

**Office of Science  
Financial Assistance  
Funding Opportunity Announcement  
DE-PS02-08ER08-21**

***Low Dose Radiation Research Program  
- Integrated Program Projects***

The Office of Biological and Environmental Research (BER) of the Office of Science (SC), U.S. Department of Energy (DOE) hereby announces its interest in receiving Integrated Program Project grant applications for new research to develop a better scientific basis for understanding risks to humans from exposures to low doses of ionizing radiation. This funding opportunity is designed to provide long-term support for stable, multi-investigator teams whose research projects are integrated to work synergistically on a focused problem in low dose research. The intent is to accelerate the discovery of critical molecular mechanisms and pathways involved in normal radiobiological responses to low dose exposure. Funded research must have the potential to ultimately increase understanding of human health outcomes from radiation exposures that are at or near current workplace exposure limits. **Please review the Supplementary Information sections below for further discussion of programmatic needs.**

**PREAPPLICATIONS**

Potential applicants are strongly encouraged to submit a preapplication that consists of up to four 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](mailto:SCLifesci.lowdose@science.doe.gov). A response will be communicated to the applicant within one week after receipt, encouraging or discouraging a formal application. Applicants who have not received a response regarding the status of their preapplication 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](http://Grants.gov), the Funding Opportunity Announcement can be found using the CFDA Number, 81.049 or the Funding Opportunity Announcement number,

DE-PS02-08ER08-21. 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:**

Dr. Noelle F Metting, Sc.D.  
U.S. Department of Energy  
Office of Biological and Environmental Research  
Phone: (301) 903-8309  
Email: noelle.metting@science.doe.gov

**SUPPLEMENTARY INFORMATION:**

The Integrated Program Projects solicitation is designed to provide long-term funding for stable, multi-investigator teams whose research projects work synergistically to elucidate a single area or problem in low dose research (see discussion of research needs, below). The Integrated Program Projects application should explain how each team member will contribute to, and benefit from, every other member within their team. Team members may have the same or different home laboratories, and should be senior-level investigators with complementary expertise. Each application should identify a responsible Principal Investigator or Director, who can devote at least 20% effort to the project. A management plan should be provided, describing how key decisions will be made and projects coordinated. The ideal Program Project will include senior-level radiation biologists and established scientists working in rapidly developing areas of biological sciences not necessarily associated with the study of radiation. However, every Program Project team must include one or more radiobiology experts.

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.

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 mechanistic responses 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/sites/entrez>, 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.

Research of particular interest to this call includes the following:

1. **Radio-adaptive responses** - as they relate to significant health outcomes
2. **Inter-individual variation** - Inter-individual variation in radiation exposure outcomes may result from polymorphisms at multiple loci that can be identified via discovery genetics strategies (systems genetics).
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.

**Applications that include a mathematical modeling component incorporating research results into mechanism-based systems biology models of tissue function will receive higher programmatic priority.** In addition to providing a modeling framework for results coming from their Integrated Program Project, this component should aim to include all relevant low dose and low dose rate biological research results available from the wider scientific community.

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.

### **Program Funding**

It is anticipated that up to three Integrated Program Project grants will be awarded in Fiscal Year 2009 from this Notice. Applications may include from two to five co-investigators, and may request up to five years of support, with annual budgets not to exceed \$1.5 M per year total costs. 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. DOE is 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.

## **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 will make final funding decisions based on the results of the peer review and internal programmatic review. 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  
April 3, 2008.