Office of Science
Notice 01-18

Low Dose Radiation Research Program
Basic Research

Department of Energy
Office of Science

Office of Science Financial Assistance Program Notice 01-18; Low Dose Radiation Research Program – Basic Research

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 their interest in receiving grant applications for research that supports the DOE/OBER Low Dose Radiation Research Program.

Research is sought by the DOE/OBER Low Dose Radiation Research Program for studies involving low LET radiation, in the following areas:

(1) Bystander effects
(2) Genomic instability
(3) Adaptive responses
(4) Endogenous oxidative damage versus low dose radiation-induced damage
(5) Genetic factors that affect individual susceptibility to low dose radiation

Applications for well-justified research in other areas (see Supplementary Information below) will also be accepted. These Programs use modern molecular tools to develop a better scientific basis for understanding exposures and risks to humans from low doses of low LET 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 01-18 by 4:30 P.M. E.S.T., February 15, 2001. Receipt of preapplications sent by email 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 22, 2001.

The deadline for receipt of formal applications is 4:30 P.M., E.D.T., May 15, 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 01-18, 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 01-18, 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 01-18. This address 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: For general 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.

SUPPLEMENTARY INFORMATION:

Description of Research Program Areas

The DOE/OBER Low Dose Radiation Research Program is faced with 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. For the present solicitation, DOE/OBER is chiefly concerned with very **low doses** of low LET radiation (x and gamma rays). There are three biological responses of specific interest for this solicitation that are most likely to meet the criteria outlined below. These include bystander effects, induction of genomic 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. <u>All applications focused on the characterization of specific biological responses, e.g., bystander effects, etc., should identify how the response of interest meets these criteria.</u> There is also considerable interest in determining whether these biological responses can be extended from studies in isolated cells to tissues or to more complex tissue-like systems. These responses are discussed here:

Bystander effects - *The biological response observed in cells that are not directly traversed by radiation but are neighbors of an irradiated cell.* Bystanders have been shown to respond with gene induction and/or production of potential genetic and carcinogenic changes. It is important for the DOE/OBER Low Dose program to determine if these so-called bystander effects can be induced by exposure to low LET (linear energy transfer) radiation delivered at low total doses or dose-rates. If such an effect is demonstrated and quantifiable, it could, potentially, increase estimates of risk from low dose radiation. This bystander effect, in essence, "amplifies" the biological effects (and the effective radiation dose) of a low dose exposure by effectively increasing the number of cells that experience adverse effects to a number greater than the number of cells directly exposed to radiation. Research is sought to:

- characterize the nature of bystander effects at low doses of low LET radiation
- determine the relationship between radiation dose and the bystander effects at low doses of low LET radiation
- quantify the induction and extent of the bystander effect at low doses of low LET radiation
- determine the mechanism of the low LET radiation-induced bystander effect

Genomic Instability - *The loss of genetic stability, a key event in the development of cancer, induced by radiation and expressed as genetic damage many cell divisions after the insult is administered.* Current evidence suggests that DNA repair and processing of radiation damage can lead to instability in the progeny of irradiated cells and that susceptibility to instability is under genetic control. However, there is virtually no information on the underlying mechanisms and how the processing of damage leads to instability in the progeny of irradiated cells several generations later. Further, while there has been considerable speculation about the role of such instability in radiation-induced cancer, its role in this process remains to be determined. Research is sought to:

- characterize the induction of genomic instability by low doses of low LET radiation
- determine the relationship between radiation dose and the induction of genomic instability by low doses of low LET radiation
- quantify the induction and extent of genomic instability induced by low doses of low LET radiation
- determine the mechanism for the induction of genomic instability by low LET radiation

Adaptive Response - *The ability of a low dose of radiation to induce cellular changes that perturb the level of subsequent radiation-induced or spontaneous damage.* If low doses of radiation regularly and predictably induce a protective response in cells to

subsequent low doses of radiation, or to spontaneous damage, this could have a substantial impact on estimates of adverse health risk from low dose radiation. The generality and the extent of this apparent adaptive response in cells irradiated with small doses of ionizing radiation needs to be quantified. Studies of the adaptive response typically focus on cellular responses to high "test" doses of radiation following low "priming" doses. However, this solicitation is mainly interested in studying the lower limits for test doses and endpoints that show adaptive response phenomenon. Research is sought to:

- characterize the adaptive response induced by low doses of low LET radiation
- determine the relationship between radiation dose and the adaptive response induced by low doses of low LET radiation
- quantify the induction and extent of the adaptive response induced by low doses of low LET radiation
- determine the mechanism for the induction of adaptive responses by low LET radiation

In addition to the three specific biological responses just described, the Program has great interest in understanding endogenous versus low dose radiation induced damage, and the mechanisms underlying individual genetic susceptibility to radiation damage.

Endogenous versus low dose radiation induced damage. A key element of this research program will continue to be the development of an understanding of the similarities and differences between endogenous oxidative damage and damage induced by low levels of ionizing radiation, as well as an understanding of the health risks from both. This information will underpin our interpretation of the biological effects of exposure to low doses of ionizing radiation. Although always needed, this information was not previously attainable because critical resources and technologies were not available. Today, technologies and resources such as those developed as part of the human genome program, e.g., coupled capillary electrophoresis and mass spectrometry systems and DNA sequence information, have the potential to detect and characterize small differences in damage induced by normal oxidative processes and low doses of radiation. A significant investment in technology development will be required to expand current capabilities for identifying and quantifying small amounts of oxidative or radiation induced damage. Radically new technologies are likely not needed but current technologies will need to be modified. Methodologies having high sensitivity as well as high signal-to-noise ratio will be critical in this effort.

A significant research effort will be required to characterize and quantify normal oxidative damage in cells and the incremental increases induced by low doses of ionizing radiation. Preference will be given to the formation of partnerships between laboratories involved in characterization and quantification of radiation and oxidative

damage and groups with expertise in or developing new technology to facilitate progress in both areas simultaneously. Although qualitative descriptions of differences and/or similarities between the types of damage induced under both conditions will be useful in the design and interpretation of experiments in other parts of the program, levels of damage induced by normal oxidative processes and incremental increases due to low dose radiation should be quantified.

Genetic factors that affect individual susceptibility to low dose radiation. The Low Dose Radiation Research Program is interested in determining if genetic differences exist making some individuals more sensitive to radiation-induced damage since these differences could result in sensitive individuals or sub-populations that are at increased risk for radiation-induced cancer. Research should focus on:

- identification of genes involved in the recognition, repair, and processing of damage induced by ionizing radiation
- determining the frequencies of polymorphisms in these genes in the population
- determining the biological significance of these polymorphisms with respect to cancer and radiation sensitivity.

Research in these areas will strongly complement ongoing initiatives at the National Institutes of Health (NIH). DOE/OBER staff will work with staff at the NIH to ensure that research in the Low Dose Radiation Research Program is complementary to and not duplicative of research funded by NIH programs.

The National Human Genome Research Institute (NHGRI) is funding research to identify common variants in the coding regions of the majority of human genes identified during the next five years with the goal of developing a catalog of all common variants. The NHGRI is also working to create a map of at least 100,000 single nucleotide polymorphisms (SNPs), the most common polymorphisms in the human genome representing single base-pair differences between two copies of the same gene. These SNPs will be a boon for mapping complex traits such as cancer, cancer susceptibility, and susceptibility to low dose radiation.

The National Institute of Environmental Health Science (NIEHS) is funding research as part of its Environmental Genome Project to understand the impact and interaction of environmental exposures on human disease. The NIEHS project includes efforts to understand genetic susceptibility to environmental agents that will allow more precise identification of the environmental agents that cause disease and the true risks of exposures. The principal focus of NIEHS research will be on chemicals, so the focus on radiation in the Low Dose Radiation Research Program is highly complementary. Initially, the Environmental Genome Project will focus on categories of genes including: xenobiotic metabolism and detoxification genes, hormone metabolic genes,

receptor genes, DNA repair genes, cell cycle genes, cell death control genes, genes mediating immune and inflammatory responses, genes mediating nutritional factors, genes involved in oxidative processes and genes for signal transduction systems.

Identification of potential susceptibility genes and polymorphisms in those genes is only the first (and perhaps the easiest) step in the program to characterize and understand genetic susceptibility. Determining the biological significance of these genetic polymorphisms with respect to cancer and radiation sensitivity is the ultimate goal and the more difficult task. The international human genome project, structural biology research, and the NHGRI and NIEHS efforts described above play important roles determining which polymorphisms are most likely to influence gene function. Population genetics and computational biology approaches will be required to estimate the potential impact on estimates of population and individual risk. Genetic epidemiology approaches will also be needed to relate specific polymorphisms and combinations of polymorphisms with cancer risk. Inbred mouse strains and other model organisms with well- characterized differences in susceptibility to radiation-induced cancer are also important tools for identifying significant polymorphisms. Direct assessment of the biological significance of candidate "susceptibility genes" can also be undertaken using animal models such as knockout and knock-in mice, mice with specific genes removed or added.

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.

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. It is our belief that the most useful research will focus on biological responses that:

- 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, and
- could potentially be linked to the development of a biologically based model for radiation risk (see DOE Office of Science Program Notice 01-17).

Alternatively, a biological response of interest could meet all of the above criteria only at high doses but may actually be absent (as opposed to 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.

The focus of research in the Low Dose Radiation Research Program should be on doses of low linear energy transfer (LET) radiation that are at or below current workplace exposure limits. In general, research in this program should focus *on total radiation doses that are less than or equal to 10 rads.* Some experiments will likely involve selected exposures to higher doses of radiation for comparisons with previous experiments or for determining the validity of extrapolation methods previously used to estimate the effects of low doses of radiation from observations made at high doses. Research that principally focuses on radiation doses greater than 10 rads, high LET radiation or non-ionizing radiation will not be considered without substantial justification.

The program is currently funding a number of projects to develop micro-irradiation devices capable of delivering low doses of low LET radiation to individual cells or to specific parts of individual cells. For links to currently funded "microbeam" projects see http://lowdose.org/99meeting/abstracts/tool.html – projects 26, 28, 29 and http://lowdose.org/99meeting/abstracts/response.html – project 3. Investigators are strongly encouraged to use these or similar tools, as appropriate, in the design and conduct of their research. Funds are available to assist in the collaborative use of these or comparable tools or, in some cases, to provide low-cost micro-irradiation devices to individual investigators.

Program Funding

It is anticipated that up to $4.0 million will be available from DOE/OBER 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 5 years and will range from $200,000 to $400,000 per year (total costs). Applications requesting more than 3 years of funding will need to clearly justify the benefits of the additional years of research to the goals of the low dose radiation research program. Please note that funds are available from DOE to assist in the collaborative use of certain microbeam irradiators.

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 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.

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.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.

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 scientifically reviewed.** The application must contain an abstract or project summary, letters of intent from collaborators, and short curriculum vitas 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 scientifically 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 CFR Part 605.

John Rodney Clark
Associate Director of Science
for Resource Management

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