

Office of Energy Research

Notice 98-11

Cellular Biology Research Program

Mechanisms of Cellular Responses to Low Dose, Low Dose-Rate Exposures

Department of Energy
Office of Energy Research

Energy Research Financial Assistance Program Notice 98-11; Cellular Biology Research Program - Mechanisms of Cellular Responses to Low Dose, Low Dose-Rate Exposures

AGENCY: U.S. Department of Energy (DOE)

ACTION: Notice inviting grant applications

SUMMARY: 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 applications for research for 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 be used to 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.

DATES: Potential applicants are encouraged to submit a brief preapplication. All preapplications, referencing Program Notice 98-11, should be received by DOE by 4:30 P.M. E.S.T., March 26, 1998. A response to the preapplications discussing the potential program relevance of a formal application generally will be communicated within 7 days of receipt.

The deadline for receipt of formal applications is 4:30 P.M., E.D.T., May 7, 1998, in order to be accepted for merit review and to permit timely consideration for award in FY 1999.

ADDRESS: Preapplications, referencing Program Notice 98-11, should be sent by E-mail to joanne.corcoran@oer.doe.gov, however, preapplications will also be accepted

if mailed to the following address: Ms. Joanne Corcoran, Office of Biological and Environmental Research, ER-72, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290.

Formal applications, referencing Program Notice 98-11, should be sent to: U.S. Department of Energy, Office of Energy Research, Grants and Contracts Division, ER-64, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Notice 98-11, Ms. Debbie Greenawalt. This address must be used when submitting applications by U.S. Postal Service Express, any commercial mail delivery service, or when hand carried by the applicant.

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, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290.

SUPPLEMENTARY INFORMATION: 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 responses 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.

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. Applicants interested in being considered as a Lead Scientist for the low dose research program should indicate their interest in their research application. In addition to the information requested in the Application Guide, applicants should supplement their applications 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 application. Interested applicants 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 applicants 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.

Program Funding

It is anticipated that up to \$1.5 million will be available for grant awards during FY 1998, contingent upon the availability of funds. An additional \$0.5 million may be available during FY 1999, contingent upon the availability of funds. Multiple year funding of grant awards is expected, and is also contingent upon the availability of funds. It is expected that most awards will be from one to three years and will range from \$200,000 to \$400,000 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 FFRDCs, including the DOE National Laboratories, where appropriate, and to incorporate cost sharing and/or consortia wherever feasible.

Collaborative research applications may be submitted in several ways:

(1) When multiple private sector or academic organizations intend to propose collaborative or joint research projects, the lead organization may submit a single application which includes another organization as a lower-tier participant (subaward) who will be responsible for a smaller portion of the overall project. If approved for funding, DOE may provide the total project funds to the lead organization who will provide funding to the other participant via a subcontract arrangement. The application should clearly describe the role to be played by each organization, specify the managerial arrangements and explain the advantages of the multi-organizational effort.

(2) Alternatively, multiple private sector or academic organizations who intend to propose collaborative or joint research projects may each prepare a portion of the application, then combine each portion into a single, integrated scientific application. A separate Face Page and Budget Pages must be included for each organization participating in the collaborative project. The joint application must be submitted to DOE as one package. If approved for funding, DOE will award a separate grant to each collaborating organization.

(3) Private sector or academic organizations who wish to form a collaborative project with a DOE FFRDC may not include the DOE FFRDC in their application as a lower-tier participant (subaward). Rather, each collaborator may prepare a portion of the proposal, then combine each portion into a single, integrated scientific proposal. The private sector or academic organization must include a Face Page and Budget Pages for its portion of the project. The FFRDC must include separate Budget Pages for its portion of the project. The joint proposal must be submitted to DOE as one package. If approved for funding, DOE will award a grant to the private sector or academic

organization. The FFRDC will be funded, through existing DOE contracts, from funds specifically designated for new FFRDC projects. DOE FFRDCs will not compete for funding already designated for private sector or academic organizations. Other Federal laboratories who wish to form collaborative projects may also follow guidelines outlined in this section.

Preapplications

A brief preapplication may be submitted. The preapplication should identify on the cover sheet the institution, Principal Investigator name, address, telephone, fax and E-mail address, title of the project, and the field of scientific research. The preapplication should consist of a two to three page narrative describing the research project objectives and methods of accomplishment. These will be reviewed relative to the scope and research needs of the DOE Cellular Biology Research Program.

Preapplications are strongly encouraged but not required prior to submission of a full application. Please note that notification of a successful preapplication is not an indication that an award will be made in response to the formal application.

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 an agency's programmatic needs. Note, 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.

Information about the development and submission of applications, eligibility, limitations, evaluation, selection process, and other policies and procedures may be found in 10 CFR Part 605, and in the Application Guide for the Office of Energy Research Financial Assistance Program. 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>. The Project Description must be 25 pages or less, exclusive of attachments. The application must contain an

abstract or project summary, letters of intent from collaborators, and short curriculum vitae consistent with NIH guidelines.

Energy Research, 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/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 Catalog of Federal Domestic Assistance Number for this program is 81.049, and the solicitation control number is ERFAP 10 CFR Part 605.

John Rodney Clark
Associate Director
for Resource Management
Office of Energy Research

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