Office of Science
Financial Assistance
Funding Opportunity Announcement
DE-PS02-08ER08-20

Low Dose Radiation Research Program -Basic Biology and Modeling

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 risks to humans from exposures to low doses or low fluences of ionizing radiation. Research applications must primarily support the needs of the DOE/BER Low Dose Radiation Research Program; applications may also include complementary research of direct interest to the NASA/HRP Space Radiation Project of sufficient scientific merit to qualify for partial NASA support. Research must focus on elucidating molecular mechanisms and pathways involved in normal radiobiological responses to low dose exposure, and must have the potential to ultimately increase understanding of health outcomes from radiation exposures that are at or near current workplace exposure limits. New research that focuses on molecular and cellular responses within tissue- and higher levels of biological organization will receive higher priority. Experimental research of particular interest to this call includes radio-adaptive responses; systems genetics of inter-individual variation; low dose and/or low dose-rate effects on: a) proteomic responses, b) the immune system, c) epigenetic regulation, and d) molecular and cellular hallmarks of aging. The Programs are also interested in funding new mathematical/risk modeling projects that will incorporate the latest low dose and low dose-rate biological research into mechanism-based models of tissue function. 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 can make. **Please review the Supplementary Information sections below for further discussion of DOE and NASA programmatic needs.**

PREAPPLICATIONS

Potential applicants are strongly encouraged to submit a brief pre-application that consists of two pages of narrative describing the research objectives, the technical approach(s), and the proposed team members and their expertise. They should be sent by email to SClifesci.lowdose@science.doe.gov. A response will be communicated to the applicant within one week after receipt, encouraging or discouraging formal application. Applicants who have not received a response regarding the status of their pre-application within 7 days of submission should contact the Low Dose Program Contact immediately.

The intent in requesting a preapplication is to save the time and effort of applicants in preparing and submitting a formal project application that may be inappropriate for the program.

Preapplications will be reviewed relative to the scope and research needs as outlined in the summary paragraph and in the SUPPLEMENTARY INFORMATION. The preapplication should identify, on the cover sheet, the title of the project, the institution or organization, principal investigator name, telephone number, fax number, and e-mail address. No budget information or biographical data need be included, nor is an institutional endorsement necessary.

APPLICATION DUE DATE: June 25, 2008, 8:00 pm, Eastern Time

Applications must be submitted using Grants.gov, the Funding Opportunity Announcement can be found using the CFDA Number, 81.049 or the Funding Opportunity Announcement number, DE-PS02-08ER08-20. Applicants must follow the instructions and use the forms provided on Grants.gov.

GENERAL INQUIRIES ABOUT THIS NOTICE SHOULD BE DIRECTED TO:

Scientific/Technical Program Contact:

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SUPPLEMENTARY INFORMATION:

I. DOE Low Dose Radiation Research Program

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. Funded research must have the potential to ultimately increase understanding of health outcomes from radiation exposures that are at or near current workplace exposure limits. High risk research having the potential to rapidly advance the field is particularly encouraged. 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 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.

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. In general, research is desired that focuses on low Linear Energy Transfer (low LET) ionizing radiation (x- and gamma-rays; high-energy electrons and protons) exposures, and 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. In some cases, a biological response of interest seen only at high doses may actually be absent (as opposed to simply undetectable) at low doses of radiation; evidence is also accumulating that biological responses after low dose exposure are qualitatively different from responses after high dose exposure. Therefore, research aimed at defining the dose where the mechanisms of response shift (dose-series and time-series experiments) has high programmatic priority.

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 well known that viable biological systems have cellular and molecular surveillance mechanisms that can detect much less than a 1000-fold change in environmental conditions, including the case of radiation exposure. The radiobiological evidence from studies in various biological systems shows that low dose rate exposures often initiate adaptive, homeostatic responses. Research is sought to verify and further elucidate these responses in normal intact tissues.

The Low Dose Program is already making significant investments and progress in the important research areas of radiation-induced 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://www.lowdose.energy.gov/. 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.

Until 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. New research indicates that fundamentally different cellular and molecular responses can occur as a function of the level of biological organization (cells, tissues, or whole organisms), and that normal, intact tissue responds, in general, differently to radiation than does monoculture/monolayer cell populations. These observations are especially pronounced in the low dose range. Innovative new research is needed to explore and more fully understand low dose radiation-induced molecular and cellular responses, and subsequent health outcomes, within these higher levels of biological organization.

Experimental research of particular interest to this call includes the following:

1. **Radio-adaptive responses** - as they relate to significant health outcomes

2. **Systems genetics** - Inter-individual variation in radiation exposure outcomes may result from polymorphisms at multiple loci that can be identified via discovery genetics strategies.

3. **Low dose and/or low dose-rate effects** on:

a. ***Proteomic responses*** - Comparing proteomic response after low versus high dose exposures may provide information on underlying systemic processes.
b. ***The immune system and inflammation*** - Recent studies of experimental models of cancer underscore the absolute requirement for inflammatory and/or immune cell involvement. The effect of low dose exposure on these tissue interactions and their role in health outcomes is poorly understood.
c. ***Epigenetic regulation*** - There are epigenetic mechanisms by which radiation exposure causes an alteration of cell phenotype that persists. The signaling mechanisms establishing such epigenetic programs, and their contribution to health outcomes, are not well understood.
d. ***Molecular /cellular hallmarks of aging*** - Recent developments in the field of aging research have revealed cellular and molecular effects, the study of which may be important to the understanding of low dose radiation biology.

4. **Mathematical modeling** - Modeling is needed that incorporates the latest low dose and low dose rate biological research into mechanism-based systems biology models of tissue function. It may be a component of an experimental effort, or it may stand alone, but it should aim to include relevant research results across levels of biological organization that influence health effects at high versus low dose exposures.

Because the knowledge base of regulatory, metabolic, and signaling pathways is growing rapidly across all fields of biology, applications should point out, wherever possible, how the proposed radiobiological research might link with, clarify, and/or extend this information. Any data and results generated through funded investigations that are appropriate to share with the broader scientific community should, where possible, be provided in a format amenable to deposition in databases.

The Low Dose Program was established with the intention of supporting science that is useful to policy makers, standard setters, and the public. 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. Investigators will be expected to effectively communicate research results through publication in peer-reviewed journals. Investigators 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.

Finally, several tissue archives are available for Low Dose Program investigations. Fixed tissue samples from individual animals (rodent, canine) exposed to either external radiation or to internally-deposited radioactive materials are available for study. For information on these tissue archives, please contact Dr. Gayle Woloschak, Northwestern University; (312) 503-4322; g-woloschak@northwestern.edu.

II. 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 to studies that:

a. increase the confidence in the accuracy of extrapolating the probability of radiation-induced genetic alterations or carcinogenesis from rodents to humans;
b. reduce uncertainties in risk prediction for cancer following irradiation by protons and HZE particles;
c. provide data to develop risk projection models for central nervous system (CNS) and other degenerative tissue risks.

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.

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 $ 4 M per year for multiple years will be available for this Notice. The majority of the initial awards will be made in Fiscal Year 2009. All awards are contingent on the availability of funds and programmatic needs. Annual continuations are contingent upon the availability of appropriated funds, progress of the research, and continuing Program need. Funds for this research will come chiefly from the BER Low Dose Radiation Research Program; a portion of the available funds are from NASA for joint funding of new research, also contingent upon budget availability. 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 and NASA are under no obligation to pay for any costs associated with the preparation or submission of applications. DOE reserves the right to fund, in whole or in part, any, all, or none of the applications submitted in response to this Notice.

- **Post-doctoral applications:** Annual budgets for project applications are expected to range from $50,000 to $100,000 total costs. Applications may request project support for up to three years. Applicants must have prior permission from their supervisor and their research institution.
- **Senior Investigator applications:** Applicants may request project support for up to three years. Annual budgets for project applications are expected to range from $150,000 to $375,000 total costs.

Merit Review Criteria

Applications will be subjected to scientific merit review (peer review) and will be evaluated against the following evaluation criteria which are listed in descending order of importance 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; and
4. Reasonableness and Appropriateness of the Proposed Budget.

DOE and NASA will make final funding decisions based on the results of the peer review and internal programmatic review. NASA agrees to abide by DOE's application review procedures. Applicants selected for funding may be required to provide additional information. The evaluation process will include program policy factors such as the relevance of the proposed research to the terms of the announcement and the agencies' programmatic needs. Note that external peer reviewers are selected with regard to both their scientific expertise and the absence of conflict-of-interest issues. Both Federal and 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.

Posted on the Office of Science Grants and Contracts Web Site
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