

Program Announcement To DOE National Laboratories
LAB 01-17
*Low Dose Radiation Research Program - Pilot Modeling
Projects*

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 proposals 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.

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 proposals 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 Program Announcement LAB 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. Proposals 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.

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

The deadline for receipt of formal proposals 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: Preproposals referencing Program Announcement LAB 01-17, should be sent by E-mail to joanne.corcoran@science.doe.gov. Preproposals 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 proposals, referencing Program Announcement LAB 01-17, should be sent to: U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research, SC-72, SC-64, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Announcement LAB 01-17. This address also must be used when submitting proposals by U.S. Postal Service Express, commercial mail delivery service, or when hand carried by the proposer.

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.

Program Funding

It is anticipated that up to \$750,000 will be available for new awards during FY 2001 and FY 2002, contingent upon the availability of funds. Multiple year funding of 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

Proposers 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.

Preproposal

A preproposal should be submitted. The preproposal 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 preproposals, encouraging or discouraging formal proposals, will generally be communicated within 7 days of receipt. Notification of a successful preproposal is not an indication that an award will be made in response to the formal proposal.

Proposals

(PLEASE NOTE CRITICAL INFORMATION BELOW ON PAGE LIMITS)

DOE is under no obligation to pay for any costs associated with the preparation or submission of proposals if an award is not made.

The Project Description must be 25 pages or less, exclusive of attachments. **Proposals with Project Descriptions longer than 25 pages will be returned to proposer** and will not be reviewed. The proposal must contain an abstract or project summary, letters of intent from collaborators, and short curriculum vitae consistent with NIH guidelines.

Adherence to type size and line spacing requirements is necessary for several reasons. No proposers should have the advantage, or by using small type, of providing more text in their proposals. Small type may also make it difficult for reviewers to read the proposal. Proposals 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 proposer 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).

Proposers are expected to use the following ordered format to prepare proposals in addition to following instructions in the GUIDE FOR PREPARATION OF SCIENTIFIC/TECHNICAL PROPOSALS TO BE SUBMITTED BY NATIONAL LABORATORIES below. Proposals 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. Proposals with Project Descriptions longer than 25 pages will be returned to proposer 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

Any recipient of an award from the Office of Science, performing 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 instructions and format described below should be followed. Reference Program Announcement LAB 01-17 on all submissions and inquiries about this program.

OFFICE OF SCIENCE
GUIDE FOR PREPARATION OF SCIENTIFIC/TECHNICAL PROPOSALS
TO BE SUBMITTED BY NATIONAL LABORATORIES

Proposals from National Laboratories submitted to the Office of Science (SC) as a result of this program announcement will follow the Department of Energy Field Work Proposal process with additional information requested to allow for scientific/technical merit review. The following guidelines for content and format are intended to facilitate an understanding of the requirements necessary for SC to conduct a merit review of a proposal. Please follow the guidelines carefully, as deviations could be cause for declination of a proposal without merit review.

1. Evaluation Criteria

Proposals will be subjected to formal merit review (peer review) and will be evaluated against the following criteria which are listed in descending order of importance:

Scientific and/or technical merit of the project

Appropriateness of the proposed method or approach

Competency of the personnel and adequacy of the proposed resources

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, the uniqueness of the proposer's capabilities, and demonstrated usefulness of the research for proposals in other DOE Program Offices as evidenced by a history of programmatic support directly related to the proposed work.

2. Summary of Proposal Contents

Field Work Proposal (FWP) Format (Reference DOE Order 5700.7C) (DOE ONLY)

Proposal Cover Page

Table of Contents

Abstract

Narrative

Literature Cited

Budget and Budget Explanation

Other support of investigators

Biographical Sketches

Description of facilities and resources

Appendix

2.1 Number of Copies to Submit

An original and seven copies of the formal proposal/FWP must be submitted.

3. Detailed Contents of the Proposal

Proposals must be readily legible, when photocopied, and must conform to the following three requirements: the height of the letters must be no smaller than 10 point with at least 2 points of spacing between lines (leading); the type density must average no more than 17 characters per inch; the margins must be at least one-half inch on all sides. Figures, charts, tables, figure legends, etc., may include type smaller than these requirements so long as they are still fully legible.

3.1 Field Work Proposal Format (Reference DOE Order 5700.7C) (DOE ONLY)

The Field Work Proposal (FWP) is to be prepared and submitted consistent with policies of the investigator's laboratory and the local DOE Operations Office. Additional information is also requested to allow for scientific/technical merit review.

Laboratories may submit proposals directly to the SC Program office listed above. A copy should also be provided to the appropriate DOE operations office.

3.2 Proposal Cover Page

The following proposal cover page information may be placed on plain paper. No form is required.

Title of proposed project
SC Program announcement title
Name of laboratory
Name of principal investigator (PI)
Position title of PI
Mailing address of PI
Telephone of PI
Fax number of PI
Electronic mail address of PI
Name of official signing for laboratory*
Title of official
Fax number of official
Telephone of official
Electronic mail address of official
Requested funding for each year; total request
Use of human subjects in proposed project:
If activities involving human subjects are not planned at any time during the proposed project period, state "No"; otherwise state "Yes", provide the IRB Approval date and Assurance of Compliance Number and include all necessary information with the proposal should human subjects be involved.
Use of vertebrate animals in proposed project:
If activities involving vertebrate animals are not planned at any time during this project, state "No"; otherwise state "Yes" and provide the IACUC Approval date and Animal Welfare Assurance number from NIH and include all necessary information with the proposal.
Signature of PI, date of signature
Signature of official, date of signature*

*The signature certifies that personnel and facilities are available as stated in the proposal, if the project is funded.

3.3 Table of Contents

Provide the initial page number for each of the sections of the proposal. Number pages consecutively at the bottom of each page throughout the proposal. Start each

major section at the top of a new page. Do not use unnumbered pages and do not use suffices, such as 5a, 5b.

3.4 Abstract

Provide an abstract of no more than 250 words. Give the broad, long-term objectives and what the specific research proposed is intended to accomplish. State the hypotheses to be tested. Indicate how the proposed research addresses the SC scientific/technical area specifically described in this announcement.

3.5 Narrative

The narrative comprises the research plan for the project and is limited to 25 pages. It should contain the following subsections:

Background and Significance: Briefly sketch the background leading to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps which the project is intended to fill. State concisely the importance of the research described in the proposal. Explain the relevance of the project to the research needs identified by the Office of Science. Include references to relevant published literature, both to work of the investigators and to work done by other researchers.

Preliminary Studies: Use this section to provide an account of any preliminary studies that may be pertinent to the proposal. Include any other information that will help to establish the experience and competence of the investigators to pursue the proposed project. References to appropriate publications and manuscripts submitted or accepted for publication may be included.

Research Design and Methods: Describe the research design and the procedures to be used to accomplish the specific aims of the project. Describe new techniques and methodologies and explain the advantages over existing techniques and methodologies. As part of this section, provide a tentative sequence or timetable for the project.

Subcontract or Consortium Arrangements: If any portion of the project described under "Research Design and Methods" is to be done in collaboration with another institution, provide information on the institution and why it is to do the specific component of the project. Further information on any such arrangements is to be given in the sections "Budget and Budget Explanation", "Biographical Sketches", and "Description of Facilities and Resources".

3.6 Literature Cited

List all references cited in the narrative. Limit citations to current literature relevant to the proposed research. Information about each reference should be sufficient for it to be located by a reviewer of the proposal.

3.7 Budget and Budget Explanation

A detailed budget is required for the entire project period, which normally will be three years, and for each fiscal year. It is preferred that DOE's budget page, Form 4620.1 be used for providing budget information*. Modifications of categories are permissible to comply with institutional practices, for example with regard to overhead costs.

A written justification of each budget item is to follow the budget pages. For personnel this should take the form of a one-sentence statement of the role of the person in the project. Provide a detailed justification of the need for each item of permanent equipment. Explain each of the other direct costs in sufficient detail for reviewers to be able to judge the appropriateness of the amount requested.

Further instructions regarding the budget are given in section 4 of this guide.

* Form 4620.1 is available at web site:

<http://www.sc.doe.gov/production/grants/forms.html>

3.8 Other Support of Investigators

Other support is defined as all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors. Information on active and pending other support is required for all senior personnel, including investigators at collaborating institutions to be funded by a subcontract. For each item of other support, give the organization or agency, inclusive dates of the project or proposed project, annual funding, and level of effort devoted to the project.

3.9 Biographical Sketches

This information is required for senior personnel at the laboratory submitting the proposal and at all subcontracting institutions. The biographical sketch is limited to a maximum of two pages for each investigator.

3.10 Description of Facilities and Resources

Describe briefly the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe pertinent capabilities, including support facilities (such as machine shops) that will be used during the project. List the most important equipment items already available for the project and their pertinent capabilities. Include this information for each subcontracting institution, if any.

3.11 Appendix

Include collated sets of all appendix materials with each copy of the proposal. Do not use the appendix to circumvent the page limitations of the proposal. Information should be included that may not be easily accessible to a reviewer.

Reviewers are not required to consider information in the Appendix, only that in the body of the proposal. Reviewers may not have time to read extensive appendix materials with the same care as they will read the proposal proper.

The appendix may contain the following items: up to five publications, manuscripts (accepted for publication), abstracts, patents, or other printed materials directly relevant to this project, but not generally available to the scientific community; and letters from investigators at other institutions stating their agreement to participate in the project (do not include letters of endorsement of the project).

4. Detailed Instructions for the Budget

(DOE Form 4620.1 "Budget Page" may be used)

4.1 Salaries and Wages

List the names of the principal investigator and other key personnel and the estimated number of person-months for which DOE funding is requested. Proposers should list the number of postdoctoral associates and other professional positions included in the proposal and indicate the number of full-time-equivalent (FTE) person-months and rate of pay (hourly, monthly or annually). For graduate and undergraduate students and all other personnel categories such as secretarial, clerical, technical, etc., show the total number of people needed in each job title and total salaries needed. Salaries requested must be consistent with the institution's regular practices. The budget explanation should define concisely the role of each position in the overall project.

4.2 Equipment

DOE defines equipment as "an item of tangible personal property that has a useful life of more than two years and an acquisition cost of \$25,000 or more." Special purpose equipment means equipment which is used only for research, scientific or other

technical activities. Items of needed equipment should be individually listed by description and estimated cost, including tax, and adequately justified. Allowable items ordinarily will be limited to scientific equipment that is not already available for the conduct of the work. General purpose office equipment normally will not be considered eligible for support.

4.3 Domestic Travel

The type and extent of travel and its relation to the research should be specified. Funds may be requested for attendance at meetings and conferences, other travel associated with the work and subsistence. In order to qualify for support, attendance at meetings or conferences must enhance the investigator's capability to perform the research, plan extensions of it, or disseminate its results. Consultant's travel costs also may be requested.

4.4 Foreign Travel

Foreign travel is any travel outside Canada and the United States and its territories and possessions. Foreign travel may be approved only if it is directly related to project objectives.

4.5 Other Direct Costs

The budget should itemize other anticipated direct costs not included under the headings above, including materials and supplies, publication costs, computer services, and consultant services (which are discussed below). Other examples are: aircraft rental, space rental at research establishments away from the institution, minor building alterations, service charges, and fabrication of equipment or systems not available off-the-shelf. Reference books and periodicals may be charged to the project only if they are specifically related to the research.

a. Materials and Supplies

The budget should indicate in general terms the type of required expendable materials and supplies with their estimated costs. The breakdown should be more detailed when the cost is substantial.

b. Publication Costs/Page Charges

The budget may request funds for the costs of preparing and publishing the results of research, including costs of reports, reprints page charges, or other journal costs (except costs for prior or early publication), and necessary illustrations.

c. Consultant Services

Anticipated consultant services should be justified and information furnished on each individual's expertise, primary organizational affiliation, daily compensation rate and number of days expected service. Consultant's travel costs should be listed separately under travel in the budget.

d. Computer Services

The cost of computer services, including computer-based retrieval of scientific and technical information, may be requested. A justification based on the established computer service rates should be included.

e. Subcontracts

Subcontracts should be listed so that they can be properly evaluated. There should be an anticipated cost and an explanation of that cost for each subcontract. The total amount of each subcontract should also appear as a budget item.

4.6 Indirect Costs

Explain the basis for each overhead and indirect cost. Include the current rates.