

Program Announcement LAB 98-11
Cellular Biology Research Program
Mechanisms of Cellular Responses to Low Dose, Low Dose-rate Exposures

The Office of Biological and Environmental Research (OBER) of the Office of Energy Research (ER), U.S. Department of Energy (DOE), hereby announces its interest in receiving peer-reviewable proposals for research in support of the Cellular Biology Research Program. This Program is a coordinated multidisciplinary research effort to develop creative, innovative approaches that will provide a better scientific basis for understanding exposures and risks to humans associated with low level exposures to radiation and chemicals. Using modern molecular tools this research will provide information that will decrease the uncertainty of risk at low levels, help determine the shape of the dose-response relationships after low level exposure, and achieve acceptable levels of human health protection at the lowest possible cost.

Funding is available for research that uses broad, interdisciplinary approaches and that takes advantage of the unique resources and capabilities of the national laboratories to understand complex biological processes. Special consideration will be given to research that includes significant collaborations with other national laboratories and/or with university or industrial partners although a few outstanding single investigator initiated proposals will also be considered. Proposals should include a description of how the National Laboratory is uniquely suited to carry out the proposed research.

Current standards for occupational and residential exposures to radiation and chemicals are based on linear, no-threshold models of risk that drive regulatory decisions and estimations of cancer risk. Linear, no-threshold models assume that risk is always proportional to dose, that there is no risk only when there is no dose, and that even a single molecule or radiation induced ionization can cause cancer or disease. However, the scientific basis for these assumptions is limited and uncertain at very low doses and dose rates.

Much scientific evidence suggests that the risks from exposure to low doses or low dose rates of radiation and chemicals may be better described by a non-linear, dose-response relationship. This evidence includes long term human and animal studies and research at the cellular and molecular level on the DNA repair capabilities of cells and tissues, bystander' effects associated with low dose exposures, the effects of exposure-induced gene expression, the effects of a cell's micro environment on its response to low dose exposures, and studies of the multi-step nature of cancer development. A more definitive understanding of the biological responses induced by low dose, low

dose-rate exposures is needed to clarify the role played by these and other cell responses and capabilities in determining risk.

This research program will focus on understanding the mechanisms of molecular and cellular responses to low dose, low dose-rate exposures to radiation and chemicals to improve the scientific underpinning for estimating risks from these exposures. The program will include research to identify and characterize (1) the genes and gene products that determine and affect these cellular responses induced at low dose and dose-rates, (2) the role played by these genes and gene products in determining individual differences in susceptibility to low dose, low dose-rate exposures, and (3) methods to synthesize or model molecular level information on genes and gene products into overall health risk. The program will also communicate research results to regulators and legislators. The goal of this research program is the development of scientifically defensible tools and approaches for determining risk that are widely used, accepted, and understood.

Research is encouraged in a number of areas including, but not limited to:

- the effects of and reactions to reactive oxygen species at low doses and/or dose rates;
- the role of gene induction, DNA repair, apoptosis, and the immune system in mediating response to low dose and/or low dose-rate exposures;
- the nature and significance of bystander' effects in determining cell and tissue responses to low dose and/or low dose-rate exposures;
- the role of cell and tissue microenvironments in determining cell and tissue responses to low dose and/or low dose-rate exposures;
- development of computational techniques, e.g., algorithms and advanced mathematical approaches, for use in determining risk, that model new information from cellular and molecular studies together with available data from epidemiologic and animal studies.

DATES: Potential applicants are encouraged to submit a brief preproposal, consisting of a two to three page narrative describing the research project objectives and methods of accomplishment. Preproposals, referencing announcement LAB 98-11, should be sent by E-mail to: joanne.corcoran@oer.doe.gov no later than February 13, 1998. These will be reviewed relative to the scope and research needs of the DOE Cellular Biology Research Program. Telephone, telefax numbers, and Electronic mail addresses are required parts of the preproposals. A response to the preproposals will be provided by E-mail no later than February 19, 1998.

Formal proposals submitted in response to this notice must be received by 4:30 p.m., E.D.T., April 6, 1998, to be accepted for merit review and to permit timely

consideration for award beginning in Fiscal Year 1999. Formal proposals must be sent to: Ms. Joanne Corcoran, ER-72, Mail Stop F-237, Office of Biological and Environmental Research, Office of Energy Research, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, Attn: Announcement 98-11, this address must also be used when submitting by U.S. Postal Service Express Mail, any commercial mail delivery service, or when hand carried.

FOR FURTHER INFORMATION CONTACT: Dr. Susan Rose, telephone: (301) 903-4731 or Dr. David Thomassen, telephone: (301) 903-9817, Office of Biological and Environmental Research, ER-72, Office of Energy Research, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290..

It is anticipated that up to \$3.5 million will be available for awards during FY 1999, contingent upon the availability of funds.

A Lead Scientist will be selected from among all investigators who are successful in receiving research funds in this program. This research program will be directed by a program manager from OBER, who will be responsible for providing support and overall direction, including determining the relevance of the goals and objectives of the program. The Lead Scientist will provide scientific leadership to the community of the researchers in the research program. Proposers interested in being considered as a Lead Scientist for the low dose research program should indicate their interest in their research proposal. In addition to the information requested in the research proposal (see below), proposers should supplement their proposals by describing their qualifications to serve as a Lead Scientist for this program. The supplemental information should be provided as a separate appendix not attached to the main proposal. Interested proposers should demonstrate their understanding of the needs for and the uses of the types of scientific information likely to be developed in this research program. They should demonstrate their understanding of previous epidemiologic and experimental studies involving low dose, low dose-rate exposures to radiation or chemicals. Finally, interested proposers should demonstrate their knowledgeability of research opportunities and capabilities at National Laboratories, universities, and industry in the area of molecular and cellular responses to low dose, low dose-rate exposures.

Any recipient of an award from ER 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/nih97-1.html>, (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 announcement LAB 98-11 on all submissions and inquiries about this program.

**OFFICE OF ENERGY RESEARCH
GUIDE FOR PREPARATION OF SCIENTIFIC/TECHNICAL PROPOSALS
TO BE SUBMITTED BY NATIONAL LABORATORIES**

Proposals from national laboratories submitted to the Office of Energy Research (ER) as a result of this program announcement, will undergo scientific/technical merit review. The following guidelines for content and format are intended to facilitate an understanding of the requirements necessary for ER 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 applications 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 Cover Sheet (DOE ONLY)
- Face 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 12 point with at least 2 points of spacing between lines (leading); the type density must average no more than 17 characters per inch (the type in this paragraph meets the guidelines); 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 Cover Sheet (DOE ONLY)

The Field Work Proposal (FWP) Cover Sheet is to be prepared and submitted consistent with policies of the investigator's laboratory and the local DOE Operations Office.

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

3.2 Face Page

The face page is to include the following information.

Title of proposed project
ER 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.

3.4 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 ER 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 Energy Research. 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.er.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 \$5000 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.