OMB Approval No. 2700-0087

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

Ground-Based Studies in Space Radiobiology

NASA Space Radiation Program Element

NASA Research Announcement
Soliciting Proposals for the Period Ending June 25, 2009

Catalog of Federal Domestic Assistance (CFDA) Number: 00.000

NNJ09ZSA001N
NRA Issued: March 17, 2009
Step-1 Proposals Due: April 23, 2009
Step-2 Proposals Due: June 25, 2009

Ground-Based Studies in Space Radiobiology

I. Funding Opportunity Description ... 3
A. Introduction ... 3
B. Ground-Based Simulations ... 5
C. Background Information ... 7
D. Human Research Program Integrated Research Plan ... 10
E. NASA Radiation Program General Focus ... 11
F. Research Emphases Specific to this Solicitation ... 12
1. Radiation Quality Dependence of Carcinogenic Risk ... 12
2. Late CNS and Degenerative Risks from Space Radiation ... 14
G. NASA Safety Policy ... 15
H. Availability of Funds for Award ... 15
I. Additional Funding Restrictions ... 15
II. Award Information ... 15
III. Eligibility Information ... 16
A. Eligibility of Applicants ... 16
B. Guidelines for International Participation ... 16
C. Cost Sharing or Matching ... 18
IV. Proposal and Submission Information ... 18
A. Source of Application Materials ... 18
B. Content and Form of Proposal Submission ... 18
1. NASA Proposal Data System ... 18
2. Intent to Propose and Step-1 Proposals ... 20
3. Instructions for Preparation of Invited Step-2 Proposals ... 20
4. Submission of Proposals via Grants.gov ... 24
C. Submission Dates ... 25
V. Proposal Evaluation Process ... 25
A. Step-1 Proposal Relevancy Review ... 25
B. Step-2 Proposal Intrinsic Scientific and/or Technical Merit ... 25
C. Step-2 Proposal Review and Selection Processes ... 26
1. Compliance Review ... 26
2. Scientific and Programmatic Reviews ... 27
3. Selection ... 27
4. Ombudsman ... 28
VI. Award Administration Information ... 28
A. Award Notices ... 28
B. Administrative and National Policy Requirements ... 29
C. Program Reporting/Individual Researcher Reporting ... 29
D. Other Considerations ... 30
VII. Contacts ... 30
VIII. References ... 31
A. General References ... 31
B. Selected Workshop Reports ... 32
IX. Appendix A ... 33
X. Appendix B ... 40

Ground-Based Studies in Space Radiobiology
[NRA NNJ09ZSA001N]

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.F).
- For Step-2 proposals: Proposals must identify Integrated Research Plan risks and gaps addressed by the research (Section I.D).
- For Step-2 proposals: The length of the project description of the proposal cannot exceed 20 pages using standard (12 point) type (Section IV.B.3).
- For Step-2 proposals: If your proposal is a revised version of a previously submitted proposal, you must address prior review comments (2 pages maximum) in a section separate from the project description (Section IV.B.3).
- For Step-2 proposals: If your proposal is a continuation of current NASA-supported research, you must provide specifics (2 pages maximum) to the productivity of your NASA-funded research in a section separate from the project description (Section IV.B.3).
- For Step-2 proposals: Your proposal must meet requirements of the Compliance Review section of this solicitation (Section V.C.1).

I. Funding Opportunity Description

A. Introduction

This National Aeronautics and Space Administration (NASA) Research Announcement (NRA) solicits ground-based proposals for the Space Radiation Program Element (SRPE) components of the Human Research Program (HRP). Proposals are solicited by the SRPE in the area of Space Radiation Biology utilizing beams of high energy heavy ions simulating space radiation at the NASA Space Radiation Laboratory (NSRL), at Brookhaven National Laboratory (BNL) in Upton, New York.

Within NASA, the HRP is responsible for all research and development activities associated with astronaut health and performance. The SRPE is charged by the HRP to

understand the effects of radiation on the health, safety and efficiency of astronauts, both during and after their missions.

The major goal of NASA's space radiation research is to enable the human exploration of space within acceptable risks from space radiation. Space radiation is distinct from common terrestrial forms of radiation because it is composed of high-energy protons and heavy ions, along with the secondary radiation produced in shielding and tissue. Research to be supported will seek to: reduce the uncertainties in risk predictions for cancer and acute radiation risks; provide the necessary data and knowledge to develop risk projection models for central nervous system (CNS) and other degenerative tissue risks; and significantly advance the understanding of the mechanisms of biological damage that underlies radiation health risks. This research is also expected to provide a substantial contribution to the scientific basis for eventual development of biological countermeasures to these risks as appropriate.

Because there are no human epidemiological data for these radiation types, risk estimation must be derived from mechanistic understanding based on radiation physics, and on molecular, cellular, tissue, and organismal radiation biology related to cancer, central nervous system, and other risks of concern to NASA. The core values of the space radiation program demand that **all recommendations and requirements shall be developed only on the basis of research conducted according to the highest standards of scientific inquiry, addressing clearly stated, falsifiable hypotheses, and using the most advanced, recognized methods available.** While flight studies are recognized as a possible component in the validation of radiation risk predictions, the scientific evidence is expected to be acquired on the ground by irradiations simulating exposure to components of space radiation--the most significant of which are the high energy charged particles delivered by accelerator beams.

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. The background information presented here and the list of references are intended to provide a useful starting point for such scientists as well as for expert radiobiology researchers not necessarily familiar with the idiosyncrasies 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.F. 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 will be declined without review.

Proposals must be submitted electronically. Proposers can use either Grants.gov. (http://www.grants.gov/) or NSPIRES (http://nspires.nasaprs.com) for proposal submission. All proposers, team members, and agency officials must be registered before proposal submission with NSPIRES as described under section IV.B.1 regardless of the electronic submission system used. NSPIRES remains the only system through which a Step-1 proposal can be continued as a Step-2 proposal. Proposers invited to submit a full Step-2 proposal who elect to use Grants.gov will not find their Step-1 proposal information available within Grants.gov.

Step 1 proposals will be accepted between March 17, 2009 and April 23, 2009 (Step-1 proposals will not be accepted after 5:00 PM Eastern, April 23, 2009); invited Step 2 proposals will be accepted between April 24 and June 25, 2009 (Step-2 proposals will not be accepted after 5:00 PM Eastern, June 25, 2009).

B. Ground-Based Simulations

Research proposals are expected to utilize beams of charged particles available at the NSRL and to address experimental data obtained with such beams in ways leading to significant predictions that can be tested in future experiments. This NRA does not request proposals for flight research.

NASA plans to operate the NSRL for about 1000 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. The NSRL is an irradiation facility based on BNL Booster Synchrotron beams -- ions from protons to gold with primary energies in the range of 50-3000 MeV/nucleon. Activities at the NSRL are a joint effort of BNL's Collider-Accelerator Department, providing accelerated ion beams; the Biology Department, providing experimental area support; and the Medical Department, which provides animal care facilities and cell laboratories. The NSRL includes irradiation stations, beam controls, and laboratory facilities required for most radiobiological investigations.

Normally, circular beam spots are provided, with diameters up to 20 cm and center-to-edge uniformity between 1% and 5% (depending on dose rate—high dose rate beams are less uniform than low-dose rate beams). 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 heavy ions and protons, respectively are possible. Investigators currently funded by the NASA Space Radiation program participate in research using these beams, and coordination of beam use with these investigators and institutions is actively encouraged. In particular, a dosimetry group is available for investigators requiring their assistance.

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 station, and laboratory space and animal facilities in the Brookhaven Medical 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 a laminar flow hood and incubator, 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 Medical Department, subject to standard use charges. BNL also has on-site housing accommodation for users (dormitory and apartment-style units).

A full set of beams and energies required to accomplish the radiation program objectives continues to be developed with input from the science community and BNL experts. The following Table lists the beams currently available:

Beam*	**Energy, MeV/u**	**LET, keV/µm**	**Range in Water, cm**
protons	150	2	15.7
protons	1000, 2500	0.25, 0.22	323, 850
^{12}C	290	13	16.9
^{16}O	600, 1000	17, 14	39, 81
^{28}Si	300, 600, 1000	70, 51, 44	7.3, 22, 46
^{37}Cl	300, 500	92, 80	6.0, 14.9
^{48}Ti	300, 500, 1100	175, 134, 106	5, 11.5, 37
^{56}Fe	300, 600, 1000	240, 181, 150	4.3, 13, 27
August 1972 or September 1989 proton spectra	50-2000	NA	NA
Mixed p+Fe	1000, 1000	NA	NA

*He, Ne, Mg, Ar, and Ca beams will become at available at NSRL in 2011.

Proposers selected for award through this NASA Research Announcement (NRA) will receive guidance on how to apply for NSRL beam time and BNL resources. 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.

Investigators selected for funding will need to meet BNL requirements for experiment scheduling in order to gain access to beams and irradiation facilities. NASA negotiates beam delivery directly with BNL, and investigators proposing to use these irradiation facilities shall 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.

NASA and BNL have established an agreement to allow interested investigators to perform "Piggyback" experiments for the purpose of obtaining preliminary data once every three years. Interested parties should contact Dr. Betsy Sutherland (see below) to learn about the application requirements for Piggyback experiments. In this program, modest studies are permitted that can be conducted within the resources of peer reviewed and approved investigations.

Investigators wishing to utilize other facilities 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 (e-mail: rusek@bnl.gov), Dr. Peter Guida (e-mail: guida@bnl.gov), or Dr. Betsy Sutherland (e-mail: bms@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.

C. Background Information

NASA is concerned with the health risks to astronauts following exposures to galactic cosmic rays (GCR) and solar particle events (SPE). The major GCR types include p, He, C, O, Ne, Si, Ca, and Fe with a broad energy spectra from a few 10's of MeV/u to above 10,000 MeV/u. 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 high charge and energy (HZE) nuclei about every few months. For groups of interacting cells, GCR traversals of a group are more frequent. These fluence rates correspond to tissue doses or effective dose-rates of about 0.4-0.8 mGy/d and 1-2.5 mSv/d, respectively. SPE's are low to medium-energy protons with smaller components of helium and heavy nuclei. SPE dose-rates are variable over the course of a SPE varying between 0-100 mGy/hr inside a vehicle and between 0-500 mGy/hr if an astronaut is exposed during extra-vehicular activity in deep space or on the surface of the moon. SPE dose-rates may also vary several-fold between tissue sites because of the variable energy spectra of the protons or other nuclei.

Energy deposition in biomolecules, cells, and tissues is distinct when comparing protons and HZE nuclei to common forms of terrestrial radiation. For the particles composing 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 space about once per day. The rate of energy deposition per unit length of a particle trajectory is described by the 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 the particle velocity, β or kinetic energy, and its charge, Z approximately in proportion to Z^2/β^2. As the velocity (or the 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 and late (i.e., after a mission) risks to the central nervous system (CNS), degenerative risks such as heart disease and cataracts, 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 risk is a concern for both GCR and SPE. The current model of cancer risks used by NASA is the one recommended by the NCRP (2000) and uses the double detriment life-table, and a radiation dependent cancer mortality rate estimated from human epidemiology data for low LET radiation. The mortality rate is scaled to the effects for the low dose-rates and radiation types in space using a dose- and dose-rate effectiveness factor (DDREF) and 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. Other risks are discussed below.

Radiobiological studies have been conducted using x- or gamma-rays as standards of comparison to space radiation components because of the availability of human data for these radiation types. 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) gamma-ray dose to the (generally lower) nuclear dose resulting in the same 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, 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 have a higher value of RBE's at a fixed value of LET. Above the

RBE versus LET peak for a given charge number, 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. Nevertheless, it 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.

For some endpoints in tissue, including carcinogenesis, excess relative risk (ERR) or excess additive risk (EAR) may be used as the basis for comparing risks to spontaneous or gamma-ray risks, and additional information on the time dependence of these quantities may be obtained, which is valuable for risk assessment. For cancer risk projections, mortality or incidence rates for space radiation components are scaled to available human data for low LET radiation using RBE's or excess relative risk or excess additive risk derived from experimental models. The mechanisms and biological effects associated with HZE nuclei may be different from those attributable to gamma-rays for the same, or similar, macroscopic endpoints. For example, an observation of reduced latency of disease with increasing LET would not be described using RBE values. For these and other reasons, the description of radiation action is not complete without an understanding of the processes leading to an observed result. The DDREF is used to reduce risk coefficients derived from acute gamma-ray epidemiology data, largely based on the study of the atomic-bomb survivors, to low dose-rate exposure conditions. This approach introduces uncertainties for low dose-rate gamma-rays into risk estimates for protons and HZE nuclei.

Estimating CNS and degenerative risks from space radiation is difficult because of the limited human epidemiology data for these risks and scarcity of experimental data for space radiation components in biological models. Therefore, research on new approaches to risk assessment that provide quantitative estimates for these risks may be warranted. NASA is seeking information to determine risk limits for protons and HZE nuclei-induced early or late CNS effects and for degenerative risks including heart disease. Important changes such as oxidative damage, neuroinflammation, and neurogenesis, and changes in animal cognitive performance and motor skills have been observed for doses of 0.5 Gy or lower of HZE nuclei. However, an approach to extrapolate such observations to possible cognitive and performance changes, or late CNS effects in astronauts has not been discovered. Furthermore, the effects of combined neuronal stressors including mixed HZE nuclei plus solar proton irradiation, or GCR and SPE in combination with possible stressors from other flight factors that may potentially impact behavior and performance have not been studied.

The understanding of countermeasures (including shielding) to space radiation risks is hindered at this time because the large uncertainties in risk projection models, and indicate a lack of mechanistic understanding and data for assessing the possible need or effectiveness of countermeasures for specific space missions. 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 nuclei changes as it loses energy and slows down inside the material. Inaccuracies in risk assessment models prevent the proper evaluation of shielding material selection and reduce the ability of NASA to apply cost-benefit analysis to shielding evaluations.

Biological countermeasures including dietary anti-oxidants are expected to provide risk reduction for low LET radiation delivered at high dose and dose-rate, however their effectiveness at low dose-rates and for high LET radiation is less clear. Understanding the mechanisms of oxidative damage and possible reduction through anti-oxidants is a goal of space radiation research. Mechanistic studies of possible biochemical routes for countermeasure actions must be combined with approaches to extrapolate model system results to humans for such countermeasures to be used operational by NASA. **For these reasons, NASA's current research program endeavors to establish the scientific basis for the model to human risk extrapolation problem in order to firmly establish the level of need for biological countermeasures and, if needed, develop methods to properly assess the effectiveness of such countermeasures.**

D. Human Research Program Integrated Research Plan

NASA has developed the HRP Integrated Research Plan (IRP) 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 recently the National Academy of Sciences (NAS) Institute of Medicine (IOM) "Bioastronautics Roadmap: A Risk Reduction Strategy for Human Exploration of Space."

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

Each radiation risk has an associated set of research and technology gaps listed in Appendix A. In the radiation area, the current IRP identifies 4 risks and 37 research and technology gaps. The four categories of radiation risks in the HRP IRP:

1. Carcinogenesis with 14 gap areas,
2. Acute and Late Effects in the Central Nervous System with 8 gap areas,
3. Degenerative Tissue Damage including heart disease and cataracts with 7 gap areas,
4. Acute Radiation Syndromes with 8 gap areas.

The proposer shall examine and understand the Space Radiation section of the IRP, fill-in the appropriate check-box in Appendix A, and briefly specify in the proposal how the proposed research will address these risks and gaps. However, not all risks or gap areas are being solicited in this NRA because they are already being addressed or will be so in future solicitations. Such gaps are shaded and listed as "NA", and do not contain a check-box in the Appendix A. A similar assessment will be performed by NASA to understand how the proposed research addresses the IRP risks and gaps. **Proposals that do not identify what IRP risks and gaps are being addressed by their research will be declared noncompliant and declined without review. Proposers must fill-in the check-boxes for the IRP radiation gaps as part of their proposal mapping these risks and questions to hypotheses and research aims (Section IV.B.3.a).**

E. NASA Radiation Program General Focus

Space radiation research areas emphasize the application of mechanistic understanding to mammalian models to achieve significant reductions in the uncertainties in risk projections for cancer, risks to the CNS and other degenerative risk caused by space radiation. Biological effects of importance include DNA damage processing, signal transduction, cell cycle controls, cellular differentiation, endocrine and paracrine signaling, altered methylation patterns, genomic instability, apoptosis, genetic sensitivity or resistance, persistent oxidative damage, inflammation, and immune function. This research is intended to develop approaches to understand the effects of protons, helium, and HZE nuclei as modifiers of these processes. The use of such understanding to develop new 3D human cell culture or transgenic mouse models of human tissues improving our ability to extrapolate estimates of cancer, CNS and other risks to humans is a priority. New experimental approaches to these problems are warranted, and ultimately must provide quantitative data in support of risk assessment uncertainty reduction and mitigation development and assessment.

It is recognized that progress in these areas will depend on progress in the understanding of how space radiation may modify fundamental biological processes. These include DNA structural and functional changes caused by radiation, such as mutations and DNA recombination and repair; basic metabolic controls important in biology and known to be modulated by radiation; genomic instability, modifications of cell cycle controls and apoptosis, especially in relation to cellular repair mechanisms; changes to tissue structure including the extra-cellular matrix, mechanisms of tissue and organ response to radiation including signal transduction and inflammation; and "bystander" or non-targeted effects. Investigators are encouraged to review summaries of the research currently funded in the Space Radiation Program Element by accessing the NASA Task Book referenced in section VIII.A and performing an advanced search by checking "Radiation Health."

Studies may include animals, tissues (animal or human), or cells (animal or human), including adult human stem cells. **For proposals utilizing animal models, proposals are encouraged to use animals at an age reflective of the ages of astronauts (35-55 y) 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 functionally characterized transgenic and mutant species as well as comparative biology approaches that enhance the research scope. 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). Experimental approaches should seek to apply single cell and tissue assays, and functional pathway and systems biology approaches using genomics, proteomics, bioinformatics, functional imaging, etc. to space radiation risk assessments.

F. Research Emphases Specific to this Solicitation

Proposed studies must directly address the following high-priority research topics emphasized by the Space Radiation Program Element for FY2009. One or more topics of interest may be addressed in single proposals

In addition to the currently funded studies at NASA (referenced in section I.E.), investigators are encouraged to review the research currently being conducted by the NASA Centers of Research (NSCOR) in leukemia, solid cancer, DNA damage repair and CNS risks to avoid duplicative studies. Information on these NSCORs can be found in the NASA Taskbook referenced in Section VIII.A using the advanced search function. Check the Human Research box, enter keyword "NSCOR" and check the following boxes: "Radiation Biology", "Radiation Health" "Radiation Effects".

1. Radiation Quality Dependence of Carcinogenic Risk

Radiation quality effects represent the largest uncertainty in cancer risk assessments from space radiation. The radiation quality factors, Q(L) in use at NASA were recommended by the NCRP Report No. 132 (2000) and originate in a report of the International Commission on Radiological Protection from 1990. The experimental studies that are at

the foundation of the Q(L) relationship are based on many biological endpoints and irradiation types that likely have little relevance to the carcinogenesis process and that are not representative of the charges and energies of space radiation components, respectively. 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. Such cancer development processes include but are not limited to the following: loss-of-heterozygosity (LOH), genetic instability, evasion of apoptosis and DNA damage checkpoints, aberrant telomere changes and function, premature senescence, insensitivity to growth signals, aberrant DNA methylation and replication stress, changes in the extra-cellular matrix, and altered proliferation or differentiation. In addition, the role of non-targeted effects and the possible unique damage types produced by HZE nuclei, and the delta-rays surrounding the tracks of HZE nuclei decrease confidence in the use of a risk assessment model based on radiation quality factors and linear dose responses. 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 uncertainty reduction and ultimately the development of new systems biology models of cancer risks.

The current research announcement seeks new experimental studies of radiation quality effects that will link two or more cancer development processes with the underlying mechanisms for such endpoints and their possible inter-relationships. The following areas of research are of priority:

- Research that establishes new assays or applies existing assays to improve the understanding of radiation quality effects using two or more cancer development processes that are important in radiation carcinogenesis,
- Research that will establish the shape of the response curve of these processes at low fluence, and
- Research that will establish the relative roles of cells directly traversed by HZE nuclei, cells traversed by delta-ray alone or non-targeted effects in inducing the cancer processes.
- **Moreover, the above research must be coupled with research that will improve the understanding of the molecular pathways, and genetic, cellular or tissue basis that links the two or more cancer development processes under investigation**.

In the Radiation Quality Studies of Carcinogenic Risk emphasis area, SRPE is interested in obtaining statistically meaningful data on the fluence or dose dependencies for cancer processes for the particle species matrix listed in the Table that follows. Higher doses than listed in this Table should be used in experimental plans only to support observations at the specificed doses. Animal studies should address how cancer processes are modulated by LET using three or more ion beams. Cellular studies should in addition consider in more detail the LET dependence including how track structure modulates responses.

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.

Table. Required Irradiation Types for Radiation Quality Studies of Carcinogenic Risk

Radiation Type	*LET*	*Dose-Range*
Gamma-rays	NA	0-1 Gy
Protons (E=1000 MeV)	0.24	0-1 Gy
Helium (250 MeV/u)	2	0-1 Gy
Oxygen (250 MeV/u)	25	0-0.8 Gy
Silicon (400 MeV/u)	65	0-0.8 Gy
Titanium (1000 MeV/u)	107	0-0.5 Gy
Iron (1000 MeV/u)	151	0-0.5 Gy
Iron (600 MeV/u)	180	0-0.5 Gy
Iron (300 MeV/u)	250	0-0.5 Gy

2. Late CNS and Degenerative Risks from Space Radiation

Changes related to late CNS and other degenerative risks (e.g. coronary heart disease) are a concern for long duration lunar missions, and for a Mars mission. It is not known if these risks would occur at the doses that will be encountered on these missions, which are no more than 0.2 Gy for heavy ions or 1 Gy for protons. Genetic factors may also influence the risk of late CNS effects and degenerative risks from space radiation. In order to further establish the importance of experimental findings on these risks, new understanding using animals representative of these risks, and on the problem of how to extrapolate from the research model to astronauts are needed. Specific priorities in support of these objectives are the following:

- Research with animal models of radiation quality **and low fluence (less than one ion per cell or 0.15 Gy**) **or low proton doses (less than 1 Gy)** dependencies of late CNS risks such as early onset of dementia or Alzheimer's disease and cardiac risks from HZE nuclei, solar protons or combined HZE nuclei and proton irradiations
- Studies that determine if early molecular, cellular, and tissue environment changes in the hippocampus or coronary arteries indicative of dementia or heart disease, respectively will occur at significant levels below doses of 0.2 Gy or heavy ions or 1 Gy of protons.

It is expected that the proposed research in each Emphasis area shall be undertaken at NSRL using fluence levels and nuclei representative of GCR or SPE. Proposals shall address how research will lead to quantitative assessments of radiation quality effects for research on cancer related processes, or low HZE fluence or low proton dose dependences for CNS and degenerative risks research.

G. 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.

H. Availability of Funds for Award

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.

I. Additional Funding Restrictions

The construction of facilities is prohibited unless specifically required in this announcement. For further information on the allowability of costs, refer to the cost principles cited in the *NASA Federal Acquisition Regulations (FAR) Supplement Provision* and the *Guidebook for Proposers*. (References in Section VIII.)

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.

Profit for commercial organizations is allowed under contract awards only.

Regardless of whether functioning as a team lead or as a team member, proposing personnel from NASA Centers shall propose budgets based on Full Cost Accounting (FCA). Non-NASA U.S. Government organizations shall propose based on FCA unless no such standards are in effect; in that case such proposers shall 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 three years; however, two or 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 10 investigations may be selected by SRPE. **It is anticipated that SRPE awards will average $350,000 per year (total cost) and shall not exceed $385,000 per year for cellular based studies, and $450,000 per year for studies with a significant animal component.** Proposers are required to propose at least three ion types to be reviewed by SRPE upon selection, including an appropriate number of dose (fluence) levels, and a reference radiation if necessary. 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 September 2009 and the grant will be awarded in a reasonable timeframe thereafter.

III. Eligibility Information

A. Eligibility of Applicants

All categories of 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 proposing entity is expected to be responsible for administering the project according to the management approach presented in the proposal. The proposing 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 or a competing factor in the selection process.

B. Guidelines for International Participation

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 the participation of the U.S. entity only 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 funding/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; that 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. All proposals must be received before the established closing date. Those received after the closing date will be treated in accordance with

Appendix B, paragraph (g). 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 shall be advised when a decision on endorsement can be expected. Successful and unsuccessful foreign entities will be contacted directly by letter from 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. 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 NASA FAR Supplement Part 1835.016-70 for additional information on international participation, which can be referenced at http://www.hq.nasa.gov/office/procurement/regs/1835.htm#35_016-70.
Also see NASA Policy Directive 1360.2 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_002A_&page_name=main

Export Control Guidelines Applicable to Proposals Including Foreign Participation

Proposals that include 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 http://www.pmdtc.org/ and http://www.bis.doc.gov/.

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 located at http://www.hq.nasa.gov/office/procurement/regs/1816.doc#OLE_LINK3.

IV. Proposal and Submission Information

A. Source of Application Materials

Unless specifically stated otherwise in this NRA, applicants shall prepare proposals in accordance with the "Instructions for Responding to NASA Research Announcements," NASA Federal Acquisition Regulations (FAR) Supplement (NFS), Part 1852.235-72 (http://www.hq.nasa.gov/office/procurement/regs/5228-41.htm#52_235-72). This instruction, hereafter referred to as the *NASA FAR Supplement Provision*, can be referenced in its entirety in Appendix B of this document.

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/.

Except where specifically stated otherwise in this NRA, applicants must prepare proposals in accordance with the *NASA FAR Supplement Provision* and the standards in the *Guidebook for Proposers*. **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. 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 and times.**

Proposers can use either Grants.gov. (http://www.grants.gov/) or NSPIRES (http://nspires.nasaprs.com) for proposal submission. All proposers, team members, and agency officials must be registered before proposal submission with NSPIRES regardless of the electronic submission system used. 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. Proposers invited to submit a full Step-2 proposal who elect to use Grants.gov will not have any information provided by the proposer in a Step-1 proposal available within Grants.gov.

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 web site will provide a list of all elements that make up an electronic proposal, and the system will conduct an element check to identify any item(s) that is(are) apparently missing or incomplete. 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 *NASA FAR Supplement Provision*. 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 = 1.5"; Right, top, bottom = 1.0").

Step-1 proposals shall be electronically submitted by April 23, 2009. Electronic submission of Step-1 proposals will be open between March 17 and April 23, 2009. All submitters of Step-1 proposals will be informed by via e-mail (as provided on the Step-1 proposal cover page) no later than two weeks after the Step-1 proposal due date that they are, or are not, invited to submit a full Step-2 proposal. **Submitters who do not receive notification as to their invitation status by May 1, 2009 should contact NASA (Section VII).**

The NSPIRES system will guide proposers through submission of all required proposal information. Please note that the Proposal Summary, Business Data, Program Specific 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 and Program Specific Data 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.F); the hypotheses and specific aims of the proposal; 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.

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.

3. Instructions for Preparation of Invited Step-2 Proposals

Step-2 proposals are due June 25, 2009. **Step-2 proposals will be accepted from invited proposers only.** All Step-2 proposals must meet the requirements for responding

to an NRA as outlined in the *NASA FAR Supplement Provision.* Chapter 2 of the *Guidebook for Proposers* provides detailed discussions of the content and organization of proposals for electronic submission.

The NSPIRES system will guide proposers through submission of all required proposal information. 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.

NSPIRES allows for the upload of several proposal components as individual documents. If your Step-1 proposal document is listed as an attachment to your Step-2 proposal, you must delete your Step-1 proposal document and replace it with your Step-2 proposal document.

To ensure proper Step-2 proposal transmission, please provide only **one** .PDF attachment upload ordered as follows:

1. *Integrated Research Plan Response Form (see IV.B.3.a below)*
2. *Animal Care or Human Subjects certifications, if applicable (see IV.B.3.b below)*
3. *Response to prior review, if applicable (see IV.B.3.c below)*
4. *Productivity of funded NASA research, if applicable (see IV.B.3.d below)*
5. *Scientific / Technical Project Description (see section IV.B.3.e below)*
6. *References and Citations*
7. *Management Approach (see Appendix B)*
8. *Personnel Curriculum Vitae (see Appendix B)*
9. *Facilities and Equipment (see Appendix B)*
10. *Budget Justification of Proposed Costs (see Appendix B)*
11. *Letters of Collaboration / Support*
12. *Appendices / Reprints*

The PDF upload must not be password protected or locked in any way. 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 institution official (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 listed due dates.

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

a) HRP Integrated Research Plan

The investigator shall examine and understand the radiation research section of the Integrated Research Plan (IRP). 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 mapping these risks and questions to 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 provisions is required. In addition, the application must include a statement from the applicant institution certifying that the proposed work will meet all Federal and local human subject requirements and/or animal care and use requirements.

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

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

Additional Requirements for Research Employing Human Subjects A letter signed by the Chair of the proposer's Institutional Review Board (IRB) identifying the proposal submitted to NASA by title and certifying approval of proposed human subjects protocols and procedures should be included with each copy of the proposal. IRB certifications for other research proposals or grants cannot be substituted (even if they employ the same protocols and procedures). If IRB certification is pending on the proposal due date,

include a copy of a letter signed by the IRB Chair identifying the proposal by title and indicating the status of the IRB review process at the time of submission. IRB certification must be received no later than 90 days after the proposal due date. NASA will require current IRB certification prior to each year's award.

Additional Requirements for Research Employing Animals Specific information describing and justifying the use of animal subjects must be included in the proposal. A letter signed by the Chair of the Institutional Animal Care and Use Committee (IACUC) identifying the proposal submitted to NASA by title and certifying approval of the proposed animal research protocols and procedures should be included with each copy of the proposal. The institution's Public Health Service Animal Welfare Assurance Number must be included on the IACUC certification. IACUC certifications for other research proposals or grants agreements cannot be substituted (even if they employ the same protocols and procedures). If IACUC certification is pending on the proposal due date, include a copy of a letter signed by the IACUC Chair identifying the proposal by title and indicating the status of the IACUC review process at the time of submission. IACUC certification must be received no later than 90 days after the proposal due date. NASA will require current IACUC certification prior to each year's award.

IRB or IACUC certifications shall be included as part of the proposal submission, preceding the research description of the proposal. If approval is pending at the time of proposal submission, a statement indicating such shall be included, preceding the project description as part of the main proposal upload. Additional information can be referenced in Appendix B, Section (c)(11).

c) Revised Proposals

Proposals that are revised versions of proposals previously submitted within the last three years shall be clearly designated as such and shall contain an explanation of how the revised proposal has addressed criticisms from previous review. This explanation shall be presented preceding the research description as part of the main proposal upload and is limited to two pages. These two pages are not considered part of the 20-page project description. Related changes to the research plan shall be highlighted in the body of the project description. Proposal reviewers will be provided with the evaluations of prior submissions. **Revised proposals not identified as such will be returned to the submitter without panel review and not considered for funding.** Proposers in doubt as to whether a proposal is a revision or a new submission are encouraged to contact Kevin Willison (kwillison@nasaprs.com, phone 202-479-9030 x242) at NASA Research and Education Support Services.

d) Continuation of NASA-Funded Research

Proposals that are continuations of current NASA-funded research shall provide specifics to the productivity of the supported research including progress in experiments at NSRL, research publications and new findings, and attendance at the NASA Annual Investigators meeting. This explanation shall be presented preceding the research description as part of the main proposal upload and is limited to two pages. These two pages are not considered part of the 20-page project description. Related impacts to the

proposed research plan shall be highlighted in the body of the project description. **Proposals that request continued NASA support that do not include this productivity section will be returned to the submitter without panel review and not considered for funding.**

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

The length of the project description of the proposal shall not exceed 20 pages using standard (12 point) type. Text shall have the following margins: left = 1.5"; Right, top, bottom = 1.0". Referenced figures must be included in the 20 pages of the project description; however figure captions can use a 10 point font. The proposal shall 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 shall be clearly stated. **Proposals that exceed the 20-page limit for the project description will be declined without review. Cited literature and all other proposal sections are not considered part of the 20-page project description.** Reviewers are not required to consider information presented as appendices or to view and/or consider Web links in their evaluation of the proposal. Additional information can be referenced in Appendix B, Section (c)(4).

f) 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**).

4. Submission of Proposals via Grants.gov

Instructions for submitting proposals to NASA via Grants.gov may be found on the Grants.gov portal at http://www.grants.gov/.

All proposers, team members, and agency officials must be registered with NSPIRES before proposal submission as described under section IV.B.1 regardless of the electronic submission system used.

NSPIRES remains the only system through which a Step-1 proposal can be continued as a Step-2 proposal. Proposers invited to submit a full Step-2 proposal who elect to use Grants.gov will not have any information provided by the proposer in a Step-1 proposal available within Grants.gov.

C. Submission Dates

Solicitation Announcement Identifier: NRA NNJ09ZSA001N
Step-1 Proposals Due: 5:00 PM Eastern, April 23, 2009
Step-2 Proposals Due: 5:00 PM Eastern, June 25, 2009
Estimated Selection Announcement: September 2009
NASA Selecting Official: Human Research Program Manager

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 with no significant mechanistic basis or likely gain in scientific knowledge are not acceptable. Experimental studies not directly relevant to improved interpretation of experiments already conducted with such radiation will not be funded.

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. Proposals should take into account the impact of gender, age, nutrition, stress, genetic predisposition, or sensitivity to other factors of importance in managing space radiation risks. For relevant and compliant proposals, the primary criterion for an award will be scientific merit.

All of the following criteria will be used in determining the merit 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?
- **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?

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 both this announcement, the *Guidebook for Proposers*, and the *NASA FAR Supplement Provision*. Upon receipt, proposals will be reviewed for compliance with these requirements including:

(1) The proposal project description must be no more than 20 pages in length, and should be titled and numbered as its own section.
(2) Submission of appropriate Institutional Review Board (IRB) or Animal Care and Use Committee (ACUC) certification for all proposals using human or animal test subjects.
(3) Submission of an appropriate and justified budget for a funding period not exceeding that described in the NRA.
(4) Proposals that are revised versions of proposals previously submitted must be clearly designated as such and must contain an explanation of how the revised proposal has addressed criticisms from previous review. 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) Proposals that are continuations of current NASA support research must provide specifics to the productivity of your NASA-funded research in a section separate from the project description. This explanation should be presented in a separate form of no more than two pages. Related impacts to the research plan should be highlighted in the body of the project description.

(6) Identification of Integrated Research Plan risks and questions addressed by the research.
(7) Submission of all other appropriate information as required by this NRA.

Note: At NASA's discretion, non-compliant proposals may be eliminated from the review process and declined without further review.

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 merit review, which carries the highest weight in final evaluation and selection. The other factors are approximately equal in weight to each other. Deficiencies in any one of these factors 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 Appendix B, Section (k).

Additionally, 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.

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

An ombudsman has been appointed to hear and facilitate the resolution of concerns from offerors, potential offerors, and contractors during the pre-award and post-award phases of this acquisition. 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 contract 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, Melanie W. Saunders, 2101 NASA Parkway, Houston, Texas, 77058, 281-483-0490, fax 281-483-200, email melanie.saunders-1@nasa.gov. Concerns, issues disagreements, and recommendations which cannot be resolved a the installation may be referred to the NASA ombudsman, James A. Balinskas, the Director of the Contract Management Division, at 202-358-0445, fax 202-358-3083, email james.a.balinskas@nasa.gov. Please do not contact the ombudsman to request copies of the announcement, 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. The selection letters will include a statement indicating the selected organization's business office will be contacted by a NASA Grant Officer. Any

costs incurred by the investigator in anticipation of an award are at their own risk until contacted by the NASA Grant Officer. Selection notification will be made by a letter signed by the selecting official. The NASA Procurement Office will determine the type of award instrument, request further business data, negotiate the resultant action, and are the only personnel with the authority to 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 Appendix B, Section (k)(2).

B. Administrative and National Policy Requirements

Grant awards are subject to the NASA Grant Handbook. This handbook consists of four sections that prescribe the policies and procedures relating to the award and administration of NASA grants. Section A provides the text of provisions and special conditions and addresses NASA's authority, definitions, applicability, amendments, publications, deviations, pre-award requirements and post-award requirements currently covered by 14 CFR part 1260. Section B relates to grants with institutions of higher education, hospitals, and other nonprofit organizations. Sections A and B, with the special considerations in subpart 1260.4(b), apply to awards with commercial firms that do not involve cost sharing. Section C adopts the administrative requirements of OMB Circular No. A-102 and relates to administrative requirements for grants to state and local governments. Section D relates to awards with commercial firms. The Handbook is located at http://ec.msfc.nasa.gov/hq/grcover.htm.

C. Program Reporting/Individual Researcher Reporting

Annual Reporting and Task Book Reporting for Grant Recipients
The PI shall provide an annual written report to NASA on or before the anniversary of the start of funding. 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 Task Book. The Task Book includes descriptions of all peer-reviewed activities funded by the Exploration Systems Mission Directorate (ESMD). 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:

- an abstract;
- a bibliographic list of publications;
- copies of publications; and
- a statement of progress, including a comparison with the originally proposed work schedule.

Final Report for Grant Recipients
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. This information 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
- an appendix with bibliography and copies of all publications and reports. Any publications or other public materials containing data are particularly important to include in this section.

D. Other Considerations

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.

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

Francis A. Cucinotta, Ph.D.
Lyndon B. Johnson Space Center
National Aeronautics and Space Administration
Code SK
2101 NASA Road 1
Houston, TX 77058
Telephone: (281) 483-0968
Fax: (281) 483-3058
E-mail: francis.a.cucinotta@nasa.gov

Additional contracting information for this NRA is available from:

Vanessa R. Beene
Lyndon B. Johnson Space Center
National Aeronautics and Space Administration
Code BH
2101 NASA Road 1
Houston, TX 77058
Telephone: (281) 244-5257
Fax: (281) 244-5331
E-mail: vanessa.r.beene@nasa.gov

VIII. References

A. 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 Task Book is available online at the following address:
http://taskbook.nasaprs.com/peer_review/index.cfm

Human Research Program Integrated Research Plan
http://stic.jsc.nasa.gov/dbase/dis/jsc/hrp-47065_reva.pdf

NASA Federal Acquisition Regulations Supplement. This document is available online at the following address:
http://www.hq.nasa.gov/office/procurement/regs/nfstocA.htm

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 and Cooperative Agreement Handbook. This document is available online at the following address:
http://ec.msfc.nasa.gov/hq/grcover.htm

National Academy of Science, Institute of Medicine and National Research Council, Bioastronautics Roadmap A Risk Reduction Strategy for Human Exploration of Space. 2005. Washington D.C. National Academy Press. Web address:
http://www.nap.edu/books/030909948X/html/

A Nicogossian, C Huntoon, and S Pool. (Eds.) **Space Physiology and Medicine, 3rd ed**. Lea & Febiger. Philadelphia, PA (1994).

FASEB Journal, Vol. 13, Supplement, **Cell & Molecular Biology Research in Space**. (1999).

Brain Research Reviews, **Space Neuroscience Research**. Volume 28, Numbers 1/2, Special Issue, (1998).

Annals of the ICRP, 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60, Pergamon Press, Oxford (1990).

National Council on Radiation Protection and Measurements: Radiation Protection Guidance for Activities in Low-Earth Orbit. NCRP Report No. 132, Bethesda MD (2000).

National Council on Radiation Protection and Measurements: Information Needed To Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit. NCRP Report No. 153 Bethesda MD (2006).

NASA Space Radiation Health Program Strategic Plan:
http://spaceresearch.nasa.gov/docs/radiation_strat_plan_1998.pdf

Space Radiation Health Project at Johnson Space Center:
http://haco.jsc.nasa.gov/projects/space_radiation.htm

B. Selected Workshop Reports

Modeling Human Risk: Cell & Molecular Biology in Context. June, 1997. Ernest Orlando Lawrence Berkeley National Laboratory Report LBNL-40278. Berkeley, CA

Models for Evaluation of Radiation Risk Factors. *Radiation Research* Volume 156, No. 5, Part 2 (2001).

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

1.1 Risk of Radiation Carcinogenesis from Space Radiation

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.

1.2 Risk of Acute or Late Central Nervous System Effects from Space Radiation

Acute and late radiation damage to the central nervous system (CNS) may lead to changes in motor function and behavior, or neurological disorders. Radiation and synergistic effects of radiation with other space flight factors may affect neural tissues, which in turn may lead to changes in function or behavior. Data specific to the spaceflight environment must be compiled to quantify the magnitude of this risk using animal models and 2-dimensional or 3-dimensional cell culture models of human or other vertebrate cells. If this is identified as a risk of high enough magnitude then appropriate protection strategies should be employed.

1.3 Risk of Degenerative Tissue or other Health Effects from Space Radiation

Space radiation exposure may result in degenerative tissue diseases (non-cancer or non-CNS) such as cardiac, circulatory, or digestive diseases, and cataracts. Hereditary risks to the first and subsequent generations of crew off-spring also are a concern. The mechanisms and the magnitude of influence of radiation leading to these diseases are not well characterized. Radiation can cause increased molecular, cellular, and ultimately tissue damage, which may lead to acute or chronic disease of susceptible organ tissues. Data specific to the spaceflight environment must be compiled using appropriate cell culture and small animal models and an approach to extrapolate this data to humans developed in order to quantify the magnitude of this risk to determine if additional protection strategies are required.

1.4 Acute Radiation Risks from Space Radiation

Radiation and synergistic effects of radiation may place the crew at significant risk for acute radiation sickness including prodromal risks, significant skin injury as well as death from a major solar event (SPE) or combined SPE and galactic cosmic rays, such that the mission or crew survival may be

placed in jeopardy. Crew health and performance may be impacted by a large SPE or the cumulative effect of GCR and SPEs. Beyond Low Earth Orbit, the protection of the Earth's atmosphere 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. 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 spaceflight environment must be compiled to quantify the magnitude of increase of this risk and to develop appropriate protection strategies.

Radiation Carcinogenesis - Specific Gaps

Cancer 1: How can experimental models of tumor development for the major tissues (lung, colon, stomach, breast, liver, and leukemias) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk projections?	☐
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 models of cancer risk be applied to reduce the uncertainties in radiation quality effects from SPE's and GCR?	☐
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 gender 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 evaluated the effectiveness of CM's? How can epidemiology data and scaling factors support this approach?	☐
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 their significant synergistic effects from other spaceflight 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 level of accuracy do NASA’s space environment, transport code and cross sections describe	NA

radiation environments in space (ISS, Lunar, or Mars)?	
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 are the optimal biodosimetry methods for Lunar and Mars missions, and are biomarker approaches needed?	NA

4.2 Acute and Late Risks to the CNS - Specific Gaps

CNS-1: Is there a significant probability that space radiation would lead to immediate or acute functional changes in the CNS during a long-term space mission and if so what are the mechanisms of change? Are there threshold doses for these effects?	NA
CNS - 2: Is there a significant probability that space radiation exposures would lead to long-term or late degenerative CNS risks if so what are the mechanisms of change?	☐
CNS - 3: How does individual susceptibility including hereditary pre-disposition (Alzheimer's, Parkinson's, apoE) and prior CNS injury (concussion or other) alter significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?	☐
CNS - 4: What are the most effective biomedical or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?	NA
CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS risks 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?	NA
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?	☐
CNS - 7: What are the best shielding approaches to protect against CNS risks, and are shielding approaches for CNS and cancer risks synergistic?	NA
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)?	NA

Degenerative Risks (Non-cancer) - Specific Gaps

Degen - 1: How can tissue specific risk models be developed for the major degenerative tissue risks, including heart, circulatory, endocrine, digestive, lens and other tissue systems in order to estimate GCR and SPE risks for degenerative diseases?	☐
Degen - 2: What are the mechanisms of degenerative tissues risks in the heart, circulatory, endocrine, digestive, lens and other tissue systems? What surrogate endpoints do they suggest?	☐
Degen - 3: What are the progression rates and latency periods for degenerative risks, and how do progression rates depend on age, gender, radiation type, or other physiological or environmental factors	☐
Degen - 4: How does individual susceptibility including hereditary pre-disposition alter degenerative tissue risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?	☐
Degen - 5: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?	NA
Degen - 6: What are the most effective biomedical or dietary countermeasures to degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CM's additive, synergistic or antogonistic to other Risks?	NA
Degen - 7: Are their significant synergistic effects from other spaceflight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify the degenerative risk from space radiation?	NA

Acute Radiation Syndromes - Specific Gaps

Acute - 1: What are the probabilities for various acute effects from SPE's including RBE's and dose-rate modifiers?	NA
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?	NA
Acute - 3: Are their synergistic effects arising from other spaceflight factors (microgravity, stress, immune status, bone loss, etc.) that modify acute risks from space radiation including modifying thresholds for such effects? (post PPBE)	NA
Acute - 4: What are the probabilities of hereditary, fertility, and sterility effects from space radiation?	NA
Acute - 5: What are the optimal SPE alert and dosimetry technologies for EVAs?	NA
Acute - 6: What are the most effective shielding approaches to mitigate acute radiation risks, how do we know, and implement?	NA
Acute - 7 What are the most effective biomedical or dietary countermeasures to mitigate acute radiation risks?	NA
Acute - 8: How can Probabilistic risk assessment be applied to SPE risk evaluations for EVA, and combined EVA+IVA exposures?	NA

X. Appendix B

NASA FAR Supplement Provision
NFS 1852.2325-72
Instructions for Responding to NASA Research Announcements
(November 2004)

(a) General.

(1) Proposals received in response to a NASA Research Announcement (NRA) will be used only for evaluation purposes. NASA does not allow a proposal, the contents of which are not available without restriction from another source, or any unique ideas submitted in response to an NRA to be used as the basis of a solicitation or in negotiation with other organizations, nor is a pre-award synopsis published for individual proposals.

(2) A solicited proposal that results in a NASA award becomes part of the record of that transaction and may be available to the public on specific request; however, information or material that NASA and the awardee mutually agree to be of a privileged nature will be held in confidence to the extent permitted by law, including the Freedom of Information Act.

(3) NRAs contain programmatic information and certain requirements which apply only to proposals prepared in response to that particular announcement. These instructions contain the general proposal preparation information which applies to responses to all NRAs.

(4) A contract, grant, cooperative agreement, or other agreement may be used to accomplish an effort funded in response to an NRA. NASA will determine the appropriate award instrument. Contracts resulting from NRAs are subject to the Federal Acquisition Regulation and the NASA FAR Supplement. Any proposal from a large business concern that may result in the award of a contract, which exceeds $5,000,000 and has subcontracting possibilities should include a small business subcontracting plan in accordance with the clause at FAR 52.219-9, Small Business Subcontracting Plan. (Subcontract plans for contract awards below $5,000,000, will be negotiated after selection.) Any resultant grants or cooperative agreements will be awarded and administered in accordance with the NASA Grant and Cooperative Agreement Handbook (NPR 5800.1).

(5) NASA does not have mandatory forms or formats for responses to NRAs; however, it is requested that proposals conform to the guidelines in these instructions. NASA may accept proposals without discussion; hence, proposals should initially be as complete as possible and be submitted on the proposers' most favorable terms.

(6) To be considered for award, a submission must, at a minimum, present a specific project within the areas delineated by the NRA; contain sufficient technical and cost information to permit a meaningful evaluation; be signed by an official authorized to legally bind the submitting organization; not merely offer to perform standard services or to just provide computer facilities or services; and not significantly duplicate a more specific current or pending NASA solicitation.

(b) NRA-Specific Items. Several proposal submission items appear in the NRA itself: the unique NRA identifier; when to submit proposals; where to send proposals;

number of copies required; and sources for more information. Items included in these instructions may be supplemented by the NRA.

(c) The following information is needed to permit consideration in an objective manner. NRAs will generally specify topics for which additional information or greater detail is desirable. Each proposal copy shall contain all submitted material, including a copy of the transmittal letter if it contains substantive information.

(1) Transmittal Letter or Prefatory Material.

(i) The legal name and address of the organization and specific division or campus identification if part of a larger organization;

(ii) A brief, scientifically valid project title intelligible to a scientifically literate reader and suitable for use in the public press;

(iii) Type of organization: e.g., profit, nonprofit, educational, small business, minority, women-owned, etc.;

(iv) Name and telephone number of the principal investigator and business personnel who may be contacted during evaluation or negotiation;

(v) Identification of other organizations that are currently evaluating a proposal for the same efforts;

(vi) Identification of the NRA, by number and title, to which the proposal is responding;

(vii) Dollar amount requested, desired starting date, and duration of project;

(viii) Date of submission; and

(ix) Signature of a responsible official or authorized representative of the organization, or any other person authorized to legally bind the organization (unless the signature appears on the proposal itself).

(2) Restriction on Use and Disclosure of Proposal Information. Information contained in proposals is used for evaluation purposes only. Offerors or quoters should, in order to maximize protection of trade secrets or other information that is confidential or privileged, place the following notice on the title page of the proposal and specify the information subject to the notice by inserting an appropriate identification in the notice. In any event, information contained in proposals will be protected to the extent permitted by law, but NASA assumes no liability for use and disclosure of information not made subject to the notice.

Notice Restriction on Use and Disclosure of Proposal Information

The information (data) contained in [insert page numbers or other identification] of this proposal constitutes a trade secret and/or information that is commercial or financial and confidential or privileged. It is furnished to the Government in confidence with the understanding that it will not, without permission of the offeror, be used or disclosed other than for evaluation purposes; provided, however, that in the event a contract (or other agreement) is awarded on the basis of this proposal the Government shall have the right to use and disclose this information (data) to the extent provided in the contract (or other agreement). This restriction does not limit the Government's right to use or disclose this information (data) if obtained from another source without restriction.

(3) Abstract. Include a concise (200-300 word if not otherwise specified in the NRA) abstract describing the objective and the method of approach.

(4) Project Description.

(i) The main body of the proposal shall be a detailed statement of the work to be undertaken and should include objectives and expected significance; relation to the present state of knowledge; and relation to previous work done on the project and to related work in progress elsewhere. The statement should outline the plan of work, including the broad design of experiments to be undertaken and a description of experimental methods and procedures. The project description should address the evaluation factors in these instructions and any specific factors in the NRA. Any substantial collaboration with individuals not referred to in the budget or use of consultants should be described. Subcontracting significant portions of a research project is discouraged.

(ii) When it is expected that the effort will require more than one year, the proposal should cover the complete project to the extent that it can be reasonably anticipated. Principal emphasis should be on the first year of work, and the description should distinguish clearly between the first year's work and work planned for subsequent years.

(5) Management Approach. For large or complex efforts involving interactions among numerous individuals or other organizations, plans for distribution of responsibilities and arrangements for ensuring a coordinated effort should be described.

(6) Personnel. The principal investigator is responsible for supervision of the work and participates in the conduct of the research regardless of whether or not compensated under the award. A short biographical sketch of the principal investigator, a list of principal publications and any exceptional qualifications should be included. Omit social security number and other personal items which do not merit consideration in evaluation of the proposal. Give similar biographical information on other senior professional personnel who will be directly associated with the project. Give the names and titles of any other scientists and technical personnel associated substantially with the project in an advisory capacity. Universities should list the approximate number of students or other assistants, together with information as to their level of academic attainment. Any special industry-university cooperative arrangements should be described.

(7) Facilities and Equipment.

(i) Describe available facilities and major items of equipment especially adapted or suited to the proposed project, and any additional major equipment that will be required. Identify any Government-owned facilities, industrial plant equipment, or special tooling that are proposed for use. Include evidence of its availability and the cognizant Government points of contact.

(ii) Before requesting a major item of capital equipment, the proposer should determine if sharing or loan of equipment already within the organization is a feasible alternative. Where such arrangements cannot be made, the proposal should so state. The need for items that typically can be used for research and non-research purposes should be explained.

(8) Proposed Costs (U.S. Proposals Only).

(i) Proposals should contain cost and technical parts in one volume: do not use separate "confidential" salary pages. As applicable, include separate cost estimates for salaries and wages; fringe benefits; equipment; expendable materials and supplies; services; domestic and foreign travel; ADP expenses; publication or page charges;

consultants; subcontracts; other miscellaneous identifiable direct costs; and indirect costs. List salaries and wages in appropriate organizational categories (e.g., principal investigator, other scientific and engineering professionals, graduate students, research assistants, and technicians and other non-professional personnel). Estimate all staffing data in terms of staff-months or fractions of full-time.

(ii) Explanatory notes should accompany the cost proposal to provide identification and estimated cost of major capital equipment items to be acquired; purpose and estimated number and lengths of trips planned; basis for indirect cost computation (including date of most recent negotiation and cognizant agency); and clarification of other items in the cost proposal that are not self-evident. List estimated expenses as yearly requirements by major work phases.

(iii) Allowable costs are governed by FAR Part 31 and the NASA FAR Supplement Part 1831 (and OMB Circulars A-21 for educational institutions and A-122 for nonprofit organizations).

(iv) Use of NASA funds--NASA funding may not be used for foreign research efforts at any level, whether as a collaborator or a subcontract. The direct purchase of supplies and/or services, which do not constitute research, from non-U.S. sources by U.S. award recipients is permitted. Additionally, in accordance with the National Space Transportation Policy, use of a non-U.S. manufactured launch vehicle is permitted only on a no-exchange-of-funds basis.

(9) Security. Proposals should not contain security classified material. If the research requires access to or may generate security classified information, the submitter will be required to comply with Government security regulations.

(10) Current Support. For other current projects being conducted by the principal investigator, provide title of project, sponsoring agency, and ending date.

(11) Special Matters.

(i) Include any required statements of environmental impact of the research, human subject or animal care provisions, conflict of interest, or on such other topics as may be required by the nature of the effort and current statutes, executive orders, or other current Government-wide guidelines.

(ii) Identify and discuss risk factors and issues throughout the proposal where they are relevant, and your approach to managing these risks.

(iii) Proposers should include a brief description of the organization, its facilities, and previous work experience in the field of the proposal. Identify the cognizant Government audit agency, inspection agency, and administrative contracting officer, when applicable.

(d) Renewal Proposals.

(1) Renewal proposals for existing awards will be considered in the same manner as proposals for new endeavors. A renewal proposal should not repeat all of the information that was in the original proposal. The renewal proposal should refer to its predecessor, update the parts that are no longer current, and indicate what elements of the research are expected to be covered during the period for which support is desired. A description of any significant findings since the most recent progress report should be included. The renewal proposal should treat, in reasonable detail, the plans for the next period, contain a cost estimate, and otherwise adhere to these instructions.

(2) NASA may renew an effort either through amendment of an existing contract or by a new award.

(e) Length. Unless otherwise specified in the NRA, effort should be made to keep proposals as brief as possible, concentrating on substantive material. Few proposals need exceed 15-20 pages. Necessary detailed information, such as reprints, should be included as attachments. A complete set of attachments is necessary for each copy of the proposal. As proposals are not returned, avoid use of "one-of-a-kind" attachments.

(f) Joint Proposals.

(1) Where multiple organizations are involved, the proposal may be submitted by only one of them. It should clearly describe the role to be played by the other organizations and indicate the legal and managerial arrangements contemplated. In other instances, simultaneous submission of related proposals from each organization might be appropriate, in which case parallel awards would be made.

(2) Where a project of a cooperative nature with NASA is contemplated, describe the contributions expected from any participating NASA investigator and agency facilities or equipment which may be required. The proposal must be confined only to that which the proposing organization can commit itself. "Joint" proposals which specify the internal arrangements NASA will actually make are not acceptable as a means of establishing an agency commitment.

(g) Late Proposals. Proposals or proposal modifications received after the latest date specified for receipt may be considered if a significant reduction in cost to the Government is probable or if there are significant technical advantages, as compared with proposals previously received.

(h) Withdrawal. Proposals may be withdrawn by the proposer at any time before award. Offerors are requested to notify NASA if the proposal is funded by another organization or of other changed circumstances which dictate termination of evaluation.

(i) Evaluation Factors.

(1) Unless otherwise specified in the NRA, the principal elements (of approximately equal weight) considered in evaluating a proposal are its relevance to NASA's objectives, intrinsic merit, and cost.

(2) Evaluation of a proposal's relevance to NASA's objectives includes the consideration of the potential contribution of the effort to NASA's mission.

(3) Evaluation of its intrinsic merit includes the consideration of the following factors of equal importance:

(i) Overall scientific or technical merit of the proposal or unique and innovative methods, approaches, or concepts demonstrated by the proposal.

(ii) Offeror's capabilities, related experience, facilities, techniques, or unique combinations of these which are integral factors for achieving the proposal objectives.

(iii) The qualifications, capabilities, and experience of the proposed principal investigator, team leader, or key personnel critical in achieving the proposal objectives.

(iv) Overall standing among similar proposals and/or evaluation against the state-of-the-art.

(4) Evaluation of the cost of a proposed effort may include the realism and reasonableness of the proposed cost and available funds.

(j) Evaluation Techniques. Selection decisions will be made following peer and/or scientific review of the proposals. Several evaluation techniques are regularly used within

NASA. In all cases proposals are subject to scientific review by discipline specialists in the area of the proposal. Some proposals are reviewed entirely in-house, others are evaluated by a combination of in-house and selected external reviewers, while yet others are subject to the full external peer review technique (with due regard for conflict-of-interest and protection of proposal information), such as by mail or through assembled panels. The final decisions are made by a NASA selecting official. A proposal which is scientifically and programmatically meritorious, but not selected for award during its initial review, may be included in subsequent reviews unless the proposer requests otherwise.

(k) Selection for Award.

(1) When a proposal is not selected for award, the proposer will be notified. NASA will explain generally why the proposal was not selected. Proposers desiring additional information may contact the selecting official who will arrange a debriefing.

(2) When a proposal is selected for award, negotiation and award will be handled by the procurement office in the funding installation. The proposal is used as the basis for negotiation. The contracting officer may request certain business data and may forward a model award instrument and other information pertinent to negotiation.

(l) Additional Guidelines Applicable to Foreign Proposals and Proposals Including Foreign Participation.

(1) 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 funding/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.

(2) 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. All proposals must be received before the established closing date. Those received after the closing date will be treated in accordance with paragraph (g) of this provision. 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.

(3) 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.

(4) 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).

(m) Cancellation of NRA. NASA reserves the right to make no awards under this NRA and to cancel this NRA. NASA assumes no liability for canceling the NRA or for anyone's failure to receive actual notice of cancellation.

(End of provision)