REPORT OF A SUBCOMMITTE TO THE DEPARTMENT OF ENERGY BIOLOGICAL AND ENVIRONMENTAL RESEARCH ADVISORY COMMITTEE ON THE LOW DOSE RADIATION RESEARCH PROGRAM

1. Description and History of the Program

The Department of Energy's Low Dose Radiation Research Program (LDRRP) supports studies of cellular and molecular responses to radiation exposures at less than 100 millisieverts (10 rem).

It is the Program's goal to utilize cellular and molecular biological observations as well as animal models in order to derive a more robust estimate of risks to human health at low doses. Radiation exposures at these levels encompass the principal human exposures from industrial, environmental, and medical sources. The associated risks, estimated by most advisory and regulatory agencies, are based upon extrapolation of epidemiologic results obtained from higher doses, particularly from survivors of atomic bombings in Hiroshima and Nagasaki, using the so-called linear no threshold (LNT) model and justified, in part, by biophysical modeling. Such an approach is necessary because there are statistical limitations in the epidemiologic data available in the low dose region. In pursuit of the goal of reducing uncertainty in risk estimates, originators of the Program asked the following questions:

- Are there similarities and differences between endogenous oxidative damage and that produced by low-dose radiation damage and, if so, how do these impact on human health?
- How might the biological phenomena of bystander effects, induction of genomic instability, and radio-adaptive responses affect cancer risks from radiation?

- Are there exposure levels (thresholds) below which normal cellular processes effectively deal with radiation damage, which, in turn, could be designated as below regulatory concern?
- Are there genetic factors that affect individual susceptibility to low-dose radiation and, consequently impact on cancer risk in some sub-populations?

To address these questions, the Program has supported 243 projects (95 in national laboratories and 148 in universities and academic medical centers) since its inception in 1998. In the past two years, funding levels have been at ~$17M per annum. In 2007, 19 projects were funded in national laboratories at $7.7M and 48 in universities and academic medical centers at $9.4M; 12 grants were jointly funded with NASA. In addition, a small amount ($82K) was expended on conferences. An assiduous communications activity by Antone Brooks, former Chief Scientist, has kept the radiation research community up-to-date with the activities of the Program; annual workshops have been held for the active investigators.

In 2005, there was a Committee of Visitors report on OBER life science programs that included the LDRRP. It covered the quality and effectiveness of merit review procedures, selection of reviewers, profile of the research portfolio, and management of the Program. The review was generally favorable. A number of recommendations concerning the review process and the selection of proposals were made.

2. Charge to the Subcommittee

In a letter to the Chair, dated 11 June 2007, the Under Secretary for Science requested that the Biological and Environmental Research Advisory Committee (BERAC) undertake a review of the BER LDRRP. He wanted the Program to be evaluated "with respect to its original research plan, the current state of the field of radiation biology, and its relationship to contemporary cancer biology". Specifically he asked the review to address 1. The scientific accomplishments, quality and technical innovation of the Program's research portfolio; 2. Whether the portfolio is taking best advantage of

advances in biological research and integrative models; 3. Whether the growing body of scientific knowledge and new biological paradigms provide justification for reconsideration of risk estimate models that are used for setting regulatory dose limits, and: 4. Whether there are additional biological issues or technical hurdles to be addressed in order to inform regulatory policy. (The charge letter is enclosed as Appendix 1).

Sensing that the third charge reached beyond the usual scope of BERAC scientific review[1], the Chair of BERAC requested that it be modified to an evaluation as to whether the growing body of scientific knowledge may lead to new biological paradigms for understanding low dose radiation effects on health that might be of interest to policy makers.

3. Membership of the Subcommittee and Methods of Procedure

Members of the subcommittee and their affiliations are given in Appendix 2. Their expertise includes radiation biology and biophysics, molecular genetics, radiation oncology, epidemiology, and cancer biology. They were drawn from universities, academic medical centers, and national research agencies.

A preliminary conference call among the subcommittee members was held on 6 October 2007 to clarify the charge, to identify material that would be needed to conduct the review, and to set the agenda for a meeting of the subcommittee. It was determined that the subcommittee would examine the output of recent projects by way of the written record – papers published or in press, progress reports and annual summaries. In addition, the subcommittee would hear from the past and present program managers, the past and present chief scientists, and a select number of current investigators. The latter were asked to provide their opinions on whether/how research has led to new models for understanding low-dose effects and what technical hurdles, if any, need to be overcome before risk estimates can be reassessed.

[1] Guidelines for regulatory purposes are usually proposed by national and international advisory groups such as NCRP and ICRP. Risk estimates are also provided by the National Academies (BEIR reports) and the United Nations (UNSCEAR).

The subcommittee met on 10-11 December 2007 at the American Geophysical Union in Washington DC (See Appendix 3 for the agenda). After hearing from program managers and scientists, the members reviewed 56 current and recently completed projects. The purpose was not to review individual investigators *per se* but to assess the scope and quality of the overall Program. It drafted a preliminary response to the Under Secretary's charges before adjourning.

4. Findings and Recommendations

Scientific accomplishments, quality and technical innovation

During the past 10 years, there has been a major change in the direction of radiobiological research with a new emphasis being placed on gene expression, proteomics, adaptive responses, genomic instability and bystander effects as well as on the employment of tissue and three dimensional cellular models. At the same time the research has been directed toward improved understanding of the mechanisms underlying radiation carcinogenesis and hereditary genetic effects. The Program has played a major role in advancing both areas of research, leading to results demonstrating that:

- DNA damage from low dose ionizing radiation (IR) differs from that produced by endogenous reactive oxygen species
- Changes in gene expression from the unirradiated state differ after exposure to high or low doses
- A large number of genes with diverse functions are responsible for variations in radiation sensitivity
- There are striking differences in the response of two dimensional and three dimensional cell cultures to low dose radiation
- The extracellular matrix is important in system biological responses to IR

In its review of 56 currently and recently supported program investigators, the subcommittee rated 75% of the projects as good-to-excellent and 25% as poor-to-fair.

Although the quality was mixed, and the subcommittee had no benchmarks with which to compare this profile, it was clearly weighted toward the high end. The subcommittee was impressed with the progress that had been made in many laboratories, given that investigators were looking for small effects against a big background. Indeed, a significant fraction of important radiobiological observations from the past decade have been due to LDRRP support.

Projects were judged on the basis of the paper trail of laboratory reports and on the record of publications. The subcommittee assumed that a critical measure of scientific quality is to be found in peer-reviewed journals. Thus, it used the latter as an important criterion. More than 500 papers have been published under program support since its inception, most in the first-line radiation research literature[2]. However, the publications are rather unevenly divided among laboratories with some being highly productive while others rather less so. Generally, it was this lack of published work that accounted for the assessment by the subcommittee that some projects were in the poor-to-fair range[3].

In reviewing the paper record, the subcommittee noted that progress reports varied in content and quality. Many highlighted approaches and methods rather than results and interpretations. Although this is understandable in the early stages of new projects, it is expected that mature ones would register some findings, preliminary as they may be. In addition, the format for reporting progress in the national laboratories differs significantly from that of the university and academic medical centers. The subcommittee believes that some common structure in reporting progress would be desirable for quality control and comparative purposes.

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[2] Fewer papers have been published in first-line, high-impact life science journals. However, this is a common for disciplines that are narrowly focused as is the field of radiation biology.

[3]The published record has a number of reviews, many written by the former Chief Scientist whose task was to communicate the findings of program investigators to a wider audience. These are generally well-done and the subcommittee has no criticism of them. However, it might be useful in the future to separate reviews from papers that report new findings. . Some publications were meeting abstracts while others were not peer-reviewed. These should also be clearly separated from peer-reviewed publications or eliminated from publication lists.

In the Program's broad perspective, null results can be as important as positive ones. Thus, some mechanism of broadcasting these negative results to the low dose radiation research community would be of value, particularly when low and high dose responses are compared.

In any event, a record of peer-reviewed publication, emphasizing quality, should be a central determinant in the decision to renew funding of ongoing projects and certainly taken into account in the judgment of new ones.

Thus, the subcommittee feels that there is a need for more explicit expectations and monitoring of progress during and at the end of funded projects. With a mission-oriented program such as this, one might well expect project proposals to include clear timelines and milestones for planned work throughout the project duration, although we realize it is not always possible to meet these in scientific discovery. A specific requirement for annual reports would encourage principal investigators to work toward the proposed plan and enable the Program Manager and reviewers to ensure that the project is staying on track and making progress toward its stated goals. Deviation from the initial goals would require explanation and Program Manager concurrence, if substantial. A more complete final report at the end of the project would allow its overall performance to be evaluated properly and assist in decisions concerning follow-on or new proposals from the same investigator. It would also make publicly available the full outputs of projects if journal publication was, for some reason, delayed.

A fair number of the Program's investigators have additional funding from sources other than the LDRRP and several progress reports acknowledge such outside sources. Indeed, joint funding with NASA is built into the Program, and both agencies have derived significant benefit from this modest investment[4]. While there is no problem with projects drawing support from multiple sources, potential overlap should be monitored carefully for duplication. In a few cases, there were publications that acknowledged LDRRP

[4] Other agencies (NIEHS, NIAID, Homeland Security) might find this a useful way to leverage some of their research funding as well.

support but had no discernable low dose component. The Program's management should monitor publications for relevance and use this information to evaluate productivity when funding decisions are made.

A number of technical innovations have been introduced by project investigators. These include the design and utilization of three dimensional culture systems, specifically mutated cell lines, optical methods for determining damage responses, innovative methods using microbeams and other schemes for providing low dose and low dose-rate exposures.

Some of these methods are expensive to establish and maintain, making them relatively unavailable to many independent laboratories. Making these technologies accessible to LDRRP investigators would be a useful attribute of the Program, particularly for those located in national laboratories. Some exemplary technologies are low dose and low dose-rate irradiators, special optical equipment, and single molecule sequencing. The collaborative Glue Grants[5] are one mechanism for sharing these but other means to enhance access to specialized technologies should also be considered.

In its reaching out to a wider community, the subcommittee commends the LDRRP for its continued support of multidisciplinary workshops, such as those presented with the American Statistical Association, and encourages the provision of more such opportunities for dialogue and deliberations between investigators in the experimental, computational, epidemiological, risk assessment and other related areas of the radiation sciences to the benefit of the Program's ultimate goal.

Exploitation of advances in biological research and integrative models

Based upon the material provided and discussions with several investigators, it is apparent that researchers are familiar with many current technologies available in

[5] Glue Grants are to "enable laboratories with complementary expertise to develop and apply innovative or collaborative approaches to low dose research". In addition, "comparative studies between laboratories already using similar experimental approaches are also encouraged".

molecular and cellular biology and their laboratory methods are reflective of this. These include the tools of microarrays, proteomic profiling, optical imaging and others. Many investigators are looking at the perturbation of signaling pathways by low dose radiation exposure including mechanisms of DNA repair. A number are examining differential gene expression at low and high doses. At least one laboratory is concerned with the relationship between genetic and epigenetic phenomena and how both may be influenced by radiation exposure *in utero*. Perhaps underutilized are the techniques of gene silencing and informative transgenic and knock-out mouse models; these are likely to be useful, for example, in determining critical pathways in radiation-induced carcinogenesis.

As transgenic and knock-out animals become more important to the research program, particularly in studying variations in radiation sensitivity and mechanisms of radiation carcinogenesis, establishing a central facility (perhaps one at a national laboratory) might be considered. This could effect an economy of scale and/or, at least, make such experimental systems available to a larger group of investigators who might otherwise be unable to afford them.

A good deal of emphasis is placed on integrative three dimensional systems (*vide supra*) including epithelial cell mixtures and epithelial-mesenchymal models. However, subcommittee members were concerned that an overemphasis on these might preclude useful information still to be harvested from simpler two dimensional cell cultures.

Low dose radiation exposure, human health, and risk estimation

A better understanding of the effects of low dose exposures on human health and subsequently more robust risk estimates are the ultimate goals of the LDRRP. There is little question that the Program has made much progress in defining the response of biological systems at several dose levels. Translating these findings into risk assessments will require further efforts in mechanistic and computational modeling. We assume the Program is meant to move in this direction; the overall aim being to develop a

progression from observation to risk estimation and, possibly, regulatory adjustment. Conceptually, this can be considered:

Phenomenologic biological observations → mechanistic (quantifiable) studies → health effects (esp. cancer) in experimental animals → risk estimates in humans (by modeling approaches and epidemiology) → regulatory adjustments.

Until now, the Program has mostly produced results in the first category with some now emerging in the second. If this mission-oriented program is to make continued progress toward its goal it will need a carefully constructed roadmap. Designing this roadmap, broadcasting it to potential investigators, writing calls for proposals, and judging them in its context are challenging tasks.

Constructing a roadmap as guidance for the future of the Program should have the highest priority. Translating mechanistic studies into health effects represents a particular challenge requiring, as it must, a complex understanding of disease promoting and disease suppressing events put into motion by exposure to low doses of radiation[6]. The biomedical science community at-large has yet to write the composite sequences for carcinogenesis at dose levels that are known to produce cancers and how such mechanisms produce stochastic outcomes and converge with epidemiologic observations. Such elaboration, as noted above, will require the interplay of experimental research and computational modeling.

Presumably, as part of the Program's overall goal, the next issue to be faced is the development of a methodology that would translate recent findings in adaptive responses, bystander effects, genomic instability and other non-targeted biological effects into mechanistic models that would lead to quantification. This should take into account low dose *cum* high dose rate exposures as occur in diagnostic and therapeutic radiology

[6] In the simplest case, there would be no biological response below a certain level of exposure and, under those circumstances, one could well argue for a threshold in health effects. Unfortunately, we know that there are molecular responses at low doses and reckoning their importance is the demanding task.

(outside of treatment fields) and low dose *cum* low dose rate exposures as found in contaminated environments and nuclear medical procedures.

An advisory committee

To construct such a roadmap, the subcommittee strongly recommends that a high-level advisory committee to the Program be established whose first task would be to develop, with the Program Manager and Chief Scientist, a list of priorities for future work. The advisory committee might well convene one or more workshops to assist them in this task. Requests for proposals would be written based on the roadmap and its priorities and applications judged by reviewers and the program management not only on scientific merit but also on how responsive they are to these. A continuing role for the advisory committee would be to monitor the Program's forward progress and to insure that appropriate procedures are in place for avoiding potential conflicts of interest.

Such a structure should encourage the principal investigators to drive their projects to the overall goals of the Program, knowing their performances will be judged accordingly and influence future funding. Implementation of this structure should make it less likely that awards will be dissipated into other activities and diverted from program purposes, as appeared to be the case in several projects from the national laboratories.

In addition, groups with differing expertise should be encouraged to work on the same systems in the hope of obtaining a more complete characterization (see note on Glue Grants). Perhaps this will be accomplished, in part, by the use of Scientific Focus Areas (SFAs) in the national laboratories whose purpose is to support team-based research efforts as well as the more traditional single investigator efforts of specific programmatic interest. Teams will be asked to provide "their scope of work in detail, including major tasks and subtasks, progress during the previous funding period, annual benchmarks (or milestones) for tracking future progress, allocation of budget and personnel, list of publications, and other relevant information". This initiative, which would bring the LDRRP into line with some other programs under the DOE Office of Science, will be

effective only if the proposals for work are congruent with the roadmap for the future of LDRRP and if progress toward the milestones and publications as well as proposals for further work are subject to strict peer-review, comparable to that applied to other groups within the Program.

Low dose activities in other countries

The European Union (EU) is currently setting up a panel of experts to draw up a roadmap for the next decade or so of EU support of research needed for better quantification of risks from low doses and low dose rates of ionizing radiation within the EURATOM program. This is, in effect, the EU low dose program that currently funds large integrated projects called RISCRAD and NOTE[7] as well as smaller ones. This group's goal is to bring into line the EU's program with that of related national groups, principally from Germany, UK, France, Finland, and Italy. We understand that the EU/EURATOM program has a memorandum of understanding with the DOE-OBER LDRRP and that there has been scientific interchange in various ways. We strongly encourage such participation as a means to strengthen the roadmaps of both DOE and EU. To that end, we suggest that sufficient travel funds be available in order for LDRRP management staff and scientists, hopefully from the advisory group, to attend the planning meetings of the EU group, some to be held beginning in 2008. The future direction of the LDRRP is a critical one and the more planning that can be applied to it, the better.

5. General Conclusions

In its 10 year existence, the DOE-OBER LDRRP has produced a number of important observations on the response of cell and tissue biological systems to doses of ionizing radiations below 100 mSv (10 rem). Some of these are strikingly different from those observed at higher doses known to result (stochastically) in human health effects. How

[7] RISCRAD – DNA damage responses, genomic instability, and radiation-induced cancer: the problem of risk at low doses. NOTE – non-targeted effects of ionizing radiation.

these differences impact on carcinogenesis and other diseases remains to be determined and should be the focus of future research.

Seventy-five per cent of the recent and current projects supported by the Program were judged to be of high quality and productivity. Those which were not were mainly lacking in a written record of results. Thus, the subcommittee believes that a greater emphasis on documenting results (both positive and negative) in progress reports as well as in a record of peer-reviewed publication is needed and should count heavily in the renewal of grants and in the awarding of new ones.

The Program investigators are using a broad range of current molecular and cellular technologies including those that measure gene expression, proteomics and signal transduction as well as devices for optical imaging, two dimensional and three dimensional modeling and regional irradiation. Additional emphasis might be put on the utilization of gene silencing and transgenic animals in the next phase of investigations. The subcommittee also recognizes technical innovations introduced by project investigators. In those instances where new technologies are expensive or difficult to produce, we recommend that the Program make it possible for them to be shared among participating laboratories.

The subcommittee approves of and encourages collaborative studies among program investigators as well as with laboratories whose principal focus may not be radiation. Such collaboration is provided through OBER "Glue Grants" and through joint funding with other agencies, especially NASA. Joint funding is an effective mechanism for leveraging DOE spending in this area but close monitoring that the monies are spent in the low dose area must be assured.

The subcommittee places the greatest importance on planning for the next phase of low dose radiation research. The LDRRP is on the path of turning from phenomenologic biological observations to quantitative mechanistic ones, which, in turn, can be related to health effects and, ultimately, human disease. The use of computational models will be

needed to help meet this goal. To this end, a carefully constructed roadmap will be required; one that will guide investigators in the future and to whose milestones they can be held accountable. To assist in this, a high-level advisory group should be assembled both to create the roadmap and help OBER staff in monitoring progress. In constructing this roadmap, consultation with outside agencies especially with those engaged in a similar exercise, such as the EU/EURATOM program, is strongly encouraged.

We are still uncertain on how doses of ionizing radiation equivalent to those received from medical exposure and from the workplace impact human health. Until the effects can be made quantifiably explicit we will be forced to estimate the risks by extrapolation. To the extent we over- or underestimate these there is a penalty to be paid[8]. It is the premise of LDRRP that the science of experimental radiation biology[9] can provide a more certain estimate. In this aspiration, the United States is now joined by other nations. The subcommittee supports continuation of the Program with recommendations we hope will help move it toward its ultimate goal.

[8] In overestimating, there are opportunity costs to the extent it precludes certain activities or exaggerates the degree required, for example, of cleaning contaminated sites. In underestimating, the health costs will be greater than those currently assumed.

[9] In this, the DOE Low Dose Program is an important component of the United States' radiation research portfolio.

Appendix 1: Charge from the Under Secretary for Science

Under Secretary for Science
Washington, DC 20585

June 11, 2007

Dr. Michelle S. Broido
Associate Vice Chancellor for Basic Biomedical Research
and Director, Office of Research, Health Sciences
University of Pittsburgh
Scaife Hall, Suite 401
3550 Terrace Street
Pittsburgh, PA 15261

Dear Dr. Broido:

With this letter, I am charging the Biological and Environmental Research Advisory Committee (BERAC) to undertake a review of the BER Low Dose Radiation Research Program. In April 1998, BERAC approved a Research Program Plan prepared by its Low Dose Radiation Research Program Plan Subcommittee, with recommendations extending out ten years on research needs, funding requirements, and program management. Since its subsequent inception in 1999, DOE's Low Dose Program has followed a research strategy aimed at rapidly advancing the understanding of biological responses to low dose and/or low dose rate ionizing radiation exposures, in order to determine whether such exposures present a health risk to people. It has consistently supported the highest quality, competitively peer-reviewed research, pushing the scientific community to study ever lower doses, in ever more relevant biological systems. In the intervening years, exciting new biological paradigms have emerged as a direct result of the low dose field of radiation research.

At this time it is appropriate to evaluate the Low Dose Program with respect to its original research plan, the current state of the field of radiation biology, and its relationship to contemporary cancer biology. The BERAC review should address the following issues:

1. Assess the scientific accomplishments, the quality, and the technical innovation of the Program's research portfolios.

2. Assess whether the current portfolio is taking best advantage of advances in biological research and integrative models.

3. Evaluate whether this growing body of scientific knowledge and new biological paradigms provide sufficient scientific justification for reconsideration of the risk estimate models that currently set regulatory dose limits for DOE workers and the public.

4. Identify any additional critical biological issues or technical hurdles that the Program needs to address in order to wholly inform regulatory policy.

I suggest you meet with Drs. Michael Viola and Noelle Metting to develop a format for the review. They can provide names of experts in the low dose radiation biology and risk regulatory fields whom you may want to consider asking to assist in the BERAC review.

I would like to have your review report from BERAC at its fall 2007 meeting and very much appreciate your help in this matter.

Sincerely,

Raymond L. Orbach

Raymond L. Orbach

cc: Viola, Michael
Thomassen, David
Metting, Noelle

Appendix 2: Members of the review subcommittee

S. James Adelstein (Chair)
Harvard Medical School

C. Norman Coleman
National Cancer Institute

Shirley A. Fry
Formerly, Oak Ridge Associated Universities

Dudley Goodhead
MRC Radiation and Genome Stability Unit

John B. Little
Harvard School of Public Health

Jac A, Nickoloff
University of New Mexico

Julian Preston
US Environmental Protection Agency

Thomas M. Roberts
Dana-Farber Cancer Institute

Appendix 3: Agenda for the subcommittee's meeting

REVIEW OF DOE-OBER LOW-DOSE RADIATION PROGRAM
DECEMBER 10-11, 2007
WASHINGTON DC

December 10

8:00-8:30 am

8:30-9:30am Introduction to the program, program management, program budget, proposal and post-award review
David Thomassen – past Program Manager
Noelle Metting – current Program Manager
Frank Sulzman – NASA representative

9:30-10:30am Program goals, accomplishments and Prospects
Antone Brooks – past Chief Scientist
Mary Helen Barcellos-Hoff – current Chief Scientist

10:30-10:45am Break

10:45-12:45pm **Scientists and Subcommittee only**
Select program investigators' view on whether/how research has led to new models for understanding low-dose effects and what technical hurdles, if any, need to be obviated to inform risk estimates
David Brenner, Randy Jirtle, William Morgan, Leslie Redpath, Betsy Sutherland, Andrew Wyrobek

12:45-2:00pm Working Lunch
Review of morning presentations

2:00-3:30pm Individual Project Review 1
(6m each) ~14 projects

3:30-5:00pm Individual Project Review 2
(6m each) ~14 projects

6:00-6:30pm- Working Dinner

December 11

8:30 – 10:00am Individual Project Review 3
(6m each) ~14 projects

10:00-10:30am Break

10:30-12:00n Individual Project Review 4
(6m each) ~14 projects

12:00-2:00pm Working Lunch
Conclusions – develop statements on

1. Quality, productivity and technical innovation
2. Taking advantage of current biologic research including integrative models
3. Emergence of new biologic paradigms and implications for risk estimates
4. Critical biologic issues or technical hurdles needing address

2:00 pm Discussion of report

2:30pm Adjourn
Report to the Acting Associate Director and Program Manager