Office of Science
Notice 02-15

Low Dose Radiation
Research Program - Basic Research

Department of Energy

Office of Science Financial Assistance Program Notice 02-15; 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) and the Office of Biological and Physical Research (OBPR), National Aeronautics and Space Administration (NASA), hereby announce their interest in receiving grant applications for well justified research that supports the DOE/OBER Low Dose Radiation Research Program, and that may include complementary research of direct interest to the NASA/OBPR Space Radiation Health Program that is of sufficient scientific merit to qualify for partial NASA support. These Programs use modern molecular tools to develop a better scientific basis for understanding exposures and risks to humans from low dose and low fluence radiation.

Research areas of particular programmatic interest include:

- Endogenous oxidative damage versus low dose radiation-induced damage
- Radio-adaptive responses
- Bystander effects
- Individual genetic susceptibility to low dose radiation exposure

Please review the Supplementary Information section below for further discussion of programmatic needs.

DATES: Preapplications (letters of intent) are strongly encouraged, but not mandatory. A response to preapplications discussing the potential program relevance of a formal application will be communicated within one week.

The deadline for receipt of formal applications is 4:30 P.M., E.D.T, April 16, 2002, in order to be accepted for merit review and to permit timely consideration for award in Fiscal Year 2002 and Fiscal Year 2003.

ADDRESSES: One-page preapplications referencing Program Notice 02-15, should be sent by E-mail to joanne.corcoran@science.doe.gov, or by facsimile transmission to (301) 903-8521. 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 02-15, 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 02-15. 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: Dr. Noelle Metting for general scientific or technical questions, telephone: (301) 903-8309, E-mail: noelle.metting@science.doe.gov, Office of Biological and Environmental Research, SC-72, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290. For specific information on NASA/OBPR interests, contact Dr. Walter Schimmerling, telephone: (202) 358-2205, E-mail: wschimmerling@hq.nasa.gov, NASA Headquarters, Mail Code UB, Washington, DC 20546-0001.

SUPPLEMENTARY INFORMATION: 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 Linear Energy Transfer (LET) radiation (electrons, x- and gamma-rays). The focus of research should be on doses of low linear energy transfer radiation that are at or near 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 projects utilizing the "systems biology" or "discovery science" approach, including the tools of comparative genomics and proteomics, are especially sought. Research projects that use experimental protocols or cell microenvironments that will lead to an understanding of radiobiological responses in intact human tissue are also strongly encouraged. This research program will be a success if the science it generates is useful to policy makers, standard setters, and the public. Successful applicants will be expected to effectively communicate research results whenever possible through education and outreach, so that current thinking and the public debate reflect sound science.

The NASA/OBPR Space Radiation Health Program is charged with providing input for the determination of health risks to humans visiting the space radiation environment. NASA is especially interested in human exposure to low fluences of high-energy particulate ionizing radiation (protons and heavy ions). Where possible, projects that address the interests of both DOE/OBER and NASA/OBPR are particularly encouraged. Applications whose principal focus is on low LET radiation are encouraged to include complementary research with high-energy particulate ionizing radiation that leverages progress, resources, and technology used for the low

LET radiation research (see Specifics for NASA below). Investigators with currently funded low dose projects may also apply for supplementary funding to address closely related research of interest to NASA.

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. In the present context, the research considered to be most useful will focus on biological responses that:

- Are known to be induced at low doses of radiation,
- Have the potential to directly impact (i.e., increase or decrease) 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, and
- Could potentially lead to the development of biological predictors (biomarkers) of individual risk.

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, and delimiting the unique doses where these mechanisms shift is important.

Endogenous oxidative damage in relation to low dose radiation induced damage - A key goal of this research program will remain the elucidation of similarities and differences between endogenous oxidative damage and damage induced by low levels of ionizing radiation, as well as understanding the health risks from both. This information will underpin our interpretation of the biological effects of exposure to low doses of ionizing radiation. 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, there is a need for quantification of the levels of damage induced by normal oxidative processes and incremental increases due to low dose irradiation.

Living organisms are subject to a daily plethora of environmental insults. Carcinogenesis in an individual occurs as a function of all the forces and phenomena that go into the production of that individual's phenotype. These include (but are not limited to) individual genotype, as well as current and historical aspects of diet, physical exercise, and exposures to chemicals and radiation. To understand all factors responsible for individual responses to radiation, we are also soliciting research on key factors that influence the extent of metabolic, endogenously produced oxidative damage and, concomitantly, affect susceptibility to low doses of radiation.

Radio-Adaptive Response - The ability of a low dose of radiation to induce cellular changes that alter the level of subsequent radiation-induced or spontaneous damage. If low doses of radiation regularly and predictably induce a protective response in cells exposed 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 the process of the induction itself need to be quantified, and the responsible genes and proteins discovered. By "generality" is meant quantification as a function of cell tissue type and species type; by "extent" is meant quantification as a function of priming dose, dose rate, and time constant of action.

Bystander effects - Biological responses observed in cells that are not directly traversed by radiation but are neighbors of an irradiated cell. Bystanders in cell monolayers have been shown to respond with gene induction and/or production of clastogenic changes. It is important for the DOE/OBER Low Dose program to determine if bystander effects can be induced by exposure to low LET radiation delivered at low total doses. A detrimental 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. Conversely, bystander cells may in some cases exert a protective effect on the irradiated cell or cells, although very few studies of this type of effect have been tried. More importantly, entirely different types or levels of bystander effects may be occurring in three-dimensional tissues and intact organisms. Hence, there is considerable interest in extending studies to tissues, or at least toward more complex tissue-like models, and priority consideration will be given to these projects. Research is sought to characterize and determine mechanisms of low LET radiation induced bystander effect, and to quantify its induction and extent as a function of dose. New research projects studying bystander effects in isolated cells or cell monolayers will be considered only in exceptionally well-justified or novel approach cases.

Individual genetic susceptibility to low dose radiation - The Low Dose Radiation Research Program is interested in determining if genetic differences exist that result in sensitive individuals or sub-populations that are at increased risk for radiation-induced cancer. For example, research could focus on genes involved in the recognition, repair, and processing of damage induced by ionizing radiation, or on genes involved in maintaining the normal degree of irreversibility of cell differentiation for a particular tissue. Of critical interest would be the identification of these genes, determining frequencies of their polymorphisms in the population, and determining the biological significance of these polymorphisms with respect to cancer and radiation sensitivity. Ingenious, high throughput approaches, that evaluate many endpoints or individuals experimentally using pooling schemes, are of particular interest. We are also interested in mouse models that speed the discovery or characterization of putative human susceptibility genes. New studies focused only on a single or a few genes will not be funded unless substantial evidence is provided that those genes play a significant role in individual susceptibility to radiation. A long-term goal is to identify any genetic polymorphisms that significantly impact individual and population-level sensitivity to radiation, and characterize their mechanism of action.

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. 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 also: http://lowdose.org/99meeting/abstracts/response.html – project 3. Investigators are encouraged to use these or similar irradiators, as appropriate, in the design and conduct of their research. Funds are available to assist in the collaborative use of these or comparable tools.

Other resource considerations - Research in the areas discussed above will strongly complement ongoing initiatives at the National Institutes of Health (NIH). DOE/OBER staff is working with staff at the NIH to ensure that research in the Low Dose Radiation Research Program is not duplicative of research funded by NIH programs.

A collaborative effort of five major centers, termed the International SNP Map Working Group, along with over 50 other contributing laboratories, are creating the largest publicly available catalog of single base-pair differences between two copies of the same gene (single nucleotide polymorphisms, or SNPs). The current catalog contains 1.4 million SNPs, each with their exact location mapped within the human genome. SNPs are the most common polymorphisms in the human genome, and some contribute to the traits that make us unique individuals. The catalog (http://www.ncbi.nlm.nih.gov/SNP/index.html) will be a boon for mapping complex traits such as cancer susceptibility and susceptibility to low dose radiation.

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.

Specifics for the Space Radiation Health Program - NASA

The primary area of emphasis of the NASA/OBPR Space Radiation Health Program is the development of mechanistic insights into biological effects of space radiation that account for radiation risks. Applications are required to be hypothesis-driven and are expected to obtain their data in ground-based experimental radiobiology studies with protons and high-energy heavy ion beams in the energy range corresponding to space radiation. This is mainly a ground-based program using accelerator facilities to simulate space radiation. In addition to the research topics already described above this includes research on non-phenomenological predictors of late cell and tissue effects and the control and modification of radiation effect mechanisms

A short description of the current Space Radiation Health Strategic Program may be found at: http://spaceresearch.nasa.gov/common/docs/1998_radiation_strat_plan.pdf. Activities of OBPR, including research opportunities, descriptions of previous tasks, and other relevant information can be found at: http://SpaceResearch.nasa.gov/. A description of the ground-based facilities and experimental program at Brookhaven National Laboratory can be found at: http://www.bnl.gov/medical/NASA/NASA-home%20frame.htm. The proton therapy facilities at Loma Linda University Medical Center are described at: http://www.llu.edu/proton/. Finally, a description of the NASA Specialized Center of Research and Training at the Lawrence Berkeley National Laboratory may be found at: http://www.lbl.gov/lifesciences/NSCORT.

Scientists working in rapidly developing areas of biological sciences not necessarily associated with the study of radiation are particularly encouraged to consider the contributions that their field of study can make to Radiation Health. Applications are required to provide evidence for expertise in radiation, either by reference to the Principal Investigator's work or by inclusion of active collaborators expert in radiation research. Hypotheses should be substantiated by presentation of preliminary data wherever feasible, or by adequate references to the published literature. Experimental applications should include a clear discussion of the relevant aspects of the required radiation dosimetry and an estimate of the statistical power of the expected results.

Research applications to which NASA will assign high priority:

a. Studies that increase the confidence in the accuracy of extrapolating the probability of radiation-induced genetic alterations or carcinogenesis from rodents to humans.
b. Determination of carcinogenic risks following irradiation by protons and HZE particles.
c. Determination if exposure to heavy ions at the level that would occur in deep space poses a risk to the integrity and function of the central nervous system.
d. Studies likely to result in the development of biological countermeasures in humans that could lead to prevention or intervention (including genetic or pharmacological agents) against effects of radiation damage in space.

Research that can lead to future space flight investigations will be welcome, and should take into account the impact of gender, age, nutrition, stress, genetic predisposition, or sensitivity to other factors of importance in managing space radiation risks.

NASA envisions that the selected applications will be structured and operated in a manner that supports the country's educational initiatives and goals (including historically black colleges and universities and other minority universities), and in particular the need to promote scientific and technical education at all levels. NASA envisions that the selected applications will support the goals for public awareness and outreach to the general public. The selected investigators are invited to participate in NASA-funded educational programs.

The applications represent an opportunity to enhance and broaden the public's understanding and appreciation of radiation effects, as specified in the DOE Low Dose Program emphasis on communication of research results and the OBPR Policy for Education and Public Outreach. Therefore, all investigators are strongly encouraged to promote general scientific literacy and public understanding of radiation induced health risk research through formal and/or informal education opportunities. If appropriate, applications should include a clear and concise description of the education and outreach activities proposed. Examples include such items as involvement of students in the research activities, technology transfer plans, public information programs that will inform the general public of the benefits being gained from the research, and/or plans for incorporation of scientific results obtained into educational curricula consistent with educational standards.

Where appropriate, the supported institution will be required to produce, in collaboration with NASA, a plan for communicating to the public the value and importance of their work.

The particles of interest to the Space Radiation Health Program are protons with energies between 20 and 1000 MeV, and nuclei of He, C, N, O, Ne, Si, Ar, Ca, Mn, and Fe, with energies between 50 and 3000 MeV/nucleon. Fluencies of interest are of the order of 1-2 particles per cell; studies with higher fluencies will need to be justified by compelling arguments, including an explanation of how the results can be applied in the low fluency regime. NASA has developed facilities for use of protons at Loma Linda University Medical School and high- energy heavy ion beams at the Brookhaven National Laboratory Alternating Gradient Synchrotron (AGS). A dedicated irradiation facility, using the Booster Synchrotron at Brookhaven, is under construction and is expected to be operational in 2003. Applications should not budget for the use of beams at these facilities, which is paid by NASA. NASA will cooperate with DOE to expand the range of technical resources available for experimentation and analysis of experimental results at Brookhaven.

Program Funding

It is anticipated that up to $2.5 million will be available from DOE/OBER for new grant awards during Fiscal Year 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. Applications whose principal focus is on low LET radiation can include complementary research on high-energy particulate ionizing radiation that leverages progress, resources and technology used for the low LET radiation research. Up to $0.5M will be available from NASA in the first year, with higher amounts projected for successive years, also contingent upon the availability of funds. Funds will be available from DOE to assist in the collaborative use of certain microbeam irradiators. NASA provides beam time at the Brookhaven AGS and the Loma Linda proton accelerator; investigators will not be required to pay for the beam time. It is expected that most awards will be from 1 to 3 years and will range from $200,000 to $500,000 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 Federally Funded Research and Development Centers (FFRDCs), including the DOE National Laboratories, where appropriate, and to incorporate cost sharing and/or consortia wherever feasible.

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 found to be scientifically meritorious and programmatically relevant will be selected in consultation with DOE and NASA selecting officials depending upon availability of funds in each agency's budget. In the course of the selection process, projects will be identified as addressing DOE requirements, NASA requirements, or both. The selected projects will be required to acknowledge support by one or both agencies, as appropriate, in all public communications of the research results.

The Application

(PLEASE NOTE CRITICAL NEW 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/guide.html. In particular, please note the instructions on Collaboration available via the World Wide Web: http://www.science.doe.gov/production/grants/Colab.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 expected to use the following ordered format, in addition to following instructions in the Application Guide for the Office of Science Financial Assistance Program.

Face Page (DOE F 4650.2 (10-91))

- **Project Abstract Page** - Single page only, should contain:
  - Title
  - PI name
  - Abstract text should concisely describe the overall project goal in one sentence, and limit background/significance of project to one sentence. Short descriptions of each individual aim should focus on what will actually be done
- **Relevance Statement** - Single page only, should identify DOE or NASA requirements that each specific aim is intended to address

- **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 (again, see information at: http://www.science.doe.gov/production/grants/Colab.html)
- **Project Description** - (The Project Description must be 20 pages or less, exclusive of attachments. **Applications with Project Descriptions longer than 20 pages will be returned to applicants and will not be reviewed for scientific merit.**) The Project Description should contain the following five parts:
    - Goals
    - Background (concisely-stated, relevant)
    - Experimental Approach
    - Preliminary Studies (and Progress, if applicable)
    - Statistical Design and Methodologies
- **Literature Cited**
- **Collaborative Arrangements** (if applicable)
- **Biographical Sketches** (limit 2 pages per senior investigator, consistent with NIH guidelines)
- **Facilities and Resources** description
- **Current and Pending Support** for each senior investigator
- **Letters of Intent** from collaborators (if applicable)

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.

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.

John Rodney Clark
Associate Director of Science
for Resource Management

Published in the Federal Register February 4, 2002, Volume 67, Number 23, Pages 5091-5095.