Office of Science
Notice 01-17

Low Dose Radiation Research Program – Pilot Modeling Projects

Department of Energy
Office of Science

Office of Science Financial Assistance Program Notice 01-17; Low Dose Radiation Research Program – Pilot Modeling Projects

Agency: U.S. Department of Energy

Action: Notice Inviting Grant Applications

SUMMARY: The Office of Biological and Environmental Research (OBER) of the Office of Science (SC), U.S. Department of Energy (DOE), hereby announces its interest in receiving applications for research that supports the Low Dose Radiation Research Program. Research is specifically sought for pilot projects that involve innovative collaborations between experimentalists and modelers to:

- model the mechanisms of key radiation-induced biological responses.
- to describe or identify strategies for developing biologically-based risk models that incorporate information on mechanisms of radiation-induced biological responses.

The Low Dose Radiation Research Program uses modern molecular tools to develop a better scientific basis for understanding exposures and risks to humans from low dose radiation that can be used to achieve acceptable levels of human health protection at a reasonable cost.

DATES: Potential applicants should submit a one page preapplication referencing Program Notice 01-17 by 4:30 P.M. E.S.T., February 1, 2001. Receipt of preapplications sent by e-mail will be acknowledged by a return message. An email response to preapplications discussing the potential program relevance of a formal application generally will be communicated by February 8, 2001.

The deadline for receipt of formal applications is 4:30 P.M., E.D.T., May 1, 2001, in order to be accepted for merit review and to permit timely consideration for award in FY 2001 and FY 2002.

ADDRESS: Preapplications referencing Program Notice 01-17, should be sent by E-mail to joanne.corcoran@science.doe.gov. Preapplications will also be accepted if mailed to the following address: Ms. Joanne Corcoran, Office of Biological and Environmental Research, SC-72, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290.

Formal applications, referencing Program Notice 01-17, should be sent to: U.S. Department of Energy, Office of Science, Grants and Contracts Division, SC-64, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Notice 01-17. This address also must be used when submitting applications by U.S. Postal Service Express, commercial mail delivery service, or when hand carried by the applicant.

FOR FURTHER INFORMATION CONTACT: Dr. David Thomassen, telephone: (301) 903- 9817, E-mail: david.thomassen@science.doe.gov, Office of Biological and Environmental Research, SC-72, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290. The full text of Program Notice 01-17 is available via the World Wide Web using the following web site address: http://www.sc.doe.gov/production/grants/grants.html.

SUPPLEMENTARY INFORMATION:

Low Dose Radiation Research Program

Background information on the Low Dose Radiation Research Program can be found in the research program plan at http://www.lowdose.org/index.html. A list of currently funded projects can be found at http://lowdose.org/research.html. A parallel request for research applications focused on understanding the biological responses to low doses of low LET ionizing radiation and on genetic factors influencing those responses will be issued (Office of Science Notice 01-18).

This research program is faced with the challenge of conducting research that can be used to inform the development of future radiation risk policy. 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.

Information on biological responses to low doses of radiation will most likely have an impact on radiation risk policy through its incorporation into biologically-based models for radiation risk. Two types of models will be important in efforts to incorporate results from current low dose radiation research into radiation risk policy: mechanistic models and biologically-based risk models.

Mechanistic models are defined as mathematical descriptions of the molecular and cellular processes involved in biological responses to radiation. One goal for these types of models will be to develop predictive capabilities for the range and nature of biological responses expected in a given system following exposure to different doses of radiation. The ability to extrapolate between different levels of biological organization (from molecules to cells to tissues to organisms) and from observations in vitro to biological responses in vivo should be improved by the development of such models.

Biologically-based risk models are defined as mathematical constructs of the key events involved in the production of an adverse health effect, e.g., cancer, in response to radiation across a range of doses of interest. Such models are likely to describe both continuous and probabilistic variables that range from key molecular probabilities of inducing cell death, replication or specific gene expression to modifiers of responses at the tissue level or even at the level of the entire organism. Mathematical predictors or estimators of radiation risk can include both epidemiological and experimental information. One likely source of input for the development and use of biologically-based risk models is mechanistic models for radiation-induced biological responses. For example, if a mechanistic model for the induction of a by-stander effect by low doses of radiation existed, information from that model could, in theory, serve as a direct source of information on an "effective radiation dose" in a biologically-based risk model.

Pilot Projects

Pilot, collaborative research projects are requested in one of two areas:

- Pilot projects to model the mechanisms of key radiation-induced biological responses.
- Pilot projects to describe or identify strategies for developing biologically-based risk models that incorporate information on mechanisms of radiation-induced biological responses.

Projects will involve research teams that include both laboratory-based scientists and scientists whose expertise is in the development or use of mathematical models. Projects can range from active research-modeling efforts to more "think tank" type efforts. Experimentalists and modelers are encouraged to interact in an iterative process of experimentation and modeling to generate and identify hypotheses, data and both experimental and modeling needs that then drive the "next steps" of both laboratory and modeling experiments. Alternatively, experimentalists and modelers could interact to identify research and modeling needs and gaps that are barriers to the development of true biologically-based risk models, to develop "what-if" type

scenarios describing how different types of biological data could and would be used in these models and to identify new modeling strategies that take into account a broader range of biological information on radiation responses.

Modeling mechanisms of key radiation-induced biological responses. Mechanistic models can and should be developed for a range of biological responses that meet the Criteria for Selection of Biological Responses described below. This portion of the program has two goals: (1) To develop models that have the potential to serve as links between data describing molecular and cellular responses to radiation and the use of that data in biologically-based risk models; and (2) To develop predictive capabilities for the range and nature of biological responses expected in a given system following exposure to different doses of radiation. It is expected that collaborations in this area will involve an iterative process of experimentation, modeling, experimentation, etc. Models of experimental data should be developed and used to make predictions about biological responses or effects that are then tested experimentally.

Description or identification of strategies to develop biologically-based risk models that incorporate information on mechanisms of radiation-induced biological responses. In many or most cases there may be such a wide gap between the nature of biological data and the state of risk models that it is premature, if not impossible, to begin incorporating biological data into these models. Research in this area will focus more on "think tank" types of activities to identify how information on biological responses to low doses of radiation could, conceptually, be incorporated into risk models. Investigators should use their knowledge of biology and modeling to develop realistic scenarios for the development of biologically-based risk models where neither current biological information nor modeling capabilities are adequate to actually develop these models. This research will follow a "what if" or "if only" type of approach where the use of theoretically obtainable but currently unavailable biological data is described for risk models that have not yet been developed. These pilot activities should have as their goal the identification of key experiments that would serve to verify key hypotheses that are generated or the preliminary design for incorporating these parameters into biologically-based risk models. Researchers might organize workshops to obtain some of the information needed to carry out their study. Pilots in this area will ordinarily be limited to 1-2 years. Successful or promising pilots will be eligible for additional funds to validate key hypotheses or to expand the scope of the research that was originally proposed. It is not the intent of this solicitation to fund the complete development of new biologically-based risk models that incorporate information on mechanisms of radiation-induced biological responses since it is our belief that it is premature to attempt to develop such models at this time.

Criteria for Selection of Biological Responses

It is our belief that the most useful research will focus on biological responses that meet each of the following criteria. The biological responses of greatest interest for this solicitation include bystander effects, induction of genetic instability and adaptive responses. Applications proposing the use of additional biological responses will be considered only if the biological responses proposed for investigation can be reasonably demonstrated to meet the criteria outlined below.

- Are known to be induced at low doses of radiation.
- Have the potential to increase or decrease the biological effects of radiation if they occur at low doses of radiation.
- Have the potential to directly impact, i.e., increase or decrease, the subsequent development of cancer or other harmful health impacts.
- Are potentially quantifiable.
- Could, potentially, be linked to the development of a biologically-based model for radiation risk.

Alternatively, a biological response of interest could meet all of the above criteria only at high doses but may actually not be induced (not simply undetectable) at low doses of radiation. Since the mechanisms of action may be different after high versus low doses of radiation, such studies would help define these mechanisms. Defining the unique doses where these mechanisms shift is important for comparing, understanding and modeling biological responses to high versus low doses of radiation.

Program Funding

It is anticipated that up to $750,000 will be available for new grant awards during FY 2001 and FY 2002, contingent upon the availability of funds. Multiple 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. It is expected that most awards will be from 1 to 3 years and will range from $100,000 to $250,000 per year (total costs).

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.

Preapplication

A preapplication should be submitted. The preapplication should contain a title, list of investigators, address, telephone, fax and E-mail address of the Principal Investigator, and no more than a one page summary of the proposed research, including project objectives and methods of accomplishment. Responses to the preapplications, encouraging or discouraging formal applications, will generally be communicated within 7 days of receipt. Notification of a successful preapplication is not an indication that an award will be made in response to the formal application.

Merit 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

(PLEASE NOTE CRITICAL INFORMATION BELOW ON PAGE LIMITS)

Information about the development and submission of applications, eligibility, limitations, evaluation, selection process, and other policies and procedures may be found in the Application Guide for the Office of Science Financial Assistance Program and 10 CFR Part 605. Electronic access to the Guide and required forms is made available via the World Wide Web at: http://www.er.doe.gov/production/grants/grants.html. 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 Project Description must be 25 pages or less, exclusive of attachments. Applications with Project Descriptions longer than 25 pages will be returned to

applicants and will not be reviewed. The application must contain an abstract or project summary, letters of intent from collaborators, and short curriculum vitaes consistent with NIH guidelines.

Adherence to type size and line spacing requirements is necessary for several reasons. No applicants should have the advantage, or by using small type, of providing more text in their applications. 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).

Applicants are expected to use the following ordered format to prepare applications in addition to following instructions in the Application Guide for the Office of Science Financial Assistance Program. Applications must be written in English, with all budgets in U.S. dollars.

- Face Page (DOE F 4650.2 (10-91)).
- Project Abstract (no more than one page).
- Budgets for each year and a summary budget page for the entire project period (using DOE F 4620.1).
- Budget Explanation.
- Budgets and Budget explanation for each collaborative subproject, if any.
- Project Description (The Project Description must be 25 pages or less, exclusive of attachments. Applications with Project Descriptions longer than 25 pages will be returned to applicants and will not be reviewed.)
- Goals
- Background
- Research Plan
- Preliminary Studies and progress (if applicable)
- Research Design and Methodologies
- Literature Cited
- Collaborative Arrangements (if applicable)
- Biographical Sketches (limit 2 pages per senior investigator)
- Description of Facilities and Resources
- Current and Pending Support for each senior investigator

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.

The Catalog of Federal Domestic Assistance Number for this program is 81.049, and the solicitation control number is ERFAP 10 CRF Part 605.

Ralph H. De Lorenzo
Acting Associate Director of Science
for Resource Management

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