Low Dose Radiation Research Program - Basic Biology and Modeling

(based on the solicitation posted on the Office of Science Grants and Contracts Web Site April 3, 2008)

The Office of Biological and Environmental Research (BER) of the Office of Science (SC), U.S. Department of Energy (DOE) and the Human Research Program (HRP), National Aeronautics and Space Administration (NASA), jointly fund new research to develop a better scientific basis for understanding risks to humans from exposures to low doses or low fluences of ionizing radiation. Research must focus on elucidating molecular mechanisms and pathways involved in normal radiobiological responses to low dose exposure, and must have the potential to ultimately increase understanding of health outcomes from radiation exposures that are at or near current workplace exposure limits. Support emphasizes research that focuses on molecular and cellular responses within tissue- and higher levels of biological organization. Experimental research of particular interest in past solicitations includes radio-adaptive responses; systems genetics of inter-individual variation; low dose and/or low dose-rate effects on: a) proteomic responses, b) the immune system, c) epigenetic regulation, and d) molecular and cellular hallmarks of aging. The Programs are also interested in new mathematical/risk modeling projects that incorporate the latest low dose and low dose-rate biological research into mechanism-based models of tissue function. The following link leads to the DOE grant information site: http://www.sc.doe.gov/grants/. Further descriptions of the Low Dose Program may be found at this DOE site: http://www.sc.doe.gov/ober/BSSD/lowdose.html.

I. Specifics for the DOE Low Dose Radiation Research Program

The DOE/BER 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. Funded research must have the potential to ultimately increase understanding of health outcomes from radiation exposures that are at or near current workplace exposure limits. High risk research having the potential to rapidly advance the field is particularly encouraged. Scientists working in rapidly developing areas of biological sciences not necessarily associated with the study of radiation are also encouraged to consider the contributions that their field can make and to propose relevant investigations. However, investigators new to radiobiology research are encouraged to consult or collaborate with radiobiology experts in order to develop realistic experimental plans.

Research must focus on elucidating molecular mechanisms and pathways involved in normal radiobiological responses to low dose exposure; exclusively phenomenological studies will not be considered. In general, research is desired that focuses on low Linear Energy Transfer (low LET) ionizing radiation (x- and gamma-rays; high-energy electrons and protons) exposures, and total radiation doses that are less than 0.1 Gray (Gy) (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. In some cases, a biological response of interest seen only at high doses may actually be absent (as opposed to simply undetectable) at low doses of radiation; evidence is also accumulating that biological responses after low dose exposure are qualitatively different from responses after high dose exposure. Therefore, research aimed at defining the dose where the mechanisms of response shift (dose-series and time-series experiments) has high programmatic priority.

Low dose-rate studies are also very desirable. In these studies it is important that the range of total doses delivered also encompass the low dose range, i.e., total doses should adequately cover the range of 0.1 Gy or less in addition to any higher total doses. It is worth noting that experimental delivery of only 0.01 Gy (1 rad) over a period of 24 hours is still an approximately 1000-fold higher dose rate than the average background radiation dose rate in the U.S. It is well known that viable biological systems have cellular and molecular surveillance mechanisms that can detect much less than a 1000-fold change in environmental conditions, including the case of radiation exposure. The radiobiological evidence from studies in various biological systems shows that low dose rate exposures often initiate adaptive, homeostatic responses. Research is sought to verify and further elucidate these responses in normal intact tissues.

Until recently, most molecular studies of radiation effects were carried out using isolated cells in monolayer culture, and the responses of those cells were then extrapolated to mammalian tissues and organisms. New research indicates that fundamentally different cellular and molecular responses can occur as a function of the level of biological organization (cells, tissues, or whole organisms), and that normal, intact tissue responds, in general, differently to radiation than does monoculture/monolayer cell populations. These observations are especially pronounced in the low dose range. Innovative new research is needed to explore and more fully understand low dose radiation-induced molecular and cellular responses, and subsequent health outcomes, within these higher levels of biological organization.

Experimental research of particular interest in 2008 included the following:

1. **Radio-adaptive responses** - as they relate to significant health outcomes

2. **Systems genetics** - Inter-individual variation in radiation exposure outcomes may result from polymorphisms at multiple loci that can be identified via discovery genetics strategies.

3. **Low dose and/or low dose-rate effects on:**

   a. ***Proteomic responses*** - Comparing proteomic response after low versus high dose exposures may provide information on underlying systemic processes.
   b. ***The immune system and inflammation*** - Recent studies of experimental models

of cancer underscore the absolute requirement for inflammatory and/or immune cell involvement. The effect of low dose exposure on these tissue interactions and their role in health outcomes is poorly understood.

c. ***Epigenetic regulation*** - There are epigenetic mechanisms by which radiation exposure causes an alteration of cell phenotype that persists. The signaling mechanisms establishing such epigenetic programs, and their contribution to health outcomes, are not well understood.

d. ***Molecular /cellular hallmarks of aging*** - Recent developments in the field of aging research have revealed cellular and molecular effects, the study of which may be important to the understanding of low dose radiation biology.

4. **Mathematical modeling** - Modeling incorporates current low dose and low dose rate biological research into mechanism-based systems biology models of tissue function. It may be a component of an experimental effort, or it may stand alone, but it should aim to include relevant research results across levels of biological organization that influence health effects at high versus low dose exposures.
Because the knowledge base of regulatory, metabolic, and signaling pathways is growing rapidly across all fields of biology, any data and results generated through funded investigations that are appropriate to share with the broader scientific community should, where possible, be provided in a format amenable to deposition in databases.
The Low Dose Program was established with the intention of supporting science that is useful to policy makers, standard setters, and the public. Successful applications will ideally have an approach or component (whether experimental or modeling) that could potentially link data from experiment to downstream health outcomes that might occur in humans. Investigators will be expected to effectively communicate research results through publication in peer-reviewed journals. Investigators will also be encouraged to communicate with the wider community of concerned persons, so that current thinking and public debate are better able to reflect sound science.

Finally, several tissue archives are available for Low Dose Program investigations. Fixed tissue samples from individual animals (rodent, canine) exposed to either external radiation or to internally-deposited radioactive materials are available for study. For information on these tissue archives, please contact Dr. Gayle Woloschak, Northwestern University; (312) 503-4322; g- woloschak@northwestern.edu.

II. Specifics for the NASA Space Radiation Project

The NASA/HRP Space Radiation Project 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/HRP Space Radiation Project 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

Research applications to which NASA will assign high priority to studies that:

a. increase the confidence in the accuracy of extrapolating the probability of radiation-induced genetic alterations or carcinogenesis from rodents to humans;
b. reduce uncertainties in risk prediction for cancer following irradiation by protons and HZE particles;
c. provide data to develop risk projection models for central nervous system (CNS) and other degenerative tissue risks.

Research is conducted utilizing beams of charged particles available at the NASA Space Radiation Laboratory (NSRL) or lower energy (< 250 MeV) protons at the Loma Linda University Medical Center Proton Treatment Facility, and to address experimental data obtained with such beams in ways leading to significant predictions that can be tested in future experiments.

The particles of interest to the Space Radiation Project are protons with energies between 20 and 1000 MeV, and nuclei of elements with atomic numbers between helium and iron, 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 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 NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory. The use of beams at these facilities is paid by NASA. NASA cooperates with DOE to provide the range of technical resources available for experimentation and analysis of experimental results at Brookhaven National Laboratory.

Merit Review Criteria
Applications will be subjected to scientific merit review (peer review) and will be evaluated against the following evaluation criteria which are listed in descending order of importance 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; and
4. Reasonableness and Appropriateness of the Proposed Budget.

DOE and NASA will make final funding decisions based on the results of the peer review and internal programmatic review. NASA agrees to abide by DOE's application review procedures. Applicants selected for funding may be required to provide additional information. The evaluation process will include program policy factors such as the relevance of the proposed research to the terms of the announcement and the agencies' programmatic needs. Note that external peer reviewers are selected with regard to both their scientific expertise and the absence of conflict-of-interest issues. Both Federal and 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.