Office of Science
Notice 03-07

Low Dose Radiation
Research Program - Basic Research

Department of Energy

Office of Science Financial Assistance Program Notice 03-07; 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 new research to develop a better scientific basis for understanding exposures and risks to humans from low dose and low fluence radiation. Topics of high priority include endogenous oxidative damage versus low dose radiation-induced damage, radio-adaptive responses, bystander effects, and individual genetic susceptibility to low dose radiation exposure. Research should employ genome-wide or proteome-wide high-throughput screening methods whenever possible, and priority will also be given to the use of three-dimensional biological models. Research should support the DOE/OBER Low Dose Radiation Research Program, and may include complementary research of direct interest to the NASA/OBPR Space Radiation Health Program of sufficient scientific merit to qualify for partial NASA support. Please review the Supplementary Information section below for further discussion of programmatic needs.

The Office of Biological and Environmental Research of the Office of Science, U.S. Department of Energy also announces its interest in receiving smaller applications for grants to support collaborative work between two or more laboratories, one or more of which should be funded to do low dose-related research. Please review the Supplementary Information section on Glue Grants, below, for further details.

In addition, we anticipate a separate request for modeling projects in the near future.

DATES: Preapplications (letters of intent), including information on collaborators, areas of research, and a one-page summary of the proposed research, should be submitted by **December 6, 2002**.

Formal applications submitted in response to this notice must be received by 4:30 p.m., E.S.T., **Thursday, February 27, 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 03-07, 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 in response to this solicitation are to be electronically submitted by an authorized institutional business official through DOE's Industry Interactive Procurement System (IIPS) at: http://e-center.doe.gov/. 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. The full text of Program Notice 03-07 is available via the Internet using the following web site address: http://www.sc.doe.gov/production/grants/grants.html.

If you are unable to submit an 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 instructions 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. 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

1) Specifics for the Low Dose Radiation Research Program (DOE)

The DOE/OBER 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. 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 LET 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. 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 through publication in peer-reviewed journals. They will also be encouraged to communicate with the wider community of concerned persons, so that current thinking and the public debate is better able to reflect sound science.

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.

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 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 evidence is accumulating that the mechanisms of action are different after high versus low doses of radiation, such studies would help define these mechanisms. Defining the doses where these mechanisms shift is of critical importance.

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 extent of the induction process need to be quantified, and the responsible genes and proteins discovered. By "generality" is meant its applicability to different cell tissue types and species; by "extent" is meant quantification over a range of priming doses, dose rates, and time constants of action.

Bystander effects *- Biological responses observed in cells that are not directly traversed by radiation but are neighbors of an irradiated cell.* 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. Bystanders in cell monolayers have already been shown to respond with gene induction and/or production of clastogenic changes. 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 exert a protective effect on the irradiated cell or cells, although very few studies to detect this effect have been tried. More importantly, entirely different types or levels of bystander effects may be occurring in three-dimensional tissues, organs, and intact organisms. Hence, only those applications that address effects in tissues, or in tissue-like models, will be considered for funding. New research projects studying bystander effects in isolated cells or cell monolayers will not be considered.

Because applications to study bystander effects are limited to three-dimensional biological models, investigators are also encouraged to propose novel bioimaging protocols for the purpose of in situ quantification.

The DOE Low Dose Program is currently funding several 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. Investigators are encouraged to use these irradiators, as appropriate, through collaborative means, and funds are available to assist in the collaborative use of these or comparable tools. Information on the microbeam irradiators can be found at: http://lowdose.tricity.wsu.edu.

Individual genetic susceptibility to low dose radiation. The Low Dose Radiation Research Program is interested in determining if genetic differences exist that result in increased risk for radiation-induced cancer in sensitive individuals or sub-populations. It may prove to be of value to address the three previously discussed research areas of interest (endogenous damage, radio-adaptive responses, and bystander effects) from the standpoint of genetic susceptibility. A major goal for this solicitation is to support additional work that seeks to identify patterns of genetic polymorphisms significantly impacting radiation sensitivity or resistance and characterizes their mechanism of action. Research should employ genome-wide or proteome-wide high-throughput

screening methods that have a chance of ultimately detecting complex, multi-gene patterns indicative of or related to susceptibility. New studies focused only on a single or even a few hundred genes will not be funded.

A new resource that is now available to all Low Dose Program investigators, but might be of particular interest to those proposing research in the area of genetic susceptibility, is a tissue repository containing cells from patients who developed second cancers following total body irradiation and hematopoietic stem cell transplantation (HSCT). Presently there are EBV-transformed cell lines from 25 individuals exposed to radiation who subsequently developed a skin tumor, and an equal number from exposed individuals that have not yet developed a second cancer. A much larger tissue resource will be available in the future. Please contact directly Dr. Jeffrey L. Schwartz, Associate Professor of Radiation Oncology, University of Washington, (206) 598-4091, E-mail: jschwart@u.washington.edu, for collaborative opportunities.

General information resources. Information on the Low Dose Radiation Research Program can be found on the web site: http://lowdose.tricity.wsu.edu. Prospective proposers are also encouraged to visit the National Center for Biotechnology Information (NCBI) website: http://www.ncbi.nlm.nih.gov/, for information on techniques and resources, and especially its Science Primer web site: http://www.ncbi.nlm.nih.gov/About/primer/snps.html, for an introduction to single nucleotide polymorphisms (SNPs).

2) Specifics for the Space Radiation Health Program (NASA)

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). 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. Investigators with currently funded low dose projects may also apply for supplementary funding to address closely related research of interest to 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%20Page.htm. The proton therapy facilities at Loma Linda University Medical Center are described at: http://www.llu.edu/llu/ci/nasa/. 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. Fluences of interest are of the order of 1-2 particles per cell; studies with higher fluences will need to be justified by compelling arguments, including an explanation of how the results can be applied in the low fluence 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.

3) Specifics for Glue Grants

The Low Dose Radiation Research Program also announces its interest in receiving applications for the purpose of supporting collaborative work between two or more laboratories, one or more of which should be funded to do low dose-related research. These small grants are primarily designed to support post-doctoral or graduate-student research that will enable laboratories with complementary expertise to develop and apply innovative new approaches to low dose research. Comparative studies between laboratories already using similar experimental approaches are also encouraged. At least one of the applicants must hold a grant focusing on low dose issues. All applicants must have at least 1 year (and preferably 2 years) of support remaining on their core grants at the time of award. Collaborative glue grants can be set up between laboratories funded by such diverse agencies as DOE, NIH/NCI, NASA, DOD, EPA, the European Union, Canada, France, and Japan, but in any case preference will be given to proposed research that is of interest to the DOE Low Dose Radiation Research Program. The proposed collaborative research should add a new dimension or approach to at least one of the studies it is linking. Applications for these small grants must follow the instructions in IIPS for electronic submission. **Please note: the Project Description should not exceed five pages.**

Program Funding

It is anticipated that up to $4 million will be available from DOE/OBER for new basic research awards during FY 2003, 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. Up to ten 3-year Glue Grants may be awarded, each averaging $60,000 total costs per year. Up to $0.5M will be available from NASA for joint funding of new research in Fiscal Year 2003, 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 $100,000 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. Additional information on collaboration is available in the Application Guide for the Office of Science Financial Assistance Program that is available via the Internet at: http://www.sc.doe.gov/production/grants/Colab.html.

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 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. 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
    - 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-relevant research that each specific aim is intended to address
- **Budget pages** for each year and a summary budget page for the entire project period (using DOE F 4620.1)
- **Budget Explanation**
- Budget pages and budget explanation for each **collaborative subproject**, if any.
- **Project Description, 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. **(Project Descriptions for Glue Grants should not exceed 5 pages.)** The Project Description should contain the following five parts:
    - Goals
    - Background (concisely-stated, relevant)
    - Experimental Approach
    - Preliminary Studies (or Progress, if this is a renewal application)
    - 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

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