

DEPARTMENT OF ENERGY

Office of Science Financial Assistance
Program Notice 03-20; Low Dose
Radiation Research Program—
Biologically-Based Risk Modeling

AGENCY: Department of Energy.

ACTION: Notice inviting 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 participation in a biologically-based risk modeling exercise, for the purposes of developing and evaluating different modeling/prediction strategies. Awardees will be asked to develop individual biologically-based models incorporating one or more phenomena such as adaptive response, bystander effects, genetic susceptibility, or genomic instability. A central aspect of this exercise will be the eventual modeling, by all awardees, of an artificially defined biological test system or archetype having a set of biological characteristics and radiation-induced endpoints for which exact probability values are either known or assigned. Please review the Supplementary Information and Application sections below for further details.

DATES: *Preapplications* (letters of intent) should be submitted by April 4, 2003. *Formal applications* are due 4:30 p.m. EDT, May 23, 2003, in order to be accepted for merit review and to permit timely consideration for award in Fiscal Year 2003.

ADDRESSES: *Preapplications* referencing Program Notice 03-20, should be sent to Ms. Joanne Corcoran by E-mail: joanne.corcoran@science.doe.gov, with a copy to Dr. Noelle Metting at: noelle.metting@science.doe.gov.

Formal applications referencing Program Notice 03-20 must be sent electronically by an authorized institutional business official through DOE's Industry Interactive Procurement System (IIPS) at: <http://e-center.doe.gov> (see also <http://www.sc.doe.gov/production/grants/grants.html>). IIPS provides for the posting of solicitations and receipt of applications in a paperless environment via the Internet. In order to submit applications through IIPS your business official will need to register at the IIPS website. The Office of Science will include attachments as part of this notice that provide the appropriate forms in PDF fillable format that are to be submitted through IIPS. Color images should be submitted in IIPS as a separate file in PDF format and identified as such. These images should

be kept to a minimum due to the limitations of reproducing them. They should be numbered and referred to in the body of the technical scientific application as Color image 1, Color image 2, etc. Questions regarding the operation of IIPS may be E-mailed to the IIPS Help Desk at:

HelpDesk@pr.doe.gov, or you may call the help desk at: (800) 683-0751. Further information on the use of IIPS by the Office of Science is available at: <http://www.sc.doe.gov/production/grants/grants.html>.

If you are unable to submit the application through IIPS, please contact the Grants and Contracts Division, Office of Science at: (301) 903-5212, in order to gain assistance for submission through IIPS or to receive special approval and instruction on how to submit printed applications.

FOR FURTHER INFORMATION CONTACT: Dr. Noelle Metting, telephone: (301) 903-8309, E-mail:

noelle.metting@science.doe.gov, Office of Biological and Environmental Research, U.S. Department of Energy, SC-72/Germantown Building, 1000 Independence Avenue, SW., Washington, DC 20585-1290.

SUPPLEMENTARY INFORMATION: The 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. The Program has focused on quantifying and understanding the mechanisms of molecular and cellular responses to low dose exposures to radiation, currently 0.1 Gy (10 rads) or less, with a view toward the lower doses. Most scientists in the field would agree that not enough is yet known about the biological consequences of low dose radiation exposure to be able to completely model human health risk. However, it is timely to begin to systematically evaluate different approaches for modeling the diversity of available information on the biological effects of low dose radiation exposure.

We define biologically-based risk models as mathematical constructs of the key biological 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 stochastic and deterministic variables that range from probabilities of inducing key molecular events such as cell death, replication or specific gene expression, to the description of responses at the tissue level or even at the level of the entire organism. Mathematical predictors or estimators of radiation risk

should ultimately be able to incorporate all available epidemiological and experimental information.

In this solicitation, applications are sought for participation in an interactive, biologically-based risk modeling exercise. The first activity for the awardees will be to participate in an initial Workshop for extensive discussions with experimental researchers and regulatory scientists. Awardees will then work to develop a biologically-based risk model that includes one or more characteristics important to low dose radiobiology.

Concurrently, awardees will participate in one or more workshops for the purpose of developing an artificially defined *biological archetype*. This biological archetype will become the core source of biological data, a biological test system for which exact probability values are either known or (temporarily) assigned. Quantitative information to be defined in the biological archetype will include definitions (specific probability values or ranges as a function of dose) for such attributes as:

- Amount of steady state endogenous DNA damage
- Yield of radiation-induced DNA damage (specific lesions)
- Efficiency of repair of radiation-induced DNA damage for specific lesions (repair capacity, saturation level, error rate)
- Radiation-induced gene expression
- Radiation-induced genomic instability
- Radiation-induced bystander effects (cell-cell communication)
- Radiation-induced adaptive responses
- Genetic susceptibility—for a population of individuals
- Current epidemiological information
- Etc...

The biological archetype will eventually be modeled by each funded awardee, for the ultimate purpose of comparing the different modeling/prediction strategies. Please note that the biological archetype will be a composite of what is presently established, supplemented where needed by best-guess, made-up data.

The long term goals of this exercise are the following: (1) To discover which mechanistic data are usable and which are the most critical inputs for development of biologically-based models to predict human health risks for low dose exposures (the exercise thus may help to define future experimental research needs); and (2) to provide new insight into how 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*.

Applicants should demonstrate knowledge of and expertise in risk modeling. They should discuss general strategies for, or demonstrate expertise in the use of, biological mechanistic data in the development of risk models. Ideally, the application should exhibit some familiarity with relevant radiation biology literature, but prior work in this field is not a prerequisite. *The Project Description must contain the following:*

1. A proposal to develop a biologically-based model taking account of one or more phenomena such as adaptive response, bystander effects, genetic susceptibility, or genomic instability. A hierarchical scheme may be proposed for developing a series of simple to complex biologically-based risk models that include successively higher numbers of biological parameters.

2. A discussion of model validation strategies, as well as a general discussion of error estimation strategies, should be included. (Of great importance will be the determination of how much error can be tolerated in each of the critical inputs.)

3. Briefly, the applicant's ideas on how one would begin to design a "biological archetype" that could be used to compare different models. (What type of biological archetype would be most useful at the present time—single cell, cell culture, tissue, mouse, man? In the future? Which characteristics of the biological archetype should be defined? Which characteristics are known at the present time?)

Information on the Low Dose Radiation Research Program can be found on the Web site: <http://lowdose.tricity.wsu.edu>.

Program Funding: It is anticipated that up to \$1,500,000 will be available for approximately 8 two-year awards, contingent upon the availability of funds. Each award will be no more than \$200,000, total costs per year. If the exercise is judged productive by administrative review, some or all awards may be extended an additional year.

Merit and Relevance 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.

The Application

(Please Note 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: <http://www.science.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.

Adherence to type size and line spacing requirements is necessary for several reasons. No applicants should have the advantage of providing more text in their applications by using small type. 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). Applications must be written in English, with all budgets in U.S. dollars.

Applicants are asked to use the following ordered format:

- Face Page (DOE F 4650.2 (10-91))
- Project Abstract Page; single page only, should contain title, PI name, and abstract text
- Budget page for the one year project period (using DOE F 4620.1)
- Budget Explanation

• Project Description; ten (10) pages or less. The application should contain the following:

a. A proposal to develop a biologically-based model taking account of one or more phenomena such as adaptive response, bystander effects, genetic susceptibility, or genomic instability.

b. A discussion of model validation strategies, as well as a general discussion of error estimation strategies, should be included.

c. Briefly, the applicant's ideas on how one would design a biological archetype that could be used to compare different models (approximately one page).

- Literature Cited
- Collaborative Arrangements (if applicable)
- Facilities and Resources
- Biographical Sketches
- Current and Pending Support
- Letters of Collaboration (if applicable)

The Office of Science, as part of its regulations, requires at 10 CFR 605.11(b) that a recipient receiving an award 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**.

DOE requirements for reporting, protection of human and animal subjects and related special matters can be found on the World Wide Web at: <http://www.science.doe.gov/production/grants/Welfare.html>.

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

Issued in Washington, DC on February 6, 2003.

John Rodney Clark,

Associate Director of Science for Resource Management.

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DEPARTMENT OF ENERGY

National Energy Technology Laboratory; Notice of Availability of a Financial Assistance Solicitation

AGENCY: National Energy Technology Laboratory, Department of Energy (DOE).