

Office of Science
Notice DE-FG02-06ER06-10

Low Dose Radiation Research Program - Basic Biology

U.S. Department of Energy

**Office of Science Financial Assistance Program Notice
DE-FG02-06ER06-10; Low Dose Radiation Research Program - Basic Biology**

AGENCY: U.S. Department of Energy
Office of Science

ACTION: Notice inviting grant applications.

SUMMARY: The Office of Biological and Environmental Research (BER) of the Office of Science (SC), U.S. Department of Energy (DOE) and the Human Research Program (HRP), National Aeronautics and Space Administration (NASA), hereby announce their interest in receiving grant applications for new research to develop a better scientific basis for understanding exposures and risks to humans from low doses or low fluences of ionizing radiation. Research must support the DOE/BER Low Dose Radiation Research Program, and may include complementary research of direct interest to the NASA/HRP Space Radiation Project of sufficient scientific merit to qualify for partial NASA support. To be considered for funding, research must focus on elucidating molecular mechanisms and pathways involved in normal radiobiological responses to low dose exposure; exclusively phenomenological studies will not be considered. New research is especially encouraged that focuses on molecular responses at tissue- and higher levels of biological organization. Scientists working in rapidly developing areas of biological sciences not necessarily associated with the study of radiation are also encouraged to consider the contributions that their field of study can make. High risk research having the potential to rapidly advance the field, and research employing genome-wide or proteome-wide methods, is particularly encouraged.

DOE/BER also announces its interest in receiving applications for special grants to support new collaborative work between two or more laboratories, one or more of which is already funded by the DOE Low Dose Program. These "glue grants" are primarily designed to support post-doctoral or graduate-student research that will enable laboratories with complementary expertise to develop and apply innovative new approaches to low dose radiation research. **Please review the Supplementary Information sections below for further discussion of programmatic needs, and for details on format for the two types of applications.**

DATES: Potential applicants are strongly encouraged to submit a brief pre-application, referencing Program Notice DE-FG02-06ER06-10, for receipt by DOE by February 22, 2006. A response to the preapplications encouraging or discouraging formal applications will be communicated to the applicants by March 3.

Formal applications submitted in response to this notice **must be received by 8:00 p.m., Eastern Time, April 26, 2006**, in order to be accepted for merit review and to permit timely consideration for award in Fiscal Year 2007.

ADDRESSES: Preapplications referencing Program Notice DE-FG02-06ER06-10, should be sent to SClifesci.lowdose@science.doe.gov. Applications submitted to the Office of Science must be submitted electronically through Grants.Gov to be considered for award (see next section).

Formal Applications

Applications submitted to the Office of Science must be submitted electronically through Grants.gov to be considered for award. The Funding Opportunity Number is: DE-FG02-06ER06-10 and the CFDA Number for the Office of Science is: 81.049. Instructions and forms are available on the [Grants.gov](http://www.grants.gov) website. Please see the information below and also refer to the "Funding Opportunity Announcement", Part IV - Application and Submission Information; H. Other Submission and Registration Requirements for more specific guidance on "Where to Submit" and "Registration Requirements." If you experience problems when submitting your application to Grants.gov, please visit their customer support website: <http://www.grants.gov/Customersupport>; email: support@grants.gov; or call 1-800-518-4726.

Registration Requirements: There are several one-time actions you must complete in order to submit an application through Grants.gov (e.g., obtain a Dun and Bradstreet Data Universal Numbering System (DUNS) number, register with the Central Contract Registry (CCR), register with the credential provider and register with [Grants.gov](http://www.grants.gov)). See <http://www.grants.gov/GetStarted>. Use the Grants.gov Organization Registration Checklist to guide you through the process. Designating an E-Business Point of Contact (EBiz POC) and obtaining a special password called an MPIN are important steps in the CCR registration process. Applicants, who are not registered with CCR and Grants.gov, should allow at **least 14 days** to complete these requirements. It is suggested that the process be started as soon as possible.

VERY IMPORTANT - Download PureEdge Viewer: In order to download the application package, you will need to install PureEdge Viewer. This small, free program will allow you to access, complete, and submit applications electronically and securely. For a free version of the software, visit the following Web site: <http://www.grants.gov/DownloadViewer>.

FOR FURTHER INFORMATION CONTACT: Send general questions to SClifesci.lowdose@science.doe.gov. For specific information on DOE interests, contact Dr. Noelle Metting, telephone: (301) 903-8309, E-mail: noelle.metting@science.doe.gov, Office of Biological and Environmental Research, U.S. Department of Energy, SC-23.1/Germantown Building, 1000 Independence Avenue SW, Washington, DC 20585-1290. For specific information on NASA/HRP interests, contact Dr. Francis Cucinotta, telephone (281) 483-0968, E-mail: francis.a.cucinotta@nasa.gov.

SUPPLEMENTARY INFORMATION

- I. Specifics for the Low Dose Radiation Research Program (DOE)
- II. Specifics for Glue Grants (DOE)
- III. Specifics for the Space Radiation Project (NASA)

I. Specifics for the Low Dose Radiation Research Program (DOE)

The DOE/BER Low Dose Radiation Research Program has the challenge of conducting research that can be used to inform the development of future national radiation risk policy for the public and the workplace. The Low Dose Program is chiefly concerned with very low doses of low Linear Energy Transfer (LET) radiation (high energy electrons and protons, x- and gamma-rays). The focus of research should be on doses of low LET radiation that are at or near current workplace exposure limits. In general, research is desired that focuses on total radiation doses that are less than 0.1 Gray (Gy) (10 rads). Some experiments will likely involve selected exposures to higher doses of radiation for comparisons with previous experiments or for determining the validity of extrapolation methods previously used to estimate the effects of low doses of radiation from observations made at high doses.

Low dose-rate studies are also very desirable. In these studies it is important that the range of total doses delivered also encompass the low dose range, i.e., total doses should adequately cover the range of 0.1 Gy or less in addition to any higher total doses. It is worth noting that experimental delivery of only 0.01 Gy (1 rad) over a period of 24 hours is still an approximately 1000-fold higher dose rate than the average background radiation dose rate in the U.S. It is probable that a normal biological system might have molecular sensors that detect and respond to a 1000-fold change in environmental conditions, and research is sought to elucidate these responses, if they exist.

Until fairly recently, most molecular studies of radiation effects were carried out using isolated cells in monolayer culture, and the responses of those cells were then extrapolated to mammalian tissues and organisms. There is already compelling evidence that molecular endpoint measurements such as gene expression and apoptosis induction can differ significantly in quality and/or quantity as a function of radiation dose, both in whole animal experimental systems and in the more artificial cell culture systems. New research indicates that molecular endpoint measurements are also qualitatively different as a function of the level of biological organization (cells, tissues, or whole organisms), and that normal, intact tissue may respond, in general, very differently to radiation than monoculture/monolayer cell populations. Innovative new research is needed to explore and more fully understand low dose radiation-induced molecular responses, and subsequent health outcomes, at these higher levels of biological organization.

New models for human health risk from low doses of radiation are also needed that incorporate the results of both low dose /dose-rate human epidemiological studies and the newer low dose / dose-rate biological studies.

Not all research on the biological effects of low doses of radiation will be equally useful for the development of radiation risk policy, though the path from basic radiation biology research to radiation risk policy is admittedly not clear at this time. In the present context, the research considered to be most useful will focus on biological outcomes after very low dose exposures and/or very low dose-rate exposures. Rather than just quantifying phenomenological outcomes,

the research goal will be to elucidate molecular mechanisms involved. Research should also study responses in cells that reside in intact tissues or whole organisms, rather than experiments entirely in cell culture. Because information on regulatory, metabolic, and signaling pathways is growing rapidly, applications should point out, wherever possible, how the proposed research might link with, clarify, and/or extend this information. Finally, successful applications will ideally have an approach or component (whether experimental or modeling) that could potentially link data from experiment to downstream health outcomes that might occur in humans.

Alternatively, a biological response of interest could meet all of the above criteria only at high doses but may actually be absent (as opposed to simply undetectable) at low doses of radiation. Since evidence is accumulating that the mechanisms of action after high doses of radiation may be different from the mechanisms of action after low doses, such studies would help define these mechanisms. Defining the doses where these mechanisms shift is of critical importance.

The Low Dose Program will be a success if the science it generates is useful to policy makers, standard setters, and the public. Successful applicants will be expected to effectively communicate research results through publication in peer-reviewed journals. Any data and results generated through the investigations that are appropriate to share with the broader scientific community should, where possible, be provided in a format amenable to deposition in databases. Successful applicants will also be encouraged to communicate with the wider community of concerned persons, so that current thinking and public debate are better able to reflect sound science.

The DOE Low Dose Program is already making significant investments and progress in topics such as DNA damage and repair, endogenous oxidative damage versus low dose radiation-induced damage, radio-adaptive responses, bystander effects, genomic instability, and individual genetic susceptibility to low dose radiation exposure. Descriptions of these topics can be found in the open literature via PubMed, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>, and on the Program website, <http://lowdose.tricity.wsu.edu/>. Information on current and past Program-funded projects, publications lists, and other information relevant to low dose radiation studies can also be found on the Program website.

The DOE Low Dose Program is currently funding several projects that have developed micro-irradiation devices capable of delivering low doses of low LET radiation to individual cells or to specific parts of individual cells. Investigators are encouraged to use these irradiators, as appropriate, through collaborative means. Information on the microbeam irradiators can be found at: http://lowdose.tricity.wsu.edu/radiobio_techniques.htm.

Several tissue repositories are available for Low Dose Program investigations. The University of Washington has a tissue repository containing cell lines derived from patients who developed second cancers following total body irradiation and hematopoietic stem cell transplantation (HSCT). Presently there are EBV-transformed cell lines from 25 individuals exposed to radiation, which subsequently developed a skin tumor, and an equal number from exposed individuals that have not yet developed a second cancer. Please contact directly Dr. Jeffrey L. Schwartz, Associate Professor of Radiation Oncology, University of Washington, (206) 598-

4091, E-mail: jschwart@u.washington.edu, for collaborative opportunities. Other available resource material are fixed animal and human tissue samples from individuals exposed to either external radiation or to internally deposited radioactive materials. For information on these tissue archives, please contact Dr. Gayle Woloschak, Northwestern University (312) 503-4322, g-woloschak@northwestern.edu.

II. Specifics for Glue Grants (DOE)

The Low Dose Radiation Research Program is also interested in receiving applications for the purpose of supporting collaborative work between two laboratories, one of which should be currently funded by the Program. These small grants are primarily designed to support post-doctoral or graduate-student research that will enable laboratories with complementary expertise to develop and apply innovative or collaborative approaches to low dose research, although comparative studies between laboratories already using similar experimental approaches are also encouraged. At least one of the applicant partners must hold a DOE grant focusing on low dose studies, and both applicant partners must have at least 1 year of support remaining on their core grants at the time of award (~November 2006). Collaborative glue grants can be set up with laboratories funded by such diverse agencies as DOE, NIH/NCI, NASA, DOD, EPA, the European Union, Canada, France, or Japan, but in any case the proposed research must be of interest to the DOE Low Dose Radiation Research Program. Applications for these small grants should review the sections above on programmatic needs, and must also follow the instructions in Grants.gov for electronic submission. Please note: the Project Description for the glue grant application should not exceed ten pages.

III. Specifics for the Space Radiation Project (NASA)

The NASA/HRP Space Radiation Project is charged with providing input for the determination of health risks to humans visiting the space radiation environment. NASA is especially interested in human exposure to low fluences of high-energy particulate ionizing radiation (protons and heavy ions). Applications whose principal focus is on low LET radiation are encouraged to include complementary research with high-energy particulate ionizing radiation that leverages progress, resources, and technology used for the low LET radiation research. Investigators with currently funded low dose projects may also apply for supplementary funding to address closely related research of interest to NASA.

The primary area of emphasis of the NASA/HRP Space Radiation Project is the development of mechanistic insights into biological effects of space radiation that account for radiation risks. Applications are required to be hypothesis-driven and are expected to obtain their data in ground-based experimental radiobiology studies with protons and high-energy heavy ion beams in the energy range corresponding to space radiation. This is mainly a ground-based program using accelerator facilities to simulate space radiation. In addition to the research topics already described above this includes research on non-phenomenological predictors of late cell and tissue effects and the control and modification of radiation effect mechanisms

A description of the current awards in the Space Radiation Project may be found at: http://taskbook.nasaprs.com/peer_review/index.cfm. (Search by checking Radiation Health) A

description of the ground-based facilities and experimental program at Brookhaven National Laboratory can be found at: <http://server.c-ad.bnl.gov/esfd/nsrl/index.html>. The proton therapy facilities at Loma Linda University Medical Center are described at: http://research.hq.nasa.gov/code_u/bcpr/index.cfm.

Research applications to which NASA will assign high priority:

- a. Studies that increase the confidence in the accuracy of extrapolating the probability of radiation-induced genetic alterations or carcinogenesis from rodents to humans.
- b. Determination of carcinogenic risks following irradiation by protons and HZE particles.
- c. Determination if exposure to heavy ions at the level that would occur in deep space poses a risk to the integrity and function of the central nervous system.

This opportunity does not request applications for flight research. Research applications are expected to utilize beams of charged particles available at the NASA Space Radiation Laboratory (NSRL) or lower energy (< 250 MeV) protons at the Loma Linda University Medical Center Proton Treatment Facility, and to address experimental data obtained with such beams in ways leading to significant predictions that can be tested in future experiments.

NASA envisions that the selected applications will be structured and operated in a manner that supports the country's educational initiatives and goals (including historically black colleges and universities and other minority universities), and in particular the need to promote scientific and technical education at all levels. NASA envisions that the selected applications will support the goals for public awareness and outreach to the general public. The selected investigators are invited to participate in NASA-funded educational programs.

The particles of interest to the Space Radiation Project are protons with energies between 20 and 1000 MeV, and nuclei of elements with atomic numbers between helium and iron, with energies between 50 and 3000 MeV/nucleon. Fluences of interest are of the order of 1-2 particles per cell; studies with higher fluences will need to be justified by compelling arguments, including an explanation of how the results can be applied in the low fluence regime. NASA has developed facilities for use of protons at Loma Linda University Medical School and high-energy heavy ion beams at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory. Applications should not budget for the use of beams at these facilities, which is paid by NASA. NASA will cooperate with DOE to provide the range of technical resources available for experimentation and analysis of experimental results at Brookhaven National Laboratory.

Program Funding

It is anticipated that up to \$3 million annually will be available from DOE/BER for approximately 15 awards for this Notice. Initial awards will be in Fiscal Year 2007, and applications may request project support for up to three years. All awards are contingent on the availability of funds and programmatic needs. Multi-year funding of grant awards is expected, and is also contingent upon the availability of appropriated funds, progress of the research, and continuing program need. Additional funds of up to \$0.5 M annually will be available from NASA for joint funding of new research, also contingent upon the availability of funds. NASA

provides beam time at the NSRL and the Loma Linda proton accelerator; investigators will not be required to pay for the beam time. DOE is under no obligation to pay for any costs associated with the preparation or submission of applications if an award is not made.

The Glue Grant awards should range between \$85,000 and \$125,000 per year, total costs, and run from 1 to 3 years.

Collaboration

Applicants are encouraged to collaborate with researchers in other institutions, such as universities, industry, non-profit organizations, federal laboratories and Federally Funded Research and Development Centers (FFRDCs), including the DOE National Laboratories, where appropriate, and to incorporate cost sharing and/or consortia wherever feasible. Additional information on collaboration is available in the Application Guide for the Office of Science Financial Assistance Program that is available via the Internet at: <http://www.sc.doe.gov/grants/Colab.html>.

Merit and Relevance Review

Applications will be subjected to scientific merit review (peer review) and will be evaluated against the following evaluation criteria listed in descending order of importance as codified at 10 CFR 605.10(d):

1. Scientific and/or Technical Merit of the Project.
2. Appropriateness of the Proposed Method or Approach.
3. Competency of Applicant's Personnel and Adequacy of Proposed Resources.
4. Reasonableness and Appropriateness of the Proposed Budget.

The evaluation will include program policy factors such as the relevance of the proposed research to the terms of the announcement and the Department's programmatic needs. External peer reviewers are selected with regard to both their scientific expertise and the absence of conflict-of-interest issues. Non-federal reviewers may be used, and submission of an application constitutes agreement that this is acceptable to the investigator(s) and the submitting institution. Applications found to be scientifically meritorious and programmatically relevant will be selected in consultation with DOE and NASA selecting officials depending upon availability of funds in each agency's budget. In the course of the selection process, projects will be identified as addressing DOE requirements, NASA requirements, or both. If a project is funded, beginning in the first year of funding, at least one member of the project team will be required to attend annual investigator meetings, and reasonable travel expenses may be submitted as part of the project budget. The selected projects will be required to acknowledge support by one or both agencies, as appropriate, in all public communications of the research results.

The Application

(PLEASE NOTE INFORMATION BELOW ON PAGE LIMITS)

Adherence to type size and line spacing requirements is necessary for several reasons. No applicants should have the advantage of providing more text in their applications by using small type. Small type may also make it difficult for reviewers to read the application. Applications must have 1-inch margins at the top, bottom, and on each side. Type sizes must be 10 point or larger. Line spacing is at the discretion of the applicant but there must be no more than 6 lines per vertical inch of text. Pages should be standard 8 1/2" x 11" (or metric A4, i.e., 210 mm x 297 mm). Applications must be written in English, with all budgets in U.S. dollars.

Applicants are asked to use the following ordered format:

- **Face Page SF-424 (R&R)**
- **Title Page**; single page, title page of your narrative must include the following:
 - Applicant/Institution:
 - Street Address/City/State/Zip:
 - Principal Investigator:
 - Address:
 - Telephone Number:
 - Email:
 - DOE/Office of Science Program Office:
 - DOE/Office of Science Program Office Technical Contact:
 - DOE Grant Number (if Renewal or Supplemental Application):
 - Is this a Collaboration? If yes, please list ALL Collaborating Institutions/Pis* and indicate which ones will also be submitting applications. * Note that collaborating applications must be submitted separately.
- **Project Abstract Page**; single page only, should contain:
 - Title
 - PI name
 - Abstract text should concisely describe the overall project goal in one sentence, and limit background/significance of project to one sentence. Short descriptions of each individual aim should focus on what will actually be done.
- **Relevance Statement**; single page only, should identify DOE- or NASA-relevant research that each specific aim is intended to address
- **Budget pages** for each year and a summary budget page for the entire project period
- **Budget Explanation**
- Budget pages and budget explanation for each **collaborative subproject**, if any.
- **Project Narrative, 20 pages or less**, exclusive of attachments. Applications with Project Narratives longer than 20 pages will be returned to applicants and will not be reviewed for scientific merit. (**NOTE: Project Narratives for Glue Grants should not exceed 10 pages.**) The project narrative should be a clear statement of the work to be undertaken and should include: objectives for the period of the proposed work and expected significance; relation to the longer-term goals of the principal investigator of the project; and relation to the present state of knowledge in the field, to work in progress by the investigator under other support, and work in progress elsewhere. The statement should outline the general plan of work, including the broad design of experiments to be undertaken, and an adequate description of experimental methods and procedures.
- **Literature Cited**

- **Biographical Sketches** (please limit to 2 pages per senior investigator, consistent with NIH guidelines)
- **Facilities and Resources** description
- **Current and Pending Support** for each senior investigator
- **Letters of Intent** from collaborators (if applicable)

The Office of Science, as part of its grant regulations, requires at 10 CFR 605.11(b) that a recipient receiving a grant to perform research involving recombinant DNA molecules and/or organisms and viruses containing recombinant DNA molecules shall comply with the National Institutes of Health "Guidelines for Research Involving Recombinant DNA Molecules", which is available via the World Wide Web at: <http://www.niehs.nih.gov/odhsb/biosafe/nih/rdna-apr98.pdf>, (59 FR 34496, July 5, 1994), or such later revision of those guidelines as may be published in the Federal Register.

DOE policy requires that potential applicants adhere to 10 CFR 745 "Protection of Human Subjects" or such later revision of those guidelines as may be published in the Federal Register. DOE requirements for reporting, protection of human and animal subjects and related special matters can be found on the World Wide Web at: <http://www.science.doe.gov/grants/Welfare.html>.

The Catalog of Federal Domestic Assistance (CFDA) number for this program is 81.049, and the solicitation control number is ERFAP 10 CFR Part 605.

Martin Rubinstein
Director
Grants and Contracts Division
Office of Science

Posted on the Office of Science Grants and Contracts Web Site
January 31, 2006.