel and is scheduled in accordance with available beam time and other laboratory resources. BNL users are required to satisfy the normal process of preparation for running at the NSRL, which includes familiarization with BNL rules and policies (safety being the paramount consideration among these) and registration with the laboratory as a guest scientist.

NASA negotiates beam delivery directly with BNL, and investigators proposing to use these irradiation facilities should not include the cost of beam time in their budgets. However, investigators should include the cost of carrying out the experiments, including animal housing and travel to BNL, and provide an estimate of the hours of beam time required to conduct their experiments. **Investigators wishing to utilize other facilities, in addition to the NSRL, must provide a detailed justification for their use and must include certification that use of those facilities will be at no cost to NASA.**

For further information regarding BNL, contact Dr. Adam Rusek (email: rusek@bnl.gov) or Dr. Peter Guida (email: guida@bnl.gov). The address is Brookhaven National Laboratory, PO Box 5000, Upton, NY 11973-5000. Information about this facility is also available at http://www.bnl.gov/medical/NASA/LTSF.asp.

D. Background Information

NASA is concerned with the health risks to astronauts following exposures to GCR and SPE. The major GCR particle types include H, He, C, O, Ne, Si, Ca, and Fe with broad energy spectra of interest primarily from ~10 MeV/n to 10,000 MeV/n. GCR exposures occur at low fluence, with each cell in an astronaut's body being traversed by a proton about every three days, helium nuclei once every few weeks, and HZE nuclei about once every few months. For groups of interacting cells, GCR traversals are much more frequent. The traversal of a cell nucleus would usually be accompanied by essentially simultaneous traversal of very large numbers of additional cell nuclei in the tissue along the track of the same particle. These fluence rates correspond to tissue doses or effective dose-rates of about 0.3-0.6 mGy/d and 1-1.8 mSv/d, respectively. SPE's are low to medium-energy protons with the energy region of most importance to human space flight extending out to a few hundred MeV. The SPE spectra include much smaller components of helium and heavy nuclei. The shapes of the energy spectra, as well as the total fluence, vary considerably from event to event. Over the course of an SPE, dose-rates can fluctuate between 0-100 mGy/hr inside the protection of a vehicle. SPE dose-rates can also differ by several-fold between tissue sites because of the variable energy spectra of the protons or other nuclei.

GCR nuclei of average energy can penetrate a substantial thickness of materials, on the order of 10's to 100's of centimeters of water or aluminum. If they suffer nuclear interactions, the lighter secondary products will lose energy at a lower rate, and therefore will be able to penetrate even further. For this reason, it is not possible to provide sufficient material to fully absorb all types of radiation in space. In addition, the relative effectiveness of nuclei will change as a function of depth of penetration, because the composition of the nuclei changes and because the LET of each nucleus changes as it loses energy and slows down inside the material.

Energy deposition in biomolecules, cells, and tissues is distinct when comparing protons and HZE nuclei to common forms of terrestrial radiation. For the particles comprising space radiation, energy deposition is highly localized along the trajectory of each particle with lateral diffusion of energetic electrons (delta-rays) away from the nuclei's path. Delta-rays from HZE nuclei and protons traverse each cell in an astronaut's body about once per day. The rate of energy deposition per unit length of a particle trajectory is described as Linear Energy Transfer

(LET). The unit generally used in radiobiology for LET is the kilo-electron volt per micrometer, or keV/µm. The LET of charged particles changes as a function of particle velocity β or kinetic energy, and its charge, Z approximately in proportion to Z^2/β^2. As the velocity (or energy) of a particle increases, the LET decreases to a minimum near a velocity of approximately 90% of the speed of light; at higher energies the LET increases very slowly due to relativistic effects. High-energy charged particles lose energy when they traverse any material. As they slow down, the LET increases to a maximum and then very rapidly decreases to zero. The low-energy maximum in LET occurs very close to the point where the charged particle loses its remaining energy and stops. Nuclear fragmentation and other nuclear interactions, including projectile fragmentation of the primary ion and target fragmentation of tissue constituents, occur as ions traverse tissue. For proton and HZE nuclei irradiation, target fragmentation, including secondary neutron production, introduces an additional high LET component into the radiation field.

Space radiation risks of concern to NASA are carcinogenesis, acute (in-flight) and late (i.e., after a mission) risks to the CNS, degenerative tissue risks such as cardiovascular disease, and acute radiation syndromes. For cancer and acute risk estimates, human epidemiology data with gamma-rays and X-rays play a key role in risk estimation models. Acute risks are a concern for SPE, while cancer, CNS, and cardiovascular risks are a concern for both GCR and SPE. The current model of cancer risks used by NASA, NSCR 2012 (Cucinotta and Kim 2013) scales cancer incidence or mortality rates estimated from epidemiology data to the effects for the low dose-rates and radiation types in space using a dose- and dose-rate effectiveness factor (DDREF) and radiation quality factor, respectively. There are large uncertainties in this model, which in order of decreasing importance are: the radiation quality factors, dose and dose-rate dependencies, the transfer or risk across populations, the determination of space radiation organ exposures, and the various errors in human data sources. In addition, there are uncertainties related to the underlying assumptions of the model due to possible qualitative differences between high- and low-LET radiations, the validity of the assumptions of linearity and additivity of effects for different radiation components, and the possible synergistic risks from other flight factors on radiation risks. Because solar protons are largely low LET, the predominant uncertainty for acute risk estimates is related to the understanding of dose-rate effects and biological effects due to non-uniform tissue dose distributions.

Radiobiological studies are conducted using gamma-rays as a standard of comparison to space radiation components because of the availability of human data for this radiation type. High-LET nuclei generally require a lower dose than gamma-rays to induce a given observable biological effect. The quantity used to describe this is the relative biological effectiveness (RBE), which is equal to the ratio of the (generally higher) dose of gamma-radiation that will produce a specified biological endpoint to the dose of (generally lower) high-LET nuclei producing the same biological endpoint. For a multitude of radiation endpoints, the RBE varies significantly as a function of LET. The RBE peaks between 100 and 200 keV/µm for many endpoints (so called maximum RBE), reflecting the optimal energy deposition in sensitive targets within cells or tissues and a decrease in the correct repair of damage. The RBE versus LET relation branches for nuclei with identical LET but distinct charge numbers (or velocity), and nuclei with smaller charge number are predicted to have a higher value of RBE's at a fixed value of LET. For a given element, beyond maximum RBE, the effectiveness for most endpoints again decreases, due

to the fact that further energy deposition in the damaged sites is wasted once a particular endpoint has been achieved. The characterization of radiation quality in terms of RBE is widely used to describe biological response to radiation, but may ignore qualitative differences in biological effects between different types of radiation. RBE is also the basis for the regulatory approach that specifies Quality Factors patterned after the LET dependence of RBE, denoted as Q (L) where L is the LET. However, it is important to remember that Q is used to estimate risk of cancer; to the extent that space radiation leads to biological endpoints not related to cancer, it is necessary to apply other criteria to evaluate the degree to which a given dose of space radiation leads to different effects for different particles. Even for the case of carcinogenesis, Q is limited to biological endpoints for which a significant response to gamma-rays can be obtained and for risks where human data for low LET radiation is pertinent. When there is no response for gamma-rays, the ensuing very large values of RBE ("infinite RBE") may be due to the lack of efficacy of gamma-rays rather than a particularly effective aspect of the high-LET radiation. Qualitative differences are suggested to lead to shorter disease latency for high LET radiation compared to low LET radiation, which is also not adequately described by the RBE approach. For these and other reasons, the description of radiation action is not complete without an understanding of the processes leading to an observed result. Further refinements in risk assessment require the understanding of distinct tissue spectra and histological differences in HZE particle and neutron induced tumors compared to background cancers in the U.S. and whether high LET particles produce more aggressive and qualitatively different cancers compared to tumors found in control animals. These factors could impact disease morbidity and cure rates, confound conversion of incidence to mortality, and complicate early detection.

In the last decade many of the so-called hallmarks of cancer have been elucidated and are suggestive of important cancer development processes that could be used to form the basis of a new description of radiation quality effects and cancer risk. Such cancer development processes include but are not limited to the following: genomic instability, angiogenesis, evasion of apoptosis and DNA damage checkpoints, insensitivity to growth signals, aberrant DNA methylation and replication stress, changes in the extra-cellular matrix, and altered proliferation or differentiation. Biological mechanisms that lead to early chromosomal changes after radiation exposure and late appearing changes in tumors and their relationships have begun to be discerned. Knowledge of the transcriptome and epigenome, and how these relate to genomic changes, are expected to play an important role in elucidating how reprogramming of cells and cancer progression occur, the role of adult tissue and cancer stem cells, and in understanding the translation from experimental models to human risk assessments, including the effectiveness of countermeasures. Research studying such processes for a variety of radiation qualities and biological models is expected to play an important role in understanding qualitative and quantitative differences between space radiation and low LET radiation leading to improved risk quantification and ultimately the development of new systems biology risk modeling approaches that link several levels of biological organization and provide new scaling methods.

Biological countermeasures developed for terrestrial applications have historically focused on treating acute radiation syndrome as a result of high dose, high dose-rate and low LET radiation exposures or to mitigate unwanted effects associated with radiotherapy. While these drug therapies may provide effective risk reduction for acute risks from solar particle events (high dose-rate, low LET exposure); their effectiveness in mitigating late effects from low dose-rates

of high LET radiation is less clear. The identification of candidate countermeasures will be aided by a mechanistic knowledge of disease specific pathways across major risk areas including the possibility of acute (in-flight) cognitive and behavioral decrements and the late effects of cancer, cardiovascular and neurodegenerative diseases. Mechanisms of HZE radiobiology that differ from low LET radiobiology include: a higher proportion and distinct types of clustered DNA damage, mutations and complex chromosomal aberrations; differences in the yields and types of oxidative species; and the spatial patterns of damage sites in cells and tissues, as well as in signal transduction and gene expression when comparing radiation qualities. Additionally, there exists the possibility of earlier tumor appearance and increased tumor metastasis for HZE ions compared to low LET radiation. Understanding the mechanisms of biological damage and approaches to extrapolate model system results to humans are not only required for accurate assessment of risk benefits but also essential for hypothesis-driven research directed at identifying and validating biological countermeasures for their approved operational use by NASA.

E. Human Research Program (HRP) Integrated Research Plan

NASA has developed the HRP Integrated Research Plan (IRP) (http://humanresearchroadmap.nasa.gov/) to identify and make publicly known the biomedical and health risks of space flight and the research and technology gaps that must be answered to reduce those risks. The IRP is an interdisciplinary tool to assess, understand, mitigate, and manage the risks to humans that are associated with long-term exposure to the space environment. It assumes an overarching strategy that integrates requirements, risks, risk factors, research and technology gaps, tasks, deliverables, and risk mitigation with the intent of directing biomedical research in support of human space flight, especially human missions of exploration. 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 such as the National Research Council (NRC) Space Studies Board's "A Strategy for Research in Space Biology and Medicine in the New Century", the National Council on Radiation Protection and Measurements (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." Additional information related to the integrated research strategy specific to central nervous system risks is included in the references in Section VIII.

Each radiation risk has an associated set of research gaps listed in Section VIII, Appendix A of this document. In the radiation area, the current IRP identifies four risks and 36 research gaps. The four categories of radiation risks in the HRP IRP are:

1. Carcinogenesis with 15 gap areas,
2. Acute and Late Effects in the Central Nervous System with eight gap areas,
3. Cardiovascular Disease and Other Degenerative Tissue Effects with eight gap areas,
4. Acute Radiation Syndromes with five gap areas.

The proposer shall examine the Space Radiation section of the IRP to understand the research gaps being solicited for under the space radiation cancer, cardiovascular disease and CNS risks as well as the special topic areas. Not all risks or gap areas are being solicited in this NRA because they are already being addressed or will be addressed in future solicitations. Such gaps are shaded and listed as "N/A" in Appendix VIII. A similar assessment will be performed by NASA to understand how the proposed research addresses the IRP risks and gaps.

Proposers must fill in the check-boxes in Appendix A to clearly identify which risks and gaps are addressed by the proposed research and describe how their research aims map to these risks and gaps (Section IV.B.3.a). Proposals that do not identify which IRP risks and gaps are being addressed by their research will be declared noncompliant and declined without review.

F. NASA Space Radiation General Research Focus

NASA space radiation research emphasizes the application of mechanistic understanding using mammalian models in order to achieve significant reductions in the uncertainties in risk projections for space radiation induced cancers, cardiovascular and other degenerative diseases, as well as acute (in flight) and late cognitive and behavioral CNS decrements with the ultimate goal of mitigating space radiation associated risks. For the CNS risks, a great challenge exists in determining how functional alterations and key biomarker changes measured in animal models are predictive of possible mission relevant performance decrements in highly skilled and trained astronauts. For the cardiovascular system and other degenerative diseases the major research emphasis is on elucidation of radiation quality effects on disease spectrum, incidence and progression and to determine if dose thresholds exist.

Given the complexity of the biological problems being addressed, it is expected that multi-scale systems approaches that relate molecular damage and modifications of signal transduction pathways to cellular and tissue effects will be important in achieving the required levels of accuracy in risk estimation required for long duration space flight. To support modeling efforts an improved understanding is required of how space radiation may modify fundamental biological processes including DNA damage processing, signal transduction, modification of cell cycle controls and apoptosis, changes to tissue structure including the extracellular matrix and cellular differentiation, endocrine and paracrine signaling within the tissue microenvironment, altered methylation patterns, genomic instability, cellular senescence, genetic sensitivity or resistance, persistent oxidative damage and chronic inflammation. Adult stem cells are of interest for elucidating tissue specific mechanisms of cancer, CNS and other degenerative risks. The use of age appropriate outbred animal strains along with transgenic models and advanced 3D cell cultures is expected to support risk characterization and facilitate extrapolation of research results to humans. An improved mechanistic understanding is required across all risk areas and therefore novel methods are warranted, which may include limited testing of biological countermeasures when justified for interrogation of potential disease pathways. Comprehensive "omics" characterization of cancers that arise due to heavy ion exposure in animal models and how these molecular changes compare to those in spontaneous and low-LET induced tumors in both animals and humans are expected to support systems biology risk modeling efforts,

extrapolation of results to human cancers, and also to drive biomarker identification for disease monitoring and future countermeasure development and testing. Ultimately experimental approaches must provide quantitative data in support of accurate risk estimation reflective of our astronaut population and the development of mitigation approaches.

Investigators are encouraged to review the research currently being conducted by the NASA Space Radiation Program Element to avoid duplicative studies. Information on these studies can be found in the NASA Task Book (http://taskbook.nasaprs.com/Publication/welcome.cfm). From the Task Book home page, click the "Search Task Book" button, and then select the Human Research Program Element: Space Radiation (SR) check box for a list of active studies. Information specific to current NASA Centers of Research (NSCOR) in leukemia, liver, lung, breast, and colorectal cancers, and CNS risks can be made by checking the Human Research Program: SR check box and entering keyword "NSCOR."

G. Research Emphases Specific to this Solicitation

Proposed studies must directly address the following high-priority research topic in Radiation Carcinogenesis emphasized by the Space Radiation Program Element.

This solicitation is focused on research that will provide the basis for accurate risk quantification reflective of our astronaut population supporting individualized risk and sensitivity assessments of cancers from exposure to space radiation**.** The current NASA cancer risk projection model (NSCR 2012) estimates the risk of radiation carcinogenesis with consideration of crew sex and age at exposure, and is based on human radiation epidemiology data and analysis, as well as research results from the NASA Space Radiation Laboratory. This model also takes into consideration healthy worker effects by limiting the extrapolation of astronaut risks to that of the non-smoking US population. However, inherent uncertainties in application of the risk estimates to individual astronauts still exist due to the use of population averages that limit their accuracy (Cucinotta and Kim 2013).

Understanding individual differences in radiation sensitivity and cancer susceptibility based on genetic and epigenetic factors and how these factors influence individual risk for development of radiation-induced cancers and other diseases is expected to support the development of more accurate tissue-specific cancer models (including leukemia, lung, breast, colorectal, stomach, liver, esophageal, skin, brain, and bladder tissues). Although information on individual susceptibility is not currently used as a discriminator in crew selection, research to uncover individual factors that influence HZE cancer processes will support informed consent, biomarker discovery and countermeasure development appropriate to the astronaut population and the spaceflight setting. Comparative studies between female and male animals for tumors that are important in both sexes, as well as studies of sex specific diseases, such as ovary and breast, to adequately describe sex dependence in risk assessments are required as well as studies to determine mechanistic basis for the higher incidence of radiation induced lung cancers in females. A related area of emphasis specific to this call are studies to determine if the spectrum

of tumor types and underlying molecular changes induced by heavy ions are similar to or distinct from spontaneous tumors and those induced by sparsely ionizing radiation, as well as, comparison of tumor latency and malignant potential of these tumors and how these relate to individual risk. Research evidence in these priority areas is crucial to verify the accuracy and support refinements in current NASA risk modeling efforts.

One of the potential products of research on space radiation induced cancer will be the identification of biomarkers that can be used to indicate and examine individual susceptibility to radiation and indicate development of adverse outcomes. Research conducted to expand mechanistic understanding of disease processes, along with acquisition of *"-omics"* datasets may facilitate biomarker identification and validation as well as enhance the ability to leverage on major progress in human cancer genomics to determine genetic, mutational, transcriptional and epigenetic landscapes of radiation induced cancers for disease detection, treatment and prediction as well as individualized risk assessment.

Such efforts are expected to play a leading role in achieving NASA's goal of risk mitigation, ultimately leading to individual based risk projections including providing experimental approaches to extrapolate from animal models to humans. Further, understanding individual sensitivity to radiation damage will be of considerable aid in informing potential crewmembers about the radiation risk associated with a particular mission assignment.

To be responsive to this solicitation, investigators must provide a realistic, quantitative assessment of the extent to which their research is likely to contribute to NASA's objectives of reducing uncertainty and improving risk estimation on the basis of sex, individual susceptibility, and age at exposure specific to the spectrum of tumors induced by high LET radiations, and the identification of potential biomarkers indicative of disease susceptibility, disease detection or outcome. Additionally, investigators must specifically address how results can be extrapolated to estimate risks to humans exposed to the space radiation environment. In this context, cross-species comparisons using intermediate biological models representative of complex human models may be of interest and studies that address the broad spectrum of tumors induced by space radiation are desirable. **It is expected that research will be conducted according to the highest standards of scientific inquiry, addressing clearly stated, falsifiable hypotheses, and using the most advanced, recognized methods available.**

In seeking to understand the impact of sex, age, and genetic predisposition in evaluating space radiation risks proposers must take into consideration the characteristics of NASA's astronaut corps. The average age of the astronaut corps is 35-55 years old with their first space mission at the age of 47 for ISS crews. The corps is comprised of approximately 30% females. Most astronauts are lifetime never-smokers; however approximately 15% of astronauts were former smokers or were exposed to high levels of second-hand smoke. Studies may include animals, tissues (animal or human), or cells (animal or human), including adult human stem cells to elucidate tissue specific mechanisms of radiation carcinogenesis. Proposers must use animals at an age reflective of the ages of astronauts during space missions. Researchers should use the model system (e.g., cell type, species) most appropriate for their research and are encouraged to take advantage of state of the art recombinant congenic mouse strains (e.g. the Collaborative Cross sub-lines, founder strains, or other out-bred lines) that more accurately reflect the genetic

heterozygosity present in the human population to identify alleles associated with radiation induced cancer susceptibility as well as comparative biology approaches that enhance the research scope.

Each proposal must identify a coordinating Principal Investigator (Director) who will be responsible for ensuring that the NSCOR includes investigators with appropriate expertise to implement proposed research. Experimental protocols should reflect careful consideration of irradiation requirements, including justified estimates of dose, dose rates, and ion beams for selected samples as well as a description of the range of possible sample sizes and their associated power. Statistical planning plays an important role in virtually all scientific research. It plays a particularly valuable role in the design of experiments, including specification of sample size(s), and also in the analysis of outcomes that address primary aims and hypotheses. As a result, PIs are highly encouraged to recruit statisticians as Co-Is, so that they can apply their skills to help produce high-quality research proposals. A bioinformatics core and mathematical modeling components may also be included as required; however, resources for such efforts should not detract from the largely experimental emphasis required by NASA for this NSCOR.

1. Cancer Risks from Space Radiation and Impact of Individual Susceptibility

NSCOR team proposals should focus their research to address <u>each</u> of the following high priority areas to the greatest extent possible:

- Research to uncover information on individual susceptibility to space radiation induced cancers that will form the basis for individualized risk assessments and countermeasures. This may include studies to understand the contribution of genes controlling sensitivity to radiation damage, known cancer susceptibility genes, as well as studies to determine unique sensitivities specific for heavy ion induced cancers.
- Research to quantify and describe the biological basis for the effects of sex on cancer risk from space radiation exposure.
- Research to understand if the tissues at risk for cancer development from low-LET radiation exposure observed in human epidemiology data are reflective of those observed in animal studies with heavy ions; and research to characterize the histological differences and possible mechanistic basis for enhancement in aggressive phenotype (decreased latency, increased frequency of occurrence, accelerated progression, enhanced metastasis) observed in HZE particle versus terrestrial radiation induced cancers.
- Research to identify biomarkers that can be used to indicate and examine individual susceptibility to space radiation and to monitor the development of adverse outcomes.
- Research that seeks to leverage on the rapidly accumulating genomic and molecular knowledge on human cancers in order to facilitate extrapolation of results obtained in animal models to the human condition.

Studies proposing the sharing of experimental animals and tissues from currently funded investigations as well as the use of archival tissues are highly encouraged. Research must

address multiple cancers across the major tissue sites (Cancer Gap-1). Proposals must address how expected results can be used to improve risk prediction on an individual basis.

2. Additional Guidance for Specific Research Emphasis

Doses corresponding to HZE particles at low fluence (less than one ion per cell), proton doses up to 1.0 Gy, and HZE particles at low doses no higher than 0.5 Gy, should be used. Because high doses of protons (>1 Gy) and HZE particles (>0.5 Gy) are not relevant to long duration human exploration missions and biological responses at low doses are dissimilar from those at high doses, experiments at high doses will not be supported by NASA without specific justification. Use of a single higher dose may be justified for protons, but experimental plans with more than one high dose are not likely to be supported. All doses for HZE particles must remain below 0.5 Gy. Inclusion of lower dose points and/or exposures to simulate low-dose rate chronic exposures present in space is important. Dose-rate studies proposing to simulate protracted exposures should ensure that total exposures also remain at or below 1 Gy for protons and 0.5 Gy for HZE particles. Individual components of mixed field studies should also remain within these exposure levels with total mixed field exposures at or below 1.5 Gy. For studies utilizing a reference field, gamma-rays (Cs or Co) should be used as the reference radiation unless otherwise specified in the Research Emphasis or Special Topic area. Significant justification needs to be provided to use X-rays with energies below 300 kVp as a reference radiation. **Before final award, proposals selected for funding will undergo a further review by SRPE on the choices of beams and doses to be used in funded research plans.**

Studies developing computational models should specifically address guidance regarding NASA's Software Sharing Policy (Section III.E). The investigation team must be willing to provide the source code, readme files and documentation on how to use the model, and ability for NASA to make the software available as an open source product. Reliance on previously developed software that is not available to NASA is not acceptable.

Note that as part of the proposal submission process, assurance of compliance with applicable federal regulations regarding human subjects or animal care and use is required (see the "Special Matters" instructions in section IV.B.3.b).

H. Structure of the NSCOR

1. Interactions among Investigators, University Partners and NASA

Teaming arrangements among investigators and research groups at the same institution and between different institutions is required and must be clearly explained. Evidence of appropriate institutional approval from each institution must be included in the proposal. The sharing of resources and responsibilities between member institution(s) must be explicitly stated in the proposal.

The management structure must be the minimum that is consistent with financial and programmatic accountability and should not impose onerous costs or procedures on the

investigators. Procedures to allocate resources and adjudicate differences of opinion need to be clearly defined and agreed upon by all participants. The primary criteria for an award will be scientific merit and programmatic relevance.

2. Expertise of Universities

Academic Departments
The different academic departments at the participating institutions must have committed personnel and facilities to accommodate the research needs of an NSCOR. There should be a plan for coordination of research activities and resource sharing. Cost sharing for educational components at the graduate and undergraduate levels from participating institutions is strongly encouraged.

Personnel
The participating institutions must have faculty with the expertise to undertake this multidisciplinary projects. The proposal should outline how the complementary expertise of the faculty will result in a teaming effort that will adequately address the research needs of the NSCOR or VNSCOR Element.

3. NSCOR Structure

Key Personnel for NSCORs

Each proposing team must have an NSCOR Director with demonstrated scientific and administrative leadership qualities. The proposal should contain a detailed and coherent management structure that is conducive to accomplishing the goals of the NSCOR and is consistent with the research goals of the space radiation research program. The positions of NSCOR Director, Associate Director(s) (if any) and Research Leads (Principal Investigators) are considered Key Personnel. Their qualifications, roles and responsibilities must be clearly defined in the proposal and may not be substituted without NASA's approval. The expertise of the key personnel should match the areas of emphasis. The Director of the NSCOR will be considered as the primary point of contact between the NSCOR and NASA. A written agreement with the proposal and a commitment to carry out their responsibilities in the event that the NSCOR is selected and funded must be signed by each participating Principal Investigator.

NSCOR Roles and Responsibilities

In order to achieve the research goals of the NSCOR, the roles and responsibilities of the individual investigators, Research Leads, Associate Director(s) and the Director must be clearly defined. The proposal must also include a description of these roles and responsibilities and interactions between partnering institutions. A description of the process for the transfer of resources and other partnering agreements between the participating institutions must be included in the proposal.

NSCOR Internal Advisory Committee

The NSCOR must propose to establish an Internal Advisory Committee to assist and support the Director to ensure that:

- the internal activities of and external interactions of the NSCOR are coordinated;
- funds are allocated and used to properly fulfill the objectives of the NSCOR;
- fair procedures are in place to adjudicate differences of opinion among the participants,
- advice on productivity and effectiveness of the NSCOR is provided to the Director; and
- appropriate interactions take place to assure information exchange and technology transfer among scientists, engineers, and administrators, and those in other public and private institutions deemed important to the effort.

The members of the Internal Advisory Committee should include faculty with appropriate expertise from all the participating institutions. The composition of this committee is at the discretion of the Director.

Members from NSCOR's or other NASA Awards may be invited by NASA to join the Cancer Biology working group.

I. NASA Safety Policy

Safety is NASA's highest priority. Safety is the freedom from those conditions that can cause death, injury, occupational illness, damage to or loss of equipment or property, or damage to the environment. NASA's safety priority is to protect: (1) the public, (2) astronauts and pilots, (3) the NASA workforce (including employees working under NASA instruments), and (4) high-value equipment and property. All research conducted under NASA auspices shall conform to this philosophy.

J. Availability of Funds for Award

Funds are not currently available for awards under this NRA. The Government's obligation to make award(s) is contingent upon the availability of the appropriated funds from which payment can be made and the receipt of proposals that NASA determines acceptable for award under this NRA.

K. Additional Funding Restrictions

The construction of facilities is not an allowed activity unless specifically stated so in the program description. For further information on the allowable costs, refer to the cost principles cited in the NASA Federal Acquisition Regulation Supplement (NFS) Part 1852.235-72, hereinafter referred to as the *NFS Provision*, located at http://www.hq.nasa.gov/office/procurement/regs/5228-41.htm#52_235-72, and the *Guidebook for Proposers*. Travel, including foreign travel, is allowed as may be necessary for the

meaningful completion of the proposed investigation, as well as for publicizing its results at an appropriate professional meeting.

This solicitation will result in grant awards only. Profit to commercial organizations under grants is not allowed.

Regardless of whether functioning as a team leader or as a team member, personnel from NASA Centers must propose budgets based on Full Cost Accounting (FCA). Non-NASA U.S. Government organizations should propose based on FCA unless no such standards are in effect; in that case such proposers should follow the Managerial Cost Accounting Standards for the Federal Government as recommended by the Federal Accounting Standards Advisory Board. For further information, see http://www.hq.nasa.gov/fullcost/.

II. Award Information

The selected proposal will be funded as a research grant in one year increments for a period of performance that typically lasts five years; however, four years periods may be considered if justified by the proposer's research plan**.** The mechanism for funding the successful proposal will be a single grant, with funding allocations to participating investigators based on the submitted budget, available funds and project review. The funding duration will depend on proposal requirements, review panel recommendations, and continuing progress of the activity. Proposals will be evaluated as described in Section V.

Depending on available funding and the results of peer review for scientific merit, up to three NSCORs may be selected by SRPE. **It is anticipated that SRPE awards will average between $1,500,000 to $1,800,000 (Maximum of $2,000,000) per year and shall not exceed $9,000,000.** NASA does not provide separate funding for direct and indirect costs; thus, the amount of the award requested is the total of all costs submitted in the proposed budget. It is estimated that the initial selection will be announced by the date listed in Section IV.C and the grant will be awarded in a reasonable timeframe thereafter.

III. Eligibility Information

A. Eligibility of Applicants

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

The applying entity must have in place a documented base of ongoing high quality research in science and technology, or in those areas of science and engineering clearly relevant to the specific programmatic objectives and research emphases indicated in this NRA. Present or prior

NASA support of research or training in any institution or for any investigator is not a prerequisite to submission of a proposal.

B. Guidelines for International Participation

1. Guidelines for International Team Members on U.S. Proposals

HRP welcomes international team members on U.S. proposals. International collaborations that demonstrate clear scientific benefits or cost savings are particularly encouraged.

Services and direct purchases provided by international team members are allowable as subcontracts on U.S. proposals. Additional information on international participation can be found at http://www.hq.nasa.gov/office/procurement/regs/1835.htm#35_016-70.

2. Guidelines for International Proposals

NASA welcomes proposals from outside the U.S. However, foreign entities are generally not eligible for funding from NASA. Therefore, unless otherwise noted in the NRA, proposals from foreign entities should not include a cost plan unless the proposal involves collaboration with a U.S. institution, in which case a cost plan for only the participation of the U.S. entity must be included. Proposals from foreign entities and proposals from U.S. entities that include foreign participation must be endorsed by the respective government agency or sponsoring institution in the country from which the foreign entity is proposing. Such endorsement should indicate that the proposal merits careful consideration by NASA, and if the proposal is selected, sufficient funds will be made available to undertake the activity as proposed.

All foreign proposals must be typewritten in English and comply with all other submission requirements stated in the NRA. All foreign proposals will undergo the same evaluation and selection process as those originating in the U.S. Facilities for particle beam irradiation at foreign institutions should be described. All proposals must be received before the established closing date. Those received after the closing date will be treated in accordance with NFS Part 1815.208. Sponsoring foreign government agencies or funding institutions may, in exceptional situations, forward a proposal without endorsement if endorsement is not possible before the announced closing date. In such cases, the NASA sponsoring office should be advised when a decision on endorsement can be expected.

Successful and unsuccessful foreign entities will be contacted directly by the NASA sponsoring office. Copies of these letters will be sent to the foreign sponsor. Should a foreign proposal or a U.S. proposal with foreign participation be selected, NASA's Office of External Relations will arrange with the foreign sponsor for the proposed participation on a no-exchange-of-funds basis, in which NASA and the non-U.S. sponsoring agency or funding institution will each bear the cost of discharging their respective responsibilities.

Depending on the nature and extent of the proposed cooperation, these arrangements may entail:

(i) An exchange of letters between NASA and the foreign sponsor; or
(ii) A formal Agency-to-Agency Memorandum of Understanding (MOU).

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, NASA funding through this NRA may not be used to support research efforts by non-U.S. organizations at any level; however, the direct purchase of supplies and/or services that do not constitute research from non-U.S. sources by U.S. award recipients is permitted. See NFS 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 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

3. Assurance of Compliance – China Funding Restriction

All proposals submitted to this NRA must comply with the following: Assurance of Compliance with The Department of Defense and Full-Year Appropriation Act, Public Law 112-10 Section 1340(a); The Consolidated and Further Continuing Appropriation Act of 2012, Public Law 112-55, Section 539; and future-year appropriations herein after referred to as "the Acts", whereas:

a) NASA is restricted from using funds appropriated in the Acts to enter into or fund any grant or cooperative agreement of any kind to participate, collaborate, or coordinate bilaterally with China or any Chinese-owned company, at the prime recipient level and at all sub-recipient levels, whether the bilateral involvement is funded or performed under a no-exchange of funds arrangement.
b) Definition: "China or Chinese-owned Company" means the People's Republic of China, any company owned by the People's Republic of China, or any company incorporated under the laws of the People's Republic of China.
c) The restrictions in the Acts do not apply to commercial items of supply needed to perform a grant or cooperative agreement.
d) By submission of its proposal, the proposer represents that the proposer is not China or a Chinese-owned company, and that the proposer will not participate, collaborate, or coordinate bilaterally with China or any Chinese-owned company, at the prime recipient level or at any sub-recipient level, whether the bilateral involvement is funded or performed under a no-exchange of funds arrangement.

4. 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, discuss whether the license has been applied for or, if not, the projected timing of the application and any implications for the schedule. Information regarding U.S. export regulations is available at Bureau of Industry (BIS) http://www.bis.doc.gov/licensing/exportingbasics.htm.

C. Cost Sharing or Matching

If an institution of higher education, hospital, or other non-profit organization wants to receive a grant from NASA, cost sharing is not required. However, NASA can accept cost sharing if it is voluntarily offered. If a commercial organization wants to receive a grant, cost sharing is required unless the commercial organization can demonstrate that they are unlikely to receive substantial compensating benefits for performance of the work. If no substantial compensating benefits are likely to be received, then cost sharing is not required but can be accepted. Acceptable forms of cost sharing are discussed in NFS Part 1816.303-70: http://www.hq.nasa.gov/office/procurement/regs/1816.doc#OLE_LINK3.

D. Data Accessibility

All data collected through research programs sponsored by NASA are considered public. Data produced from NASA-funded life sciences research must be submitted to NASA and are archived in the NASA Life Sciences Data Archive (LSDA) (http://lsda.jsc.nasa.gov/) for the benefit of the greater research and operational space flight community. Archival data products may include but are not limited to low-level (raw) data, high-level (processed) data, and data products such as calibration data, documentation, related software, and other tools or parameters that are necessary to interpret the data. Once a grant is awarded, the PI and the supporting NASA HRP Element Scientist shall work with LSDA to outline specific archiving requirements in an LSDA Data Submission Agreement. These requirements shall include which data are to be included, the format of the data, and the timeframe in which the data is expected to be submitted for archiving. The Government has the right to use and disclose all data generated from this grant:

> *"As a Federal Agency, NASA requires prompt public disclosure of the results of its sponsored research and, therefore, expects significant findings from supported research to be promptly submitted for peer reviewed publication with authorship(s) that accurately reflects the contributions of those involved. Likewise, as a general policy and unless otherwise specified, NASA no longer recognizes a "proprietary" period for exclusive use of any new scientific data that may be acquired through the execution of the award; instead, all data collected through any of its funded programs are to be placed in the public domain at the earliest possible time following their validation and calibration."*

NASA HRP recognizes the importance of the right of first publication in demonstrating and maintaining the scientific credentials of its funded investigators. In general NASA HRP intends to continue its discretionary policy of allowing the funded principal investigator(s) a period of one (1) year after final data collection from subjects or acquisition of final specimen in space

flight or ground-based investigations, before making the data available to other investigators through release from the LSDA. The details and any exceptions or special circumstances of this policy will be documented in each investigation's Data Submission Agreement. However, the NASA HRP Chief Scientist has the prerogative, at any time, to include all extant results, whether published or unpublished, in HRP's internal analyses as needed for decisions pertaining to astronaut safety, health and performance and programmatic scope and direction. These analyses will not be published within the one-year period described above unless required by law or NASA policy.

Investigators should be aware that any results published in peer-reviewed scholarly publications that are based on research that directly arises from federal funds must be submitted to NASA as part of their grant or contract obligation. Funding from NASA should be acknowledged in publications as follows:

"This material is based upon work supported by the National Aeronautics and Space Administration under Grant/Contract/Agreement No. <xxxxxx>."

A copy (hard or electronic) of any publication resulting from NASA HRP funding should be transmitted to the HRP Space Radiation Element Scientist once published.

E. Data Sharing

Investigators should have an expectation of data sharing with other efforts across the Human Research Program where projects are synergistic or use the same analog. Proposers should include a cost estimate to account for any anticipated data sharing. The adequacy of the data sharing plan will be considered by NASA when making recommendations about funding applications as appropriate. In making such considerations, prior to funding, NASA may negotiate modifications of data sharing plans with the PI. Any data sharing plans represent a commitment by the institution (and its subcontractors as applicable) to support and abide by the plan.

F. Software Sharing Policy

A software dissemination plan, with appropriate timelines, is expected in the application only if software development is a part of the application. There is no prescribed single use license for software produced through grants responding to this announcement. In accordance with federal law, NASA will protect the privacy and ownership rights of software developers. However, NASA HRP does have goals for software dissemination, and reviewers will be instructed to evaluate the dissemination plan relative to these goals:

1. The software should be freely available to biomedical researchers and educators in the non-profit sector, such as institutions of education, research institutions, and government laboratories.
2. The terms of software availability should permit the dissemination and commercialization of enhanced or customized versions of the software, or incorporation of the software or pieces of it into other software packages.

3. To preserve utility to the community, the software should be transferable such that another individual or team can continue development in the event that the original investigators are unwilling or unable to do so.
4. The terms of software availability should include the ability of researchers to modify the source code and to share modifications with other colleagues. An applicant should take responsibility for creating the original and subsequent "official" versions of a piece of software.
5. To further enhance the potential impact of their software, applicants are expected to propose a plan to manage and disseminate the improvements or customizations of their tools and resources by others. This proposal may include a plan to incorporate the enhancements into the "official" core software, may involve the creation of an infrastructure for plug-ins, or may describe some other solution.

The plan for software sharing will be evaluated during peer review together with any other resource sharing plans.

The adequacy of the software sharing plans will be considered by NASA when making recommendations about funding applications as appropriate. In making such considerations, prior to funding, NASA may negotiate modifications of software sharing plans with the Principal Investigator. Any software dissemination plans represent a commitment by the institution (and its subcontractors as applicable) to support and abide by the plan.

IV. Proposal and Submission Information

A. Source of Application Materials

All information needed to submit an electronic proposal in response to this announcement is contained in this NRA 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/.

Additionally, applicants shall prepare proposals in accordance with the "Instructions for Responding to NASA Research Announcements *NFS Provision*.

The information in this NRA **supersedes** and provides additional direction to that found in the *Guidebook for Proposers* and the *NFS Provision*. 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 NRA, and will be updated periodically between submission release and the Step-2 proposal due date.

B. Content and Form of Proposal Submission

1. NASA Proposal Data System

a) NASA Registration

This NRA 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 (PI) of a proposal in which that person is committed to participate. This data site is secure and all information entered is strictly for NASA's use only.

Every organization that intends to submit a proposal to NASA in response to this NRA, including educational institutions, industry, nonprofit institutions, NASA Centers, the Jet Propulsion Laboratory, and other U.S. Government agencies, must be registered in NSPIRES, regardless of the electronic system used to submit proposals. Such registration must be performed by an organization's electronic business point-of-contact (EBPOC) in the Central Contractor Registry (CCR).

b) Electronic Submission

Proposals must be submitted electronically. Step-1 and Step-2 proposals must be submitted electronically by one of the officials at the PI's organization who is authorized to make such a submission. All team members must be registered in NSPIRES and confirm their organizational affiliation when added to a proposal before the PI organization official can submit. It is strongly recommended that the PI work closely with his/her team members and organization official to ensure the proposal is submitted by the due date and time listed in this solicitation. **Proposals submitted after the listed due dates and times will be declared noncompliant and will be handled in accordance NFS Part 1815.208.**

Step-1 proposers can use either NSPIRES (http://nspires.nasaprs.com) or Grants.gov (http://www.grants.gov/) for proposal submission. Proposers intending to use Grants.gov should contact Kevin Willison (kwillison@nasaprs.com), Senior Scientist, NASA Research and Education Support Services to ensure that the Grants.gov system is available for Step-1 proposal submission. All proposers, team members, and agency officials must be registered before proposal submission with NSPIRES regardless of the electronic system used to submit proposals. NSPIRES remains the only system through which a Step-1 proposal can be continued as a Step-2 proposal. Proposers submitting a Step-1 proposal who receive an invitation to submit a Step-2 proposal will have the option of building on a stored Step-1 proposal within the NSPIRES database. Grants.gov will not be available for invited Step-2 submissions. All invited proposers must use NSPIRES for Step-2 proposal submission.

NSPIRES accepts fully electronic proposals through a combination of data-based information (e.g., the electronic *Cover Page* and its associated forms) and uploaded PDF file(s) that contain the body of the proposal. The system will conduct an element check to identify any item(s) that is (are) apparently missing or incomplete. Proposers are particularly encouraged to begin their submission process early.

Requests for assistance in accessing and/or using this Web site may be directed by E-mail to nspires-help@nasaprs.com or by telephone to (202) 479-9376 Monday through Friday, 8:00 AM – 5:00 PM 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. Intent to Propose and Step-1 Proposals

Proposals solicited through this NRA will use a 2-Step proposal process for which the Notices of Intent (NOI) take the form of a required Step-1 proposal. The following information **supersedes** that provided in the *Guidebook for Proposers* and provides additional direction consistent with the *NFS Provision*.

The NSPIRES system will guide proposers through submission of all required proposal information. Please note that the **Proposal Summary, Business Data, and Proposal Team are required** Cover Page Elements for a Step-1 proposal. The proposal summary should be between 100-300 words and understandable by the layman reader. These cover page elements may be modified in an invited Step-2 proposal. Budget should not be included with the Step-1 proposal.

The proposal document must be uploaded as a single .PDF file. **Step-1 proposals must address these components:** a clear indication of the relevance to the Space Radiation Program Element and mapping to the research emphases (Section I.G); the hypotheses and NSCOR sub-projects; the proposed project team. The project team is not considered binding for Step-1 and can be adjusted in an invited Step-2 proposal. No additional documents should be uploaded with the Step-1 proposal. The Step-1 proposal shall include an extended synopsis of the intended research (length not to exceed 5 pages using a standard 12-point type and the following margins: left = 1.0”; Right, top, bottom = 1.0”).

If your proposal is a resubmission, you should identify it as such in your Step-1 submission; you are not, however, required to address prior reviews unless invited to submit a full proposal. Please be aware that submission of a Step-1 proposal to re-introduce a proposal invited during a previous review cycle to submit as a Step-2 proposal, but not funded (i.e., a re-submission from a previous round of review), does not guarantee that this newly submitted Step-1 proposal will necessarily be judged as responsive to the areas of focus in the current solicitation and therefore invited to submit as a Step-2 proposal.

Step-1 proposals are prepared by the PI or a designated representative of the PI. **Step-1 proposals are submitted by an official of the PI’s organization after the PI has released the prepared proposal to the institution official.** It is strongly recommended that the PI work

closely with his/her organization official 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 dates.

To initiate a Step-1 proposal:

- Log in using your NSPIRES user name and password.
- Click on Proposals under the NSPIRES Options.
- Click on the Create Proposal button in the upper right hand corner of the screen.
- Select “Solicitation” as the source to prepare a new proposal.
- Click the button for “Ground-Based Studies in Space Radiobiology” NRA NNJ14ZSA001N-NSCOR.
- Follow the step-by-step instructions provided in NSPIRES to complete your Step-1 proposal.

Step-1 proposals shall be electronically submitted by the due date and time listed in Section IV.C. Electronic submission of Step-1 proposals will be open during the period listed in Section IV.C.

All submitters of Step-1 proposals must log in to NSPIRES on or after the Step-1 notification date listed in Section IV.C. to receive their Step-2 full proposal invitation status. A courtesy email will be generated by NSPIRES as a reminder to check full proposal invitation status; however, it is the responsibility of the submitter to log in to NSPIRES to receive their full proposal invitation status.

Decision information can be accessed in two ways:

1) After logging in, the Principal Investigator selects the "Proposals" link, the "Submitted Proposals/NOIs" link, and then clicks on the proposal submitted to the solicitation identified above. The document(s) provided by NASA will be displayed under the heading "PI Information Package" located at the bottom of the "View Proposal" page.

2) After logging in, the Authorized Organization Representative selects "Organization Mgmt" link and, from within the submitting organization, selects the "Organization Proposals" link, the "Submitted Proposals" link and then clicks on the proposal submitted to the solicitation identified above. The document(s) provided by NASA will be displayed under the heading "PI Information Package" located at the bottom of the "View Proposal" page.

3. Instructions for Preparation of Invited Step-2 Proposals

Step-2 proposals are due by the due date and time listed in Section IV.C. **Step-2 proposals will be accepted from invited proposers only.** Invited Step-2 proposals must be submitted through the NSPIRES system.

The NSPIRES system will guide proposers through submission of all required proposal information. To begin an invited Step-2 proposal, go to Proposals, Create Proposal, and then select prior-phase proposal when creating an invited Step-2 proposal. Please note that the Proposal Summary, Business Data, Budget, Program Specific Data, and Proposal Team are required Cover Page Elements for a Step-2 proposal. The proposal summary should be between 100-300 words and understandable by the layman reader. Proposal Team members carried over from a Step-1 proposal may need to login and re-confirm their affiliation and participation on the proposal. **For proposals with one or more NASA civil servant team members:** Proposers are required to enter the NASA civil servant team member name and fraction of FTE (full-time equivalent) involvement in the same field under the Item column in section F "Other Direct Costs" of the online budget. The funds requested should be entered as the Total Requested Funds for the NASA civil servant, including salary, fringe, materials, travel, etc. (see the FAQ posted alongside this document for additional budget instruction). This budget entry should be made for each year of NASA civil servant involvement, and is in addition to the agency identification under the team member section and the NASA civil servant FTE designation under the business data section.

To ensure proper Step-2 proposal transmission, please provide only **one** .PDF attachment upload ordered as below. **Specific instructions are given in this NRA that supersede those found in the NASA Guidebook for Proposers. Proposals that do not conform to these requirements may be declared noncompliant and declined without review**. For any section below without specific instruction, proposers are encouraged to reference the NASA Guidebook for Proposers; however, there are no specific submission compliance requirements for these sections (format, structure, page counts, etc.).

1. *Table of Contents*
2. *Software Sharing Plan, if applicable (see HERO Overview posted on NSPIRES alongside this NRA).*
3. *Data Sharing Plan*
4. *Integrated Research Plan Response Form (see IV.B.3.a below)*
5. *Animal Care or Human Subjects certifications, if applicable (see IV.B.3.b below)*
6. *Response to prior review, if applicable (see IV.B.3.c below)*
7. *Productivity of funded NASA research, if applicable (see IV.B.3.d below)*
8. *Vertebrate Animal Scientific Review, if applicable (see IV.B.3.e below)*
9. *Scientific / Technical Project Description (see section IV.B.3.f below)*
10. *Timeline (see Section IV.B.3.g below)*
11. *References and Citations*
12. *NSCOR Structure and Management Approach (see I.H above)*
13. *Personnel Curriculum Vitae (see Guidebook for Proposers)*
14. *Current Support (see Guidebook for Proposers)*
15. *Facilities and Equipment (see Guidebook for Proposers)*
16. *Budget Justification of Proposed Costs (see Guidebook for Proposers)*
17. *Letters of Collaboration / Support*
18. *Appendices / Reprints(see section IV.B.3hg below)*

Step-2 proposals are prepared by the PI or a designated representative of the PI. Step-2 proposals are submitted by an official of the PI's organization after the PI has released the prepared proposal to the authorized organization representative (AOR). It is strongly recommended that the PI work closely with his/her organization official to ensure the proposal is submitted by the due date and time listed in this solicitation. Proposals will not be accepted after the due dates listed in Section IV.C.

It is strongly recommended that a form containing the documented references used for the basis of the submitted budget costs and budget justification be retained by the PI during the Step-2 preparation and submission. The documented reference form will simplify and prevent delays if the Step-2 proposal is chosen for award. The documented reference of the budget data (in particular materials, supplies, equipment, and other procurement details with vendor reference) will be required by the NASA Shared Services Center as referenced in the NASA Grant Proposers Handbook and the *NFS Provision*. This form is not required for proposal submission but can be included as part of the budget justification.

While the NSPIRES system allows for the upload of CVs, letters of endorsement and other supporting documents as separate uploads, please provide the information above in only one PDF proposal document upload. It is essential that all PDF files generated and submitted meet NASA requirements. At a minimum, it is the responsibility of the proposer to:

1) Ensure that all PDF files are unlocked and that edit permission is enabled – this is necessary to allow NSPIRES to concatenate submitted files into a single PDF document; and
2) Ensure that all fonts are embedded in the PDF file and that only Type 1 or TrueType fonts are used. In addition, any proposer who creates files using TeX or LaTeX is required to first create a DVI file and then convert the DVI file to Postscript and then to PDF.

See http://nspires.nasaprs.com/tutorials/PDF_Guidelines.pdf for more information on creating PDF documents that are compliant with NSPIRES.

There is a recommended 10 MB size limit for proposals (Section 2.3(c) of the NASA Guidebook for Proposers). Large file sizes can impact the performance of the NSPIRES system. Most electronically submitted proposals will be less than 2 MB in size.

NSPIRES accepts electronic proposals through a combination of data-based information (e.g., the electronic Cover Page) and the uploaded PDF file that contains the proposal as outlined above. The NSPIRES proposal submission process ensures that a minimum set of required proposal cover page fields are completed. Provision of the proposal summary and business data elements of the cover page will be necessary in order for the AOR to submit the proposal to NASA. If either of these two proposal elements is incomplete, the "View Proposal/ Check Elements" function of NSPIRES will display red "error" flags and messages to alert the user to the information that is required but missing, and the "Submit Proposal" button will not be available. Although the PI will be able to release the proposal to the AOR, the proposal cannot be submitted by the AOR to NASA until these required fields are complete. Any additional

information that is missing will be identified by yellow "warning" flags. Proposers are reminded to check the solicitation instructions to ensure compliance with all instructions, as adherence to these two element validation checks alone is insufficient to guarantee a compliant proposal. Additionally, in those cases where instruction in the NRA contradicts an NSPIRES warning, the NSPIRES yellow “warning” may be ignored. Proposers should follow the NRA instructions closely to help ensure submission of a compliant proposal.

The NSPIRES system is limited in the character sets that can be used in filling out on-line forms. Please refer to the on-line tutorials when using special characters. Alternatively, spell out special characters where possible (such as micro rather than the Greek symbol). Applicants are encouraged to preview their proposal prior to releasing the proposal to their designated Organization by clicking the “Generate” button at the bottom of the View Proposal Screen in NSPIRES. The “Generate” feature allows applicants to preview their entire proposal in a single PDF file prior to submittal, but it is not a required step in the submission process. Please contact the NSPIRES Help Desk for assistance with this feature (e-mail nspires-help@nasaprs.com or by Telephone at 202-479-9376).

a) HRP Integrated Research Plan

The investigator must examine and understand the research emphases outlined in this NRA and the risks identified in the HRP Human Research Roadmap (http://humanresearchroadmap.nasa.gov). Section VIII, Appendix A of this NRA identifies the four categories of radiation risks in the IRP and their associated research and technology gaps. Proposers shall fill-in the check-boxes for the IRP radiation gaps as part of their proposal as well as map these risks and gaps to proposed hypotheses and research aims. This form is part of the on-line Cover page Program Specific Data collection.

b) Special Matters

For proposals employing human subjects and/or animals, assurance of compliance with human subjects and/or animal care and use requirements is mandatory.

Policies for the protection of human subjects in NASA sponsored research projects are described in NASA Policy Directive (NPD) 7100.8E “*Protection of Human Research Subjects*” (http://nodis3.gsfc.nasa.gov/displayDir.cfm?t=NPD&c=7100&s=8E)

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

NASA utilizes a just-in-time practice for approval of the use of human subjects or animals. If the Institutional Review Board (IRB)/Institutional Animal Care and Use Committee (IACUC) certification is already approved at proposal submission, attach a copy of the certification as part of the proposal.

After award, a statement must be provided 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 IRB approval and/or approval by the IACUC. NASA will require current IRB and IACUC certification prior to each year's award.

For delivery of any certifications received after the proposal due date, please contact Kevin Willison, Senior Scientist, NASA Research and Education Support Services, at kwillison@nasaprs.com.

c) Revised Proposals

Investigators submitting a proposal in response to this solicitation, and whose most recent submission that included similar specific aims to any NASA or NSBRI sponsored research announcement was not accepted, are required to submit an explanation of how the current proposal addresses criticisms from previous review cycles. This explanation shall be presented preceding the research description as part of the main proposal upload and is limited to two pages. This explanation should include changes to the current proposal as a result of review comments and, or explanation as to why prior review comments are not applicable to the current proposal.

Investigators resubmitting a proposal in response to this solicitation may only submit a proposal with similar hypothesis(es) and aims a total of three times (original submission plus two resubmissions). Significant changes must be made to the proposal hypothesis(es) and specific aims for consideration after the third attempt or the proposal will be declined without further review.

These two pages are not considered part of the 30-page project description. Proposal reviewers will be provided with the evaluations of prior submissions. Proposers must respond to prior criticisms relevant to any portion of the new proposal under consideration. Proposers who have questions concerning their response to a prior review are encouraged to contact Kevin Willison, Senior Scientist, NASA Research and Education Support Services, at kwillison@nasaprs.com.

d) Productivity of NASA-Funded Research

Proposers (minimally the Primary Investigator) currently funded by or who have received funding within the last four (4) years from any NASA funding source must provide specifics to the productivity of the supported research including progress in experiments and research publications and new findings. This explanation should be presented preceding the research description as part of the main proposal upload and is limited to two pages. These five pages are not considered part of the 30-page project description. Related impacts, if any, to the proposed research plan should be highlighted in the body of the project description. **Proposers that request continued support that do not include this productivity section will be returned to the submitter without panel review and will not be considered for funding. For prior space**

radiation proposals, productivity should focus on NSRL investigations including publications.

e) Vertebrate Animal Scientific Review (VASR) (if applicable)

Each response to this solicitation that requires vertebrate animals must address the five points outlined in Appendix B. This response should be presented as part of the main proposal upload and is limited to two pages. These two pages are not considered part of the 30-page project description. A sample VASR is provided in Appendix B.

f) Scientific/Technical Section (Project Description)

The project description should be titled and numbered as its own section. The length of the project description of the proposal cannot exceed 30 pages using standard (12 point) type. Text shall have the following margins: left = 1.5”; Right, top, bottom = 1.0”. Referenced figures and tables must be included in the 30 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, and must address the identified research emphases (Section I.G). Proposals that exceed the 30-page limit for an NSCOR project description will be declined without review. All other proposal sections are not considered part of the 30-page project descriptions.** Reviewers are not required to consider information presented as appendices or to view and/or consider Web links in their evaluation of the proposal.

g) Timeline

An additional section consisting of no more than 2 pages is required to define a project schedule for the period of performance. This section should follow the Scientific/Technical Section, and contain major milestones over the course of the project, and anticipated experiments at NSRL including ion species to be investigated.

h) Reprints and Appendices

Reprints and Appendices, 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**).

C. Submission Dates

Solicitation Announcement Identifier: NRA NNJ14ZSA001N-NSCOR

Step-1 Response Period:	**May 15, 2015 – June 22, 2015**
Step-1 Proposals Due:	**June 22, 2015; 5 PM Eastern Time**
Step-1 Notification of Status:	**July 1, 2015**
Step-2 Response Period:	**July 1, 2015 – September 10, 2015**

Step-2 Proposals Due: **September 10, 2015; 5 PM Eastern Time**
Step-2 Selection Announcement: **December 2015**

NASA Selecting Official: Human Research Program Manager or his/her designee.

V. Proposal Evaluation Process

A. Step-1 Proposal Relevancy Review

Each Step-1 proposal submitted to a NASA SRPE emphasis area will be reviewed by a minimum of three members of the Step-1 Evaluation Team. The Space Radiation Program Element (SRPE) Manager will assign the reviewers for each Step-1 proposal. It is anticipated that the Project Manager will serve as one of the reviewers on some or all of the Step-1 proposals for which he or she is responsible. Each reviewer will assign an evaluation of "relevant" or "not relevant" based upon the research emphases outlined in Section I.F. of this NRA. The Project Manager will review the individual evaluations and approve a final composite recommendation for each Step-1 Proposal.

Only those Step-1 proposals having a final evaluation of "relevant" will be invited to submit a full Step-2 proposal.

B. Step-2 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 without a significant mechanistic basis or likely gain in scientific knowledge will be viewed as unacceptable.

Proposals are required to provide evidence for expertise in radiation, either by reference to the PI's work or by the inclusion of active collaborators expert in radiation research. 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 score (significance and approach are the most important and weight more than innovation, investigators, and environment):

- **Significance:** Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or technology be advanced? What will be the effect of these studies on the concepts, methods, or products that drive this field? Is there a significant societal or economic impact?
- **Approach:** Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Is the proposed approach likely to yield the desired results? Does the applicant acknowledge potential problem areas and consider alternative tactics?

- **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?
- **Statistical Plan:** Does the study provide adequate justification for sample size? For example, is the choice of primary outcome relevant for the stated Aims? Are assumed effect magnitudes reasonable? Are assumed variability estimates reasonable? Are they estimated properly? Are they relevant for the proposed experimental design and data analysis methodology? What Type I and Type II errors are assumed? Is there room for a tradeoff here to accommodate sample size constraints and still provide useful information from the study? Do the investigators provide a reasonable data analysis plan? For example, is it appropriate for the proposed experimental design (e.g., repeated measures)? Does it address research hypotheses or aims? Is it robust to the sampling and other constraints associated with the research venue?
- **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? If this is a continuation of currently funded NASA research, have the investigators demonstrated productivity with their NASA support?
- **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?
- **Collaboration and Overall Impact:** Will the proposed NSCOR foster effective collaborations between the investigators within the NSCOR? Are the research and knowledge transfer activities strategically integrated such that the whole is greater than the sum of the parts? Are all partners vital participants in the NSCOR effort?
- **Internal Assessment:** Does the proposed NSCOR have an adequate internal advisory group in order to ensure that it will be able to meet the goals established by NASA and adjudicate internal matters efficiently?

C. Step-2 Proposal Review and Selection Processes

1. Compliance Review

All proposals must comply with the general requirements of the NRA as described in this announcement, the *Guidebook for Proposers*, and the *NFS Provision*. Upon receipt, proposals will be reviewed for compliance with these requirements including:

(1) The proposal project description must be no more than 30 pages in length, and should be titled and numbered as its own section.
(2) Submission of an appropriate and justified budget for a funding period not exceeding that described in the NRA.

(3) Proposers (minimally the Primary Investigator) currently funded by or who have received funding within the last four (4) years from any NASA funding source must address the requirements outlined in Section IV.B.3.d.
(4) Investigators submitting a proposal in response to this solicitation, and whose most recent submission that included similar specific aims to any NASA or NSBRI sponsored research announcement was not accepted, are required to submit an explanation of how the current proposal addresses criticisms from previous review cycles. This explanation should be presented in a separate form of no more than two pages. Related changes to the research plan should be highlighted in the body of the project description.
(5) A description of how the research aims map to the identified IRP risks and gaps as described in Section IV.B.3.a.
(6) Proposals that require vertebrate animals must include a Vertebrate Animal Scientific Review component as outlined in Section IV.B.3.e and Appendix B.
(7) Submission of all other appropriate information as required by this NRA.

Note: Consistent with the Guidebook for Proposers, 3.5.2, non-compliant proposals may be withdrawn from the review process and declined without further review. Compliant proposals submitted in response to this NRA 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 scientific and programmatic reviews. The overall evaluation process for Step-2 proposals submitted in response to this NRA will include a First Tier Merit Review and a Second Tier Program Balance and Cost Review.

The **first tier review** will be a merit peer-review 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 NRA and by the variety of disciplines represented in the proposals relevant to the research emphases described in this NRA. 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. The panel will be asked to include in their critique of each proposal any comments they may have concerning the proposal's budget.

Only those proposals most highly rated in the merit review process will undergo additional review. The **second tier review** will evaluate the programmatic balance and cost of all proposals in the fundable range. For NASA, this review will be conducted by SRPE Program Scientists and Managers. Evaluation of the cost of a proposed effort includes consideration of the realism and reasonableness of the proposed cost and the relationship of the proposed cost to available funds. Programmatic balance will include an evaluation of how the proposed work may help achieve an appropriate balance of scientific and technical tasks required by critical research issues faced by NASA.

3. Selection

The information resulting from these two levels of review, as described above, will be used to prepare a selection recommendation developed by NASA SRPE Program Scientist and selection for funding will be made by the selecting official identified in the Submission section of this NRA.

The most important element in the evaluation process is the first tier merit review, which carries the highest weight in final evaluation and selection. The second tier review factors are approximately equal in weight to each other. Poor review in either first or second tier review may prevent selection of a proposal.

In order to optimize resources, NASA SRPE pursues the intentional formation of investigator partnerships between individual investigators whose experiments will leverage resources by addressing different facets of the same questions. NASA anticipates that such intentional teaming arrangements will result in better utilization of available resources to resolve specific critical questions. NASA strongly encourages individual investigators submitting applications in response to this NRA to consider identifying collaborations between individual investigators as part of the development of their individual proposals and to identify this pre-coordination in their management plan. Additional information can be referenced in the *NFS Provision.*

Additionally, if in the best interest of the Federal Government:

1. Proposals submitted in response to this announcement found to have strong scientific merit that cannot be funded due to limited resources may be funded through partner programs or agencies;
2. Meritorious proposals could be considered for funding at a later time, should additional funding become available.

Before final award, proposals selected for funding will undergo a further review by SRPE on the choices of beams and doses to be used in funded research plans.

4. Ombudsman

A NASA ombudsman has been appointed to hear and facilitate the resolution of concerns from proposers during the pre-award and post-award phases of this solicitation. When requested, the ombudsman will maintain strict confidentiality as to the source of the concern. The existence of the ombudsman is not to diminish the authority of the selecting official. Further, the ombudsman does not participate in the evaluation of the proposals, source selection process, or the adjudication of formal disputes. Therefore, before consulting with an ombudsman, interested parties must first address their concerns, issues, disagreements, and/or recommendations to the contracting officer for resolution.

If resolution cannot be made by the contracting officer, interested parties may contact the installation ombudsman, Perri Fox, 2101 NASA Parkway, Houston, TX, 77058, 281-483-3157, E-mail perri.e.fox@nasa.gov. Concerns, issues, disagreements, and recommendations which

cannot be resolved a the installation level may be referred to the NASA ombudsman, Ron Poussard, Director of the Contract Management Division, at 202-358-0445, fax 202-358-3083, E-mail agency-procurementombudsman@nasa.gov. Please do not contact the ombudsman to request copies of the solicitation, verify due date, or clarify technical requirements. Such inquiries shall be directed to the contacting officer as specified in Section VII of this document.

VI. Award Administration Information

A. Award Notices

At the end of the selection process, each proposing organization will be notified of its selection or non-selection status. NASA SRPE will provide debriefings to those investigators who request one. Selection notification will be made by a letter signed by the designated NASA selecting official. The selection letters are not an authorization to begin performance. The selected organization's business office will be contacted by a NASA Grant Officer to negotiate an award. Any costs incurred by the investigator in anticipation of an award are at their own risk until contacted by NASA. The NASA Shared Services Center (NSSC) will determine the type of grant instrument, request further business data, and negotiate the resultant action. NASA Grant Officers are the only personnel with the authority to award NASA grants and obligate government funds. NASA reserves the right to offer selection of only a portion of a proposal. In these instances, the investigator will be given the opportunity to accept or decline the offer. Additional information can be referenced in the *NFS Provision.*

B. Administrative and National Policy Requirements

All grant awards are subject to the NASA Grant and Cooperative Agreement Manual (GCAM). The GCAM provides internal policy guidance to NASA Technical Officers and Grant Officers to implement government-wide and NASA-specific regulations for awarding and administering grants and cooperative agreements with educational and non-profit organizations; State, local, and Indian tribal governments; and for-profit entities when no cost-sharing is required. The government-wide regulations are set forth in the Code of Federal Regulations (CFR) 2 CFR 200 and are supplemented by NASA regulations provided in 2 CFR Part 1800The GCAM is located at http://prod.nais.nasa.gov/cgi-bin/nais/nasa_ref.cgi.

C. Program Reporting/Individual Researcher Reporting

1. Annual Reporting

The PI shall provide an annual written report to NASA. This report is due 60 days prior to the anniversary of the start of funding. Receipt of the annual report is a prerequisite for continued funding installments. This information will be used to assess the degree of progress of the project. A component of this annual report will be used for the NASA Space Life & Physical Sciences Research & Applications Division Task Book (https://taskbook.nasaprs.com/Publication/welcome.cfm). The Task Book includes descriptions

of all peer-reviewed activities funded by the Human Exploration and Operations Mission Directorate (HEOMD). The Task Book is an invaluable source of information for NASA biological and biomedical researchers as well as the external scientific and technical communities. This information will consist primarily of:

- Abstract;
- Bibliographic list of publications;
- Invention disclosures;
- Statement of progress, including a comparison with the originally proposed work schedule;
- Results of periodic data reviews

Additional reporting requirements may be added to ensure timely integration of the research or technology development.

2. Intellectual Property Reporting

The PI's institution must report each invention disclosure or patent application resulting from the grant to NASA within 60 days of investigator disclosure at https://ntr.ndc.nasa.gov.

Submission of either a hard copy of Form 1679 (https://invention.nasa.gov/assets/downloads/nf1679.pdf) to NASA Innovative Partnerships Office, NASA Johnson Space Center, Technology Transfer Office, Mail Code AO5, 2101 NASA Parkway, Houston, TX 77058 OR submission online at https://ntr.ndc.nasa.gov. In the field designating contract number, please cite NCC 9-58.

3. Final Report

A final report must be provided to NASA at the end of the award funding period, including a detailed listing of all peer-reviewed publications. The final report is a requirement for eligibility for future NASA/NSBRI solicitations. The information in this report will consist primarily of:

- Statement of the specific objectives;
- Significance of the work;
- Background;
- Overall progress during the performance period;
- Narrative discussion of technical approaches including problems encountered;
- Accomplishments related to approach; and
- Appendix with bibliography, copies of all publications and reports, and intellectual property disclosures. Any publications or other public materials containing data are particularly important to include in this section.

4. Study Archive

Ordinarily, NASA-funded research data and results are required to be archived in the NASA Life Sciences Data Archive (LSDA), the formal repository for NASA life sciences research data (http://lsda.jsc.nasa.gov). Data archiving is an on-going activity from proposal selection through final archival of the completed study. All NRA grant or contract recipients will be contacted by an LSDA archivist to initiate the archival process. Investigators will be required to sign a Data Submission Agreement (DSA) detailing data products to be submitted to LSDA.

5. Publications

All publications (including websites, presentations, or other electronic products) of any material based on or developed under NASA sponsored projects should conclude or begin with the following acknowledgement:

"This material is based upon work supported by the National Aeronautics and Space Administration under Grant/Contract/Agreement No. <xxxxxx>." Except for articles or papers published in peer-reviewed scientific, technical, or professional journals, the exposition of results from NASA supported research should also include the following disclaimer:

"Any opinions, findings, and conclusions or recommendations expressed in this article <or report, material, etc.> are those of the author(s) and do not necessarily reflect the views of the National Aeronautics and Space Administration."

As a courtesy, any releases of NASA photographic or illustrative data products should list NASA first on the credit line followed by the name of the PI institution, for example,

"Photograph <or illustration, figure, etc.> courtesy of NASA <or NASA Center managing the mission or program> and the <Principal Investigator institution>."

Please note that any research publications or presentations utilizing research data from Life Sciences Data Archive (LSDA) or crew medical data from Lifetime Surveillance of Astronaut Health (LSAH) must be submitted for review to ensure that no personally identifiable information data is included. In addition, recognition of either or both of these data sources must be included in the publication's or presentation's acknowledgments section if not otherwise included in the document.

D. Other Considerations

1. Required Travel

The proposal shall include estimated travel costs for the following:

- Experiments to be performed at BNL: This part of the budget should be based on realistic experimental protocols, using appropriate estimates of irradiation times, numbers of samples, and choice of irradiation parameters. Careful scheduling and shared use of resources should be used to highlight the synergistic advantages of the team's approach.

A minimum of two team members are usually required to perform experiments at BNL. Additional team members should be budgeted based on the complexity of the experiment and work to be performed at BNL.

- Annual Investigators meeting: All principal investigators are required to attend the Annual Space Radiation Investigators' meetings. For planning purposes, please assume Workshop will be held in the Houston, Texas area.

- Mid-Term Review: The NSCOR Director and Project Leads are required to present their research progress at a mid-term external peer review. For planning purposes, please assume review will be held in the Washington DC area.

2. Optional Travel

- Visits to NASA Lyndon B. Johnson Space Center
- Presentation at a professional society meeting (highly desirable)

VII. Contacts

Additional technical information for the NASA SRPE is available from

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Additional contracting information for this NRA is available from:

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Contracting Officer
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Houston, Texas 77058
Telephone: 281-244-8023
Fax: 281-483-4066
Email: latoy.j.jones@nasa.gov

VIII. References

General References

Guidebook for Proposers Responding to a NASA Research Announcement (NRA) is available online at the following address:
http://www.hq.nasa.gov/office/procurement/nraguidebook/

NASA Space Radiation Program:
http://spaceradiation.usra.edu/

The Health Risks of Extraterrestrial Environments, an encyclopedic site presenting a discussion of the space radiation environment and risks to human health.
http://three.usra.edu/#section=main

NASA Advanced Capabilities Division Research & Technology Task Book is available online at the following address:
http://taskbook.nasaprs.com/peer_review/index.cfm

Human Research Program Integrated Research Plan
http://humanresearchroadmap.nasa.gov/

NASA Federal Acquisition Regulations Supplement Instructions for Responding to NASA Research Announcements (Provision NFS 1852.235-72 November 2004) is available online at the following address: http://www.hq.nasa.gov/office/procurement/regs/5228-41.htm#52_235-72

Standard Format for NASA Research Announcements (NRAs) and other Announcements for Grants and Cooperative Agreements. This document is available online at the following address:
http://nodis.hq.nasa.gov/displayDir.cfm?Internal_ID=N_PR_5810_0001_&page_name=main&search_term=5810

NASA Grant Handbook and Cooperative Agreement Manual (GCAM) This document is available online at the following address:
http://prod.nais.nasa.gov/cgi-bin/nais/nasa_ref.cgi

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Selected Reports

2013 Space Radiation Review Panel: Research Plan Review for Risk of Acute and Late Central Nervous System Effects from Radiation Exposure. http://humanresearchroadmap.nasa.gov/reviews/

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The Third International Workshop on Space Radiation Research. *Radiation Research* Volume 164, No. 4, Part 2 (2005).

The Fourth International Workshop on Space Radiation Research. *Radiation Environmental Biophysics*, Volume 46, No. 2 (2007).

IX. Appendix A: Space Radiation Risks and Gaps

1.1 Risk of Radiation Carcinogenesis

In space, astronauts are exposed to ionizing radiation that is quantitatively and qualitatively different from terrestrial radiation. This environment includes protons and high-Z high-energy (HZE) ions together with secondary radiation, including neutrons and recoil nuclei that are produced by nuclear reactions in spacecraft materials or tissue. Space radiation exposure increases cancer morbidity and mortality risk in astronauts. This risk may be influenced by other space flight factors including microgravity, environmental contaminants, nutritional issues, and psychological and physiological stress. Current space radiation risks estimates are based on human epidemiology data for X-rays and gamma-ray exposure scaled to the types and flux-rates in space using radiation quality factors and dose-rate modification factors, and assuming linearity of response. There are large uncertainties in this approach and experimental models imply additional detriment due to the severity of the phenotypes of cancers formed for the heavy ion component of the galactic cosmic rays compared to cancers produced by terrestrial radiation. A Mars mission may not be feasible (within acceptable limits) unless uncertainties in cancer projection models are reduced allowing shielding and biological countermeasures approaches to be evaluated and improved, or unless mission durations are constrained.

Radiation Carcinogenesis - Specific Gaps

Cancer 1: How can experimental models of tumor development for the major tissues (lung, colon, stomach, breast, liver, and leukemia) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk projections?	☐
Cancer 2: How can experimental models of tumor development for the other tissues (bladder, skin, esophagus, brain, etc.) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk projections?	☐
Cancer 3: How can experimental models of carcinogenesis be applied to reduce the uncertainties in radiation quality effects from SPE’s and GCR, including effects on tumor spectrum, burden, latency and progression (e.g., tumor aggression and metastatic potential)?	☐
Cancer 4: How can models of cancer risk be applied to reduce the uncertainties in dose-rate dependence of risks from SPE's and GCR?	☐
Cancer 5: How can models of cancer risk be applied to reduce the uncertainties in individual radiation sensitivity including genetic and epigenetic factors from SPE and GCR?	☐
Cancer 6: How can models of cancer risk be applied to reduce the uncertainties in the age and sex dependence of cancer risks from SPE's and GCR?	☐

Cancer 7: How can systems biology approaches be used to integrate research on the molecular, cellular, and tissue mechanisms of radiation damage to improve the prediction of the risk of cancer and to evaluate the effectiveness of CM's? How can epidemiology data and scaling factors support this approach?	NA
Cancer 8: What biological countermeasures should be used to reduce SPE and GCR cancer risks? What side-effects should be tolerated vs. mission risks?	NA
Cancer 9: Are there significant synergistic effects from other space flight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, depressed nutrition, bone loss, etc.) that modify the carcinogenic risk from space radiation?	NA
Cancer 10: Are space validation experiments needed for verifying knowledge of carcinogenic or other risks prior to long-term deep space missions, and if so what experiments should be undertaken?	NA
Cancer 11: What are the most effective shielding approaches to mitigate cancer risks?	NA
Cancer 12: What quantitative models, numerical methods, and experimental data are needed to accurately describe the primary space radiation environment and transport through spacecraft materials and tissue to evaluate dose composition in critical organs for mission relevant radiation environments (ISS, Free-space, Lunar, or Mars)?	NA
Cancer 13: What are the most effective approaches to integrate radiation shielding analysis codes with collaborative engineering design environments used by spacecraft and planetary habitat design efforts?	NA
Cancer 14: What biodosimetry methods are required for exploration missions and how can biomarker approaches be used for outcome prediction and surveillance?	☐
Cancer 15: Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation cancer risk estimates?	NA

1.2 Risk of Acute and Late Central Nervous System Effects from Radiation Exposure

Possible acute and late risks to the central nervous system (CNS) from galactic cosmic rays (GCR) and solar particle events (SPE) are a documented concern for human exploration of space. Acute CNS risks include: altered cognitive function, reduced motor function, and behavioral changes, all of which may affect performance and human health. Late CNS risks include neurological disorders such as Alzheimer’s disease, dementia or premature aging. Although detrimental CNS changes are observed in humans treated with high dose radiation (e.g., gamma rays and protons) for cancer and are supported by experimental evidence showing neurocognitive and behavioral effects in animal models, the significance of these results on the morbidity to astronauts has not been elucidated. There is a lack of human epidemiology data on which to base CNS risk estimates and therefore risk projection based on scaling to human data, as done for cancer risk, is not possible for CNS risks. Research specific to the space flight environment using animal and cell models must be compiled to quantify the magnitude of this risk and to establish validity of the current PEL. In addition, the impact of radiation exposure in combination

with individual sensitivity or other space flight factors, as well as assessment of the need for biological/pharmaceutical countermeasures will be considered after further definition of CNS risk occurs.

Acute and Late Risks to the CNS - Specific Gaps

CNS - 1: What are significant adverse changes in CNS performance in the context and time scale of space flight operations? How is significance defined, and which neuropsychological domains are affected? Is there a significant probability that space radiation exposure would result in adverse changes? What are the pathways and mechanisms of change?	N/A
CNS - 2: Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases? What are the key events or hallmarks, their time sequence and their associated biomarkers?	N/A
CNS - 3: How does individual susceptibility including hereditary pre-disposition (e.g., Alzheimer's, Parkinson's, apoE allele) and prior CNS injury (e.g., concussion, severe inflammation or other) alter significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?	N/A
CNS - 4: What are the most effective biomedical or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?	N/A
CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS adverse changes or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE?	N/A
CNS - 6: How can new knowledge and data from molecular, cellular, tissue and animal models of late CNS risks or clinical human data be used to estimate late CNS risks to astronauts from GCR and SPE?	N/A
CNS - 7: What are the best shielding approaches to protect against CNS risks, and are shielding approaches for CNS and cancer risks synergistic?	N/A
CNS - 8: Are there significant CNS risks from combined space radiation and other physiological or space flight factors (e.g., sleep deprivation, psychological, microgravity, immune-endocrine systems or other)?	N/A

1.3 Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure

Degenerative diseases including cardiac, circulatory, and digestive diseases are documented following exposures to terrestrial sources of ionizing radiation (e.g., gamma rays and X-rays). This provides evidence for possible degenerative tissue effects following exposures to ionizing radiation in the form of galactic cosmic rays or solar particle events expected during long duration space travel, although the mechanisms and the magnitude of influence of radiation leading to these diseases are not well characterized. Degenerative disease risks are difficult to assess because multiple factors,

including radiation, are believed to play a role in the etiology of the diseases. Data specific to the space flight environment must be compiled to quantify the magnitude of this risk, to decrease the uncertainty in current Permissible Exposure Limits (PEL), and to determine if additional protection strategies are required.

Degenerative Risks (Non-cancer) - Specific Gaps

Degen - 1: How can tissue specific experimental models be developed for the major degenerative tissue risks, including cardiovascular, lens, digestive, endocrine, and other tissue systems in order to estimate space radiation risks for degenerative diseases?	N/A
Degen - 2: What are the mechanisms of degenerative tissue changes in the cardiovascular, lens, digestive, endocrine, and other tissue systems? What surrogate endpoints do they suggest?	N/A
Degen - 3: What are the progression rates and latency periods for radiation-induced degenerative diseases, and how do progression rates depend on age, sex, radiation type, or other physiological or environmental factors?	N/A
Degen - 4: How does individual susceptibility, including hereditary predisposition, alter radiation-induced degenerative disease processes and risk estimates? Does individual susceptibility modify possible threshold doses for these processes in a significant way?	N/A
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?	N/A
Degen - 6: What are the most effective biomedical or dietary countermeasures to mitigate degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CMs additive, synergistic, or antagonistic to other Risks?	N/A
Degen - 7: Are there synergistic effects from other space flight factors (e.g., microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify space radiation-induced degenerative diseases in a clinically significant manner?	N/A
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?	N/A

1.4 Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs)

Crew health and performance may be impacted by a major solar particle event (SPE), multiple SPEs, or the cumulative effect of GCR and SPEs. Beyond low Earth orbit, the protection of the Earth's magnetosphere is no longer available, such that increased shielding and protective mechanisms are necessary in order to prevent acute radiation sickness and impacts to mission success or crew survival. While operational monitoring and shielding are expected to minimize radiation exposures, there are EVA scenarios outside of low-Earth orbit where the risk of prodromal effects including nausea,

vomiting, anorexia, and fatigue as well as skin injury and depletion of the blood-forming organs (BFO) may occur. There is a reasonable concern that a compromised immune system due to high skin doses from a SPE or due to synergistic space flight factors (e.g. microgravity, etc.) may lead to increased risk to the BFO. The primary data available at present are derived from analysis of medical patients and persons accidentally exposed to high doses of radiation. Data more specific to the space flight environment must be compiled to quantify the magnitude of increase of this risk and to develop appropriate protection strategies.

Acute Radiation Syndromes - Specific Gaps

Acute - 1: Determine the dose response for acute effects induced by SPE-like radiation, including synergistic effects arising from other space flight factors (microgravity, stress, immune status, bone loss, etc.) that modify and/or enhance the biological response.?	N/A
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?	N/A
Acute - 4: What are the probabilities of hereditary, fertility, and sterility effects from space radiation?	N/A
Acute - 7 What are the most effective biomedical or dietary countermeasures to mitigate acute radiation risks?	N/A
Acute - 8: How can Probabilistic risk assessment be applied to SPE risk evaluations for EVA, and combined EVA+IVA exposures?	N/A

X. Appendix B: Vertebrate Animal Scientific Review

A. Vertebrate Animal Scientific Review (VASR)

If vertebrate animals are to be used, the following five points must be addressed completely by applicants in the VASR worksheet of their proposal:

1. Detailed description of the proposed use of the animals, including species, strains, ages, sex and number to be used
2. Justification of the use of animals, choice of species and numbers to be used, and proposer's assessment of potential benefits and knowledge to be gained.
3. Information on the veterinary care of the animals
4. Description of procedures for ensuring discomfort, distress, pain and injury is minimized
5. Method of euthanasia and the reasons for its selection

Each of the five points must be addressed, for all performance sites, in the VASR worksheet. The VASR worksheet will be reviewed by the scientific merit review panel and the proposal coded as either: No Vertebrate Animals, No Concerns/Acceptable, or Concerns/Unacceptable. If coded as Unacceptable, NASA staff will work with the applicant to resolve concerns prior to award. Coding of the proposal as Acceptable or No Vertebrate Animals is required prior to award.

In order to be coded as "No vertebrate animals" the vertebrate tissue used in the study will be obtained from other sources (e.g., tissue repository, animals euthanized for an unrelated purpose). The source of the tissue should be included in the VASR to validate the coding as no vertebrate animals used. If vertebrate tissues are obtained through euthanasia for tissue harvest, the proposed research is coded as use of live vertebrate animals. The generation of custom antibodies is coded as use of live vertebrate animals.

A "performance site(s)" is defined as the institutions where procedures with animals will be performed. If the applicant institution is not the site where animal work will be performed, the performance site must be identified. If there is more than one performance site, the description of animal care and use at each site must be included and must address the five points.

Applicants should be aware that NASA may release information contained in funded proposals pursuant to a Freedom of Information Act request.

B. Instructions for Scientific Reviewers

These instructions are to assist Scientific Merit Review Panel (SMRP) members in the VASR review of the proposal.

Subsequent to evaluation of the VASR worksheet by a SMRP, all proposals are coded as either: No Vertebrate Animals, No Concerns/Acceptable, or Concerns/Unacceptable.

Coding as NO VERTEBRATE ANIMALS - If vertebrate tissue used in the study is obtained from other sources (e.g., tissue repository, animals euthanized for an unrelated purpose), the proposal is coded as no vertebrate animals used. The source of the tissue should be included in the VASR to validate the coding as no vertebrate animals used. If vertebrate tissues are obtained through euthanasia for tissue harvest, the proposed research is coded as use of live vertebrate animals. The generation of custom antibodies must be coded as use of live vertebrate animals.

Coding as NO CONCERNS/ACCEPTABLE or CONCERNS/UNACCEPTABLE - Coding is based on the review of the five required points for each of the performance sites.
Performance site(s): This is defined as the institutions where procedures with animals will be performed. If the applicant institution is not the site where animal work will be performed, the performance site must be identified. If there is more than one performance site, the description of animal care and use at each site must be included and must address the five points.

C. Detailed Instructions for Preparation of the VASR

These instructions are to assist applicants in preparing their VASR information.

Preparation of the VASR worksheet:
Typically, all of the required elements for the VASR can be addressed within 1-2 pages.

Point 1 - Description of animals and how they will be used
A concise, complete description of the proposed procedures must be included in the VASR. While additional details may be included in the Research Strategy, a coherent, albeit brief, description of the proposed use of the animals must be provided within the VASR. The description must include sufficient detail to allow evaluation of the procedures. Examples of the types of procedures that should be described include blood collection, surgical procedures, administration of substances, tumor induction and post-irradiation procedures. In describing the animals, investigators must provide the following information for each species and/or strain to be used:

- Species
- Strain
- Ages
- Sex
- Number of animals to be used

Point 2 - Justifications for use of animals
Investigators must justify the use of animals in the proposed research. The justification must indicate why alternatives to animals (e.g., computer models, cell culture) cannot be used and should indicate the potential benefits and knowledge to be gained. In addressing

this point, researchers are encouraged to consider means to replace, reduce and refine the use of animals. Rationale for the choice of species must be provided. The rationale should indicate the advantages of the species chosen and why alternative species are not appropriate. If less highly evolved or simpler animal models are available, justification must be provided for using more advanced species. For example, the use of non-human primates (NHP), dogs or cats should be thoroughly justified. If NHP species are to be used, a comparison to other NHP species may be appropriate. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and the number of animals used.

Estimates for the number of animals to be used should be as accurate as possible. Justification for the number of animals to be used should include considerations of animal availability, experimental success rate, inclusion of control groups and requirements for statistical significance; cite power calculations where appropriate.

Point 3 - Veterinary care

Descriptions of veterinary care should indicate the availability of veterinarians or veterinary technicians. For example, the VASR might indicate the number of veterinarians and veterinary technicians associated with the applicant institution, and their proximity to the performance site(s). The frequency with which veterinary staff observe or monitor animals should be stated.

If survival surgeries are proposed, veterinary involvement or post-surgical monitoring should be described. For example, if animal use involves invasive approaches that might result in discomfort, distress or pain, the investigator should indicate if or when veterinary care is necessary. The indicators for veterinary intervention to alleviate discomfort, distress or pain should be described. The ways in which veterinary staff may intervene should be described.

Point 4 - Provisions to minimize discomfort, distress, pain and injury

Procedures or circumstances that may result in more than momentary discomfort, distress, pain or injury should be identified. Methods to alleviate discomfort, distress or pain should be described. If pharmacological agents are used, the agent(s) should be specified by name or class. Any additional (e.g., non-pharmaceutical) means to avoid discomfort, distress, pain or injury should be described briefly. The manner, circumstances and duration of all post-surgical provisions and care should be described. If special housing is necessary following surgery or manipulations, the VASR should describe these provisions, the duration and type of monitoring provided. If procedures (e.g., pharmacological or surgical) might lead to severe discomfort, distress, pain or injury, indicators for humane endpoints and euthanasia (e.g., severe infection, respiratory distress, failure to eat, tumor size) should be described. All of these issues are particularly important for survival surgeries. If multiple surgeries are proposed, these must be well justified and provisions to avoid any potential complications must be described. Describe how restraining devices will be used, if applicable.

Point 5 - Euthanasia
The method(s) of euthanasia must be described and must comply with the *AVMA Guidelines on Euthanasia*. If the method(s) do not comply with AVMA recommendations, the rationale and scientific justification for use of the method(s) must be provided. The indicators for euthanasia (i.e., termination of experiment or humane endpoints) should be stated. It is not sufficient to state simply that humane methods will be used, that are consistent with the recommendations of the *AVMA Guidelines on Euthanasia* or the Institutional Animal Care and Use Committee (IACUC).

References
Guidance in this document is based on NASA and PHS Policy, and federal requirements. The NASA and PHS Policy incorporate the standards in the *Guide for the Care and Use of Laboratory Animals* and require that euthanasia be conducted according to the *AVMA Guidelines on Euthanasia*. Additional background information and references are available on the Office of Laboratory Animal Welfare website (http://olaw.nih.gov).

NASA Policy and
Requirements http://nodis3.gsfc.nasa.gov/displayDir.cfm?t=NPD&c=8910&s=1B

PHS Policy
http://grants.nih.gov/grants/olaw/references/phspol.htm

Guide for the Care and Use of Laboratory Animals
http://www.nap.edu/openbook.php?record_id=5140

AVMA Guidelines on Euthanasia
http://www.avma.org/issues/animal_welfare/euthanasia.pdf

D. Worksheet to Assist in Addressing the Required Five Points of the VASR

Performance site(s):

The five points must be addressed for all performance sites.

__ If the applicant's institution is not where animal work will be performed, are all collaborative performance site(s) identified?
__ If more than one performance site is planned, are descriptions of animal care and use for each site provided?

Point 1 - Describe the animals and their proposed use; address the following for all species to be used:
__ Species
__ Strains
__ Ages
__ Sex
__ Number of animals to be used

__ A concise, but complete, description of proposed procedures (i.e., sufficient information for evaluation)

Point 2 - Provide justifications for:
__ The use of animals
__ Choice of species
__ Number of animals to be used (cite power calculations, if appropriate)

Point 3 - Provide a general description of veterinary care, including veterinary support that is specifically relevant to the proposed procedures. Indicate the following:
__ A brief account of veterinary staff and their availability
__ The regular schedule of monitoring of animals by veterinary staff
__ Any additional monitoring and veterinary support that may be required to ensure humane care, if relevant to the procedures proposed (e.g., post-surgical)
__ Indicators for veterinary intervention to alleviate discomfort, distress or pain, if relevant

Point 4 - Describe procedures to minimize discomfort, distress, pain and injury. Indicate the following:
__ Circumstances relevant to the proposed work, when animals may experience discomfort, distress, pain or injury
__ Procedures to alleviate discomfort, distress, pain or injury
__ Identify (by name or class) any tranquilizers, analgesics, anesthetics and other treatments (e.g., antibiotics) and describe their use
__ Provisions for special care or housing that may be necessary after experimental procedures
__ Plans for post-surgical care, if survival surgeries are proposed
__ Indicators for humane experimental endpoints, if relevant
__ Describe the use of restraint devices, if relevant

Point 5 - Describe methods of euthanasia:
__ Describe the method(s) of euthanasia and rationale for selection of method(s)
__ Indicate if the method is consistent with AVMA Guidelines on Euthanasia
__ Provide a scientific justification for the choice of method if not AVMA recommended

E. Example of a complete VASR

Vertebrate Animals
Aims 1-3 will be addressed *in vitro*; Aim 4 will be addressed using a mouse model of ocular infection.

1. Female Balb/c mice will be used to determine if virions treated with enzyme can cause viral keratitis, and to test the *in vivo* efficacy of the test articles. The studies will require 700 mice, 4 to 6 weeks old. Based on prior experience, 70 groups, each including 10 mice will be required over five years to achieve adequate statistical power. Ocular infection is

accomplished by scratching the cornea of anesthetized mice with a sterile needle and exposing the scarred portion of the cornea to inoculum. Test articles are applied directly to the scarified cornea as liquid or cream. Following inoculation and recovery, mice are monitored for 30 days. With the mice under anesthesia, the eyes will be examined at intervals, microscopically, and are flushed with medium with 2% serum to determine viral titers. Thirty days post-infection, with the mice under deep anesthesia, the trigeminal ganglia are removed aseptically for viral assay, followed immediately by euthanasia.

2. The proposal is to study mechanisms for the prevention of ocular disease caused by viral infections, a leading cause of blindness in the US. Mice are needed for these experiments because no alternative *in vitro* model incorporates all elements of the mammalian ocular immune system; too little is known about this system for the development of computer simulations. Mice are a well-accepted model for studying viral keratitis, assessing the virulence of viral strains and testing the efficacy of antivirals. Mice provide several advantages: a) The murine ocular immune system is similar enough to that of humans to allow extrapolation of the results; b) Their small size allows the use of smaller amounts of drugs for testing; c) The entire mouse genome is known and easily manipulated genetically, allowing extension of the work in future genetic studies. Female mice will be used due to compatibility issues. Balb/c mice will be used because they have intermediate resistance to infection. ABC-4 knockout and ABC-4 test-strains will be used. For the enzyme study, we will use 4 treatment groups: enzyme-1, enzyme-2, enzyme-3, and mock treated virus. We will also use different amounts of inoculum for each condition allowing a more accurate calculation as to the effect of the digestions on infectivity. For the test-article peptide study, we will use two formulations (one aqueous and one hydrophobic), test 4 different concentrations and also vary the treatment protocol. Two groups will receive a single dose of drug in each of the two formulations prior to the addition of virus to assess prophylactic activity. These groups will not receive any additional enzyme treatments. Two groups will be infected with virus and beginning 4 h post-infection, we will treat with each formulation and concentration 4 times daily for 7 days.

3. All mice are housed in the Animal Resources Center of the University. Animal housing rooms are under temperature and humidity control. The mice will not be subjected to water or food restrictions, and bedding material is placed in each cage. The facility is staffed by four full time veterinarians and six veterinary technicians; the veterinary staff is on site and a clinical veterinarian is available at all times. Animal care staff conducts routine husbandry procedures (e.g., cage cleaning, feeding and watering) and checks animals daily to assess their condition. Laboratory staff monitors mice when treatments are given, disease is scored or samples are collected for titering. The veterinary staff monitors mice in their home cages, weekly. If animals exhibit any indication of infection or distress, the veterinary staff confers with laboratory personnel to recommend appropriate antibiotics, analgesics or other pharmaceuticals. The veterinary staff may intervene or recommend euthanasia based on animal welfare concerns.

4. Mice will be anesthetized with isoflurane (3-5%) during the infection process, when treatments are administered and titer samples are collected. This eliminates the need for restraint devices and topical anesthetics that would interfere with the infection and disease process. For post-procedural pain relief, we will administer buprenorphine twice daily for the duration of the experiments (i.e., approximately two weeks post-inoculation). Death is not an endpoint for the studies; the Balb/c strain was chosen because of its resiliency and resistance to this particular virus. Our goal is to avoid severe infections leading to death. Though unlikely, if an animal reacts severely, it will be euthanized, based on humane indicators (e.g., failure to groom or feed). These experiments involve no post-surgical survival animals.

5. All mice will be euthanized by cervical dislocation under isoflurane anesthesia. Isoflurane ensures that the mice are unconscious, while dislocation ensures quick death. This minimizes animal distress, is effective and efficient; it is consistent with the recommendations of the *AVMA Guidelines on Euthanasia*.