

**REPORT TO THE
BIOLOGICAL and ENVIRONMENTAL ADVISORY COMMITTEE
(BERAC)**

**BY THE COMMITTEE OF VISITORS FOR
THE REVIEW OF THE LIFE SCIENCES DIVISION**

December 2005

Table of Contents

OVERVIEW AND GENERAL RECOMMENDATIONS	3
MICROBIAL GENOMICS / GENOMICS: GTL	6
LOW-DOSE RADIATION	6
STRUCTURAL BIOLOGY	7
GENOMIC AND BIOLOGICAL RESEARCH	8
INTRODUCTION	10
DOE PROGRAMS IN THE LIFE SCIENCES	11
PROGRAM MANAGEMENT	13
PROGRAM OPERATION	14
<i>Availability of Documentation</i>	14
<i>The Review Process</i>	14
<i>Communication and Future Planning</i>	14
COV PROCESS	15
MICROBIAL GENOMICS / GENOMICS: GTL	17
OVERVIEW	17
SPECIFIC COMMENTS	19
LOW-DOSE RADIATION	25
OVERVIEW	25
SPECIFIC COMMENTS	26
<i>Quality and Effectiveness of Merit Review Procedures</i>	26
<i>Quality and Effectiveness of Selection of Reviewers</i>	28
<i>Resulting Portfolio of Awards</i>	30
<i>Management of the Low Dose Program</i>	32
STRUCTURAL BIOLOGY	34
OVERVIEW	34
SPECIFIC COMMENTS	35
GENOMIC RESEARCH AND BIOLOGY RESEARCH	41
OVERVIEW	41
SPECIFIC COMMENTS	42
<i>Ethical Legal and Social Implications</i>	42
<i>Biology Research</i>	43
<i>Joint Genome Institute</i>	43
APPENDIX A	47
APPENDIX B	49
APPENDIX C	51
APPENDIX D	52
APPENDIX E	53
MICROBIAL GENOMICS / GENOMICS: GTL	53
LOW-DOSE RADIATION	60
STRUCTURAL BIOLOGY	71
GENOMIC RESEARCH AND BIOLOGY RESEARCH	76
APPENDIX F	81

EXECUTIVE SUMMARY

On 18 November 2004, Dr. Raymond Orbach, Director, Office of Science (SC), Department of Energy (DOE), charged the Biological and Environmental Research Advisory Committee (BERAC) with assembling a Committee of Visitors (COV) to assess some of the processes used to manage the research portfolio in the Life Sciences (LS) Division of the Office of Biological and Environmental Research (BER). The Life Sciences Division portfolio of scientific awards has four elements. These four elements are: (1) Genomics: GTL (including the earlier portfolio of Microbial Genomics); (2) Low-Dose Radiation; (3) Structural Biology; and (4) Genomic and Biological Research.

A COV of independent experts from the scientific community was established by BERAC in response to this charge. The COV consisted of 12 scientists, with representation from academia, the private sector, and the Federal Government; only one of the scientists is affiliated with a National Laboratory. The COV met on 17-19 May 2005, at the DOE headquarters building in Germantown, Maryland. Assistance and support was provided, as needed, by the LS staff. To maximize the effectiveness of the analysis, four subcommittees of the COV were formed – each assigned to review carefully and deeply a different element or Program of the overall LS research portfolio. The entire COV evaluated and analyzed the portfolio as a whole, provided answers to the specific questions offered by DOE, and provided recommendations.

Overview and General Recommendations

- The scientific goals for the overall Life Sciences Programs remain as visionary, if not more so, and as pragmatic and as effective as when BER Life Sciences was building the infrastructure and inventing the process for the Human Genome Project. Overall, the quality of science supported by DOE is high, the balance of high risk research is appropriate, and each of the Programs is extremely well managed in terms of planning, implementation and vision.
- The vision of BER, which is summarized as conducting “Science at the Interface” with “innovative approaches along conventional paths,” has been well developed through interactions with the community. The vision is articulated in DOE presentations and publications as being comprised of two sets of three intersecting domains; namely, one of three sets of ideas, those of the biological sciences, the physical sciences, and the computational sciences, and one of three categories of human capital or people, those from the Laboratories, the Universities, and private industry. For the LS to offer revolutionary advances for clean energy, mitigation of climate change, and environmental cleanup and other environmental challenges requires this vision be maintained and fully implemented.

- The review process, from the details of the calls for applications (RFAs) to preapplications, the actual peer review, and the actions (awards and declines), for each of the LS Programs is also very well managed, taking into account all of the requisite considerations for reviewers (such as scientific expertise, balance, avoidance of any conflicts) and the activities themselves. The COV commends the internal administrative or managerial processes of the LS Division, despite the Division having to operate with an inadequate number of staff.
- Although DOE Program Managers (PMs) are committed to provide first-rate, equitable reviews of the applications submitted to them, the staffing levels are simply inadequate for the tasks at hand. As a result, the PMs achieve efficiencies where they can, and this results in unfortunate patterns such as providing too little documentation in the file, providing inadequate detail in some correspondence with applicants, and the use of too many local reviewers. In the case of what we are calling local reviewers, the observed pattern was the selection of too many reviewers who work in close to proximity to Washington, DC. DOE has dedicated staff and DOE supports world-class science. However, the ratio of internal DOE staff to programs supported is substantially lower than that found at other funding agencies. The COV would like to see improvements in some aspects of the DOE review and documentation processes (details throughout), but the COV recognizes that these improvements will be difficult to achieve so long as the DOE program staffing remains low.
- The Genomics: GTL Program, building on BER's extraordinary and very visible successes in Microbial Genomics and on the similar spin offs from earlier and ongoing contributions in DNA sequencing, represents an exceptional Program that will address central elements of the DOE mission, that defines a role for BER that is unique among the Federal Agencies, and that should provide DOE's SC and BER with long lived recognition for creating and implementing a Program so innovative that it is transforming the entire biological sciences as well as for microbiology itself. The overall program and the individual research projects supported by and conducted through Genomics: GTL and the now-merged Microbial Genome are prime examples of innovative science. We commend the vision of the BER leadership and management that enabled the establishment, development and implementation of these efforts.
- The unique and quite effective Low Dose Radiation Program has already changed our understanding of the consequences from low dose radiation and impacted policy considerations. This Program had a very explicit mandate and has responded excellently in addressing the challenges.
- The Structural Biology Program (SB) at DOE had a strong research effort focused on explicit, traditional DOE missions. Through an immediate termination of experimental research projects, SB has been phased back to the support of research resources and infrastructure at DOE facilities; this occurred due to the deep cuts in the budget and the context of other Program priorities, which we recognize and appreciate. These remaining activities, the structural biology

resources, are well run, productive and essential for the community. Beyond the provision of infrastructure, however, advances in structural biology and its specific emphasis within the LS portfolio are essential to deliver the longer term goals of the Genomics: GTL Program, and secondarily, numerous other goals of BER, including those of the Medical Sciences Division along with approaches to remediation and other BER commitments to the DOE missions. To allow the requisite technologies, scientific expertise and knowledge base from structural biology to be applied to Genomics: GTL, we recommend the development of a novel, yet timely, Structural Proteomics (SP) sub-program, within the overall scientific framework of Genomics: GTL and managed however BER views as most effective. The SP sub-program will be unique to DOE and accelerate the delivery on the promises of GTL.

- The Genomic and Biological Research effort sustains the excellence in life sciences and genomics, originally developed by DOE in order to take advantage of National Laboratory technology, expertise, and the rich interdisciplinary environment empowering effective collaborations. The work also serves to explore what might become possible in further advancing the DOE missions. The Joint Genome Institute (JGI) is a remarkable success story, which continues to unfold and to open new vistas for insight into life sciences and for scientific vehicles by which BER can utilize biological knowledge to drive the core DOE missions in energy, environment and remediation. Similarly, the Ethical, Legal, and Social Implications (ELSI) effort expands upon the original requirement for such research within the Human Genome Project and fulfills a continuing need for the life sciences as a whole, and could contribute more generally to the science within SC. The ELSI effort effectively engages the university community, but it would be wise to expand recognition and involvement of the National Laboratory scientists as well.
- The PMs are all to be commended for their extra efforts, dedication, and commitment to funding the best science in order to meet DOE's mission requirements. The interactive intellectual environment we observed during the COV must facilitate their efforts. Science in support of DOE's missions, most notably in energy, environment and remediation, would be enhanced by the broader community being more aware of the excellent science already being funded and the opportunities for collaborations and interdisciplinary research available through DOE BER funding. Thus, an enhanced communication effort to provide the success stories and the opportunities provided by the DOE for the biological sciences is essential.
- The COV found for each area of the LS Programs that there is a need for increased financial and intellectual support for PM's travel and engagement in professional societies and in site visits to grantees as well as for review processes.
- For an enhanced communication effort to work, that is, to "get the word out," increased internal funds and authorization for travel and an increased recognition of the value of Program Managers attending scientific meetings, presenting their

portfolio and describing the contributions of the DOE, is essential. At the same time, providing this contact and communication between the community and the PMs will serve to ensure that LS PMs stay aware of the cutting edge of the relevant scientific disciplines and, therefore, can proactively find the best opportunities for the biological research to serve the missions of the DOE and the needs of society.

Microbial Genomics / Genomics: GTL

- The COV recommends GTL expansion into other areas related to energy production, bioremediation and carbon sequestration areas, to help expand, diversify, and add further value to the Program and its impact on DOE mission relevant interests.
- Increased GTL funding and expansion of the diversity of projects (notably, over the range from mid-size to large) within the Program should result in an even more robust Program that has even higher productivity and technology spin offs, i.e., that has an even higher return on the investments. The COV urges that this increase in funding and corresponding expansion of diversity occur as soon as the funds are available. The immediate impact on DOE's missions will be huge and correspondingly, this will increase the extent of scientific and societal recognition of the value of DOE funded research.
- The expansion of new facilities to support new technology development in the context of GTL, for instance, a protein production facility that could complement the current production sequencing facility (JGI), is an excellent direction in which to proceed. The COV highly recommends that SC and BER do so.
- The GTL Program currently is fairly tightly focused on a few model systems. The potential for expanding opportunities in comparative and functional genomics is great, and the opportunities are most obvious and immediate with respect to expanding beyond terrestrial systems. Expanding the Program further, into parallel areas in ocean systems and a swath of marine microbes, would further increase the relevance and impact of the Program.

Low-Dose Radiation

- This Program has already produced important information that has changed our understanding of the biological effects of low-dose radiation. The Program's focus and the inclusion of interdisciplinary teams make the DOE effort unique and especially effective.

- BER's commitment to open solicitation and competitive peer review of applications is to be commended with the highest enthusiasm. This is especially true given the small number of Program management staff and the time required in organizing, managing, and processing information from peer review panels. Reviews are well managed and the rigorous discussions and thoughtful comments have produced science of the highest quality.
- The Program could be strengthened through wider participation by members of the research community who have not traditionally been involved in radiation research, especially those who can bring new technologies to bear in collaboration with trained radiation biologists. Mechanisms to help achieve this goal are suggested.
- Among the general case for Federal staff – community engagement, the COV especially recommends that the Low Dose Radiation Program staff be encouraged and enabled to undertake additional travel, in order to recruit new applicants, stay abreast of the latest technologies and maintain awareness of ongoing funded research, and consequently allow the Program to explore a wide range of options and approaches and make rapid progress in the context of an explicit time limit for such specifically applied research.

Structural Biology

- The experimental research projects (on the essential architectural features enabling cellular response to radiation damage through DNA repair and genetic recombination) supported by the Structural Biology Program (SB) were excellent, of high impact, well focused on the DOE missions, and also research not likely ever to be funded by another agency. The research built upon the strong contributions in experimental biology arising over more than five decades through BER support. The COV understands and appreciates why priorities associated with the effects of severe budget limitations and immediate goals forced the termination of the experimental portfolio, although the consequences were quite severe and will likely impair and delay the delivery of other features of BER's contributions to the missions of DOE. BER serves as the most important conduit in the Government for bringing the overall power of the physical sciences - from technology and methodology to intellectual approaches and knowledge base - to address biological questions and seek solutions; this conduit function has driven many previous mission implementations and will continue to be essential.
- The remaining aspects of the SB funding continue to sustain important research resources within state-of-the-art facilities that serve the user community. These research resources are well run, highly productive, and effective for the community; in turn, they are essential for progress in many BER research domains. The COV recognizes their valuable role and appreciates their contributions, enabled by BER SB, in provisioning the research community.

- The COV urges the full integration of the technology and approaches of structural biology into the broader research portfolio of BER to accelerate progress and ensure the presence of research expertise essential for success by other Programs. This should begin with the creation of a sub-Program termed Structural Proteomics, as introduced above. Structural Proteomics builds on the requirements of Genomics: GTL for a full scale investigation of microbial proteomics and involves the core methods, techniques, technologies, scientific vision and knowledge base of structural biology.
- All four of the specific goals articulated by the community for Genomics: GTL explicitly require structural biology as would be established through the proposed Structural Proteomics activity. Overall, Genomics: GTL has the objective of understanding natural, multi-protein molecular machines of complex living systems; complex networks that control the assembly and operation of these machines; and the organization and biochemical capabilities of complex microbial communities. The first three GTL goals will only be achieved through contributions in support of the fourth goal; namely, developing a computational infrastructure for systems biology for modeling and the use of models for prediction of biological behavior and responses to the environment. Certainly, the four goals can only be implemented by the intimate integration of key features of structural biology into the experimental and computational research within Genomics: GTL.

Genomic and Biological Research

- The JGI has become prominent as a highly productive, reliable sequencing facility that is the Nation's most effective production pipeline for new genome-scale sequencing. The selection of targets of opportunity has allowed the JGI to grow in scope, recognition and productivity. The JGI output correspondingly achieved an even greater impact in a shorter time than anticipated, like the other outstanding DOE facilities. The need for complete genome sequences will continue; indeed, as the costs continue to decline, it is fair to say for the Nation's science that "we have only begun to sequence" and the demand and impact will extend for at least the foreseeable future.
- The JGI is now facing an extraordinary opportunity – a project with the potential to transform microbiology and all of the biological sciences. This project would involve sequencing the complete genomes of all known, culturable bacteria. A partnership with the American Society for Microbiology (ASM), the other U.S. science funding agencies, many private Foundations, and even other governments, would be possible and probably desirable. The methods and technologies are in hand, the costs are reasonable, and the incredibly powerful process and scientific production pipeline of the JGI, as well as its scientific reputation, make the process – perhaps to be termed the Year of the Microbe, or The Year of the 5K Microbial Species – fully feasible, timely, and highly attractive from many scientific perspectives. The COV has independently confirmed a tremendous

level of interest in such an idea, and we recommend a National Academy of Science study, an engagement of BER with the American Society for Microbiology, discussions with the relevant community and other performers, in order to establish the necessary details and manage the highly sophisticated intricacies of the large scale biological effort required to sustain the JGI pipeline in an effective manner. Only a deep engagement of the community would allow the pipeline to be effective, but doing so would transform the biological sciences forever, provide an incredible breadth of knowledge for annotating all genomes and accelerating the value of the life sciences for the Nation in general and for DOE's explicit missions.

- The exploratory and inevitably longer term, cutting edge biological research projects, which all effectively exploit the unique infrastructure of the National Laboratories - ranging from the scientific environment promoting outstanding and essential interdisciplinary collaborations to the successful development and deployment of advanced technology - have made numerous advances recognized as significant for exploring the complexity of biology and providing the basis for understanding how the knowledge of that complexity might be applied.
- The Program in ELSI (from genome and biology research) meets a strong societal need. The ELSI sub-Program has very effectively and productively engaged the university community. Restating our major recommendation for this program, the COV recommends, at this point in the development of ELSI, establishing a concerted effort to engage more fully the expertise and human capital of the National Laboratories in this important research effort that is essential for ensuring continued advances in the application of technology in service to society. This might become particularly important as the ELSI Program expands beyond its original portfolio.

INTRODUCTION

Overview

On 18 November 2004, Dr. Raymond Orbach, Director, Office of Science (SC), Department of Energy (DOE), charged the Biological and Environmental Research Advisory Committee (BERAC) with assembling a Committee of Visitors (COV) to assess some of the processes used to manage the research portfolio in the Life Sciences (LS) Division of the Office of Biological and Environmental Research (BER). The charge letter issued by Dr. Orbach is found in Appendix A. In response to this charge, a COV was established consisting of 12 scientists from around the country, with representation from academia, the private sector, and the Federal Government; one of the scientists from the university sector also has some affiliation with National Laboratories. Four subcommittees of the COV were formed, with each assigned to the review of a different element of the LS research portfolio. The complete roster of the COV is found in Appendix B. The COV met on 17-19 May 2005, at the Germantown, Maryland, DOE headquarters building, and the agenda for the meeting is found in Appendix C. What follows is the report from that meeting.

In 1993, the U.S. Congress enacted the Government Performance Results Act of 1993 (GPRA), an Act intended, among other things, to "... improve Federal Program effectiveness ... [and] improve internal management of the Federal Government"¹. In 2004, the Office of Management and Budget developed the Program Assessment and Rating Tool (PART), a process used to provide formal ratings effectiveness of over 25 percent of Federal Government Programs. In response to both GPRA and PART, the DOE SC implemented a number of strategic planning and evaluation processes, including the use of a COV process, to assess current management practices and of particular importance, to ensure that there are continuing improvements in the management of its over \$3 billion research budget. The COV charged with the evaluation of the LS Programs is the third COV established to review Programs within the BER.

In a "typical" COV assessment, the COV reviews *established* Programs of grants and other awards, with an emphasis on the processes of the Program as they affect the award cycle: that is, the COV team assesses: (1) the appropriateness of the solicitations issued; (2) the quality and effectiveness of the Program's merit/peer review procedures used to evaluate applications received in response to solicitations; (3) the selection of reviewers; (4) the process by which peer review and other factors are used to select those applications for which awards will be made; (5) the appropriateness of the resulting portfolio of awards, with regard to scientific issues and geographic and demographic balance; and (6) the management of the awards, once made.

The Life Sciences Division portfolio of scientific awards has four elements. These four elements are: (1) Genomics: GTL (including Microbial Genomics); (2) Low-Dose

¹ <http://www.whitehouse.gov/omb/mgmt-gpra/gplaw2m.html>

Radiation; (3) Structural Biology; and (4) Genomic and Biological Research. For reasons that will be discussed below, not all components of the LS research activities fit into the traditional mold of Programs reviewed by a COV. For that reason, only part of this COV report will deal with the traditional assessment of the award process. We will also consider the scientific effectiveness of the Programs for which a conventional assessment of actions (RFAs or calls for applications, review processes, declines, awards, supplements, etc.) is not appropriate.

The Life Sciences Division is a well-established component within BER and has long played a leading role in the Nation's research portfolio, as well as that of BER. For example, the recently completed Human Genome Project had its origins within the Division. Many of the excellent components currently within LS derive from the HGP itself, and from other long-standing, high-quality LS activities.

DOE Programs in the Life Sciences

Although several different Federal Agencies provide support for life science research, there is little real duplication and overlap among them, as each agency brings a unique focus to its support for the life sciences. The National Institutes of Health (NIH) emphasize health-related research; the National Science Foundation (NSF) emphasizes basic research, often with an ecological or evolutionary twist; and the Department of Agriculture stays close to agriculturally related topics. The DOE's support for life science emphasizes those areas that can uniquely contribute to the DOE mission and also those that can uniquely benefit from DOE strengths, such as large-scale science, instrument-intensive research, and multi-disciplinary methods emphasizing chemistry, computation, and physics.

In any review or other consideration of the LS portfolio of the SC of the U.S. Department of Energy, it is crucially important to emphasize the distinction of the DOE BER Life Sciences Programs from the Programs of other Federal Agencies in order to explain and document the vision and activities of the Programs and provide the explicit rationale for the existence of these DOE programmatic efforts. Specifically, for the DOE LS Programs in Structural Biology (now Research Resources), Genomic Research (Sequencing) and Applied Biology Research, Genomics: GTL and Microbial Genomics (environmental genomics), and Low-Dose Radiation, the research represented in the portfolio is distinct in its emphasis from the strictly biomedical Programs administered by the NIH and also the Department of Defense (DOD), and the very basic science biology Programs administered by the NSF. The overall vision and portfolio of research and the individual awards of the DOE BER Programs in life science research supported by the DOE are distinct in that the Programs are mechanistic in focus and highly interdisciplinary, and represent the successful interdigitation of biology with other scientific disciplines such as chemistry, computation, and physics. This interdisciplinary approach adds a novel perspective and important scientific information and consequently, knowledge and understanding that could not be obtained by either the more basic biology-focused, or the health care application-driven approaches. DOE/BER biology Programs have also invested significantly in scientific infrastructure that has helped to jumpstart progress in many areas of biology. A prime example of this type of investment

is the Joint Genome Institute's (JGI) Community Sequencing Program, which along with bold investments in computational biology, proteomics, and novel functional genomics technologies, has revolutionized the study of microbial communities and other complex biological systems.

Their deep commitment to advancing the DOE's missions and the meticulous care by which the LS staff conduct business deserves emphasis. The commitment and the basis for the meticulous attention to overarching vision, rationale, and administrative details around review and other actions can be found in the official statement of the BER from their Federal web site:

For over 50 years, the Biological and Environmental Research (BER) Program has been advancing environmental and biomedical knowledge that promotes national security through improved energy production, development, and use; international scientific leadership that underpins our Nation's technological advances; and research that improves the quality of life for all Americans. BER supports these vital national missions through competitive and peer-reviewed research at national laboratories, universities, and private institutions. In addition, BER develops and delivers the knowledge needed to support the President's National Energy Plan.

Such careful attention to the DOE missions, and the ongoing recognition and review of the work supported by other agencies, coupled with managerial and scientific excellence, has helped the Program over the past decade focus even more carefully on DOE missions and to sustain distinct and novel innovative Programs. We urge the DOE SC and the BER to publicize these novel contributions through publications in the journals of professional societies, through participation in major national and international meetings, and through an increase in the number of site visits that Program Managers (PMs) can conduct. It is very important for the scientific community and our Nation that DOE "get the word out" about its simultaneous commitment to excellence and the uniqueness for its LS Programs.

Our review of the application actions and philosophy of BER provided the COV team with a broad picture of the Programs, a clear reminder of the important contributions of BER, and insight into the exciting, novel research supported at this time. The COV commends DOE for its commitment to the unique capabilities and leadership that it brings to the Nation's portfolio of life science research. DOE's experience with highly instrumented "big science" research has allowed it to play a critical leadership role in moving life science research into the 21st century. The COV believes it is important that DOE continue its leadership role in these areas. This general leadership benefits the life science community in general and the DOE mission in particular. For example, it was DOE vision and leadership that initiated the human genome project, the results of which have transformed all areas of life science work, both applied and theoretical. At the same time, the results of that transformation have profoundly advanced DOE's ability to address life science areas directly associated with the DOE mission, such as renewable energy or bioremediation. The COV recommends that DOE avoid a short-sighted policy that would require all of its life science work to have an immediate DOE-mission

relevance. Instead, DOE should take care to pursue both a long-term strategic vision (in which DOE's unique strengths advance all of the Nation's life-science research) and a shorter-term practical vision (in which DOE uses the fruits of its long-term advances to address DOE mission-relevant challenges).²

Program Management

A prior COV (Environmental Remediation Sciences Division, 2004) offered several general suggestions regarding Program management. Many of those suggestions are still applicable and we reiterate them here. We also offer some new comments.

- The COV is aware that a prior COV has recommended that BER set goals for, and keep records of, funding demographics in terms of underrepresented groups, junior scientists, and new investigators/independent viewpoints. The COV is also aware that BER has indicated that this is not permitted under current DOE operating guidelines. Without wishing to unduly flog a dead horse, this COV suggests that, given the strong initiatives elsewhere in the government in support of ensuring diversity in the Nation's research community, that BER should perhaps seek a reconsideration of this issue by DOE leadership.
- In general, the solicitation and review processes work well, and the current PMs appear dedicated to the ultimate success of the Programs in terms of fundamental research contributing to DOE's long-term mission and goals.
- Although the members of the panels of peer-reviewers appear to be appropriately selected, the COV strongly recommends that the panel expertise, and the range of opinion presented, be augmented through the use of mail reviews. Such reviews should be incorporated for each application that is evaluated.
- We are convinced that PMs do not have adequate time to interact constructively with potential applicants, administer review with the care it deserves, monitor funded activities through interactions (including site visits) with investigators, and keep current with the state of research in areas of current and potential interest. This would be addressed by increasing the number of Ph.D. level staff, or through hiring of masters-level individuals who could handle some more routine duties that existing administrative staff do not have the training to handle. A further need is for adequate travel funds to allow the BER PMs to maintain contact with cutting edge science and to explain and promote the Programs at important national scientific meetings as well as to monitor and evaluate the contributions of BER's research support.

² This topic will also be considered in the context of the Joint Genome Institute later in this document.

Program Operation

Availability of Documentation

- The COV, for this subset of the actions, occasionally found the documentation for award decisions to be incomplete, especially for older awards. Most of the files for awards made to academic investigators contained concise, written justification for the award decisions. However, this was not always the case for awards made to investigators at National Laboratories. We recommend that a written justification for the PMs' decisions be placed in every file. We are aware that BER has initiated policies to this effect and we commend them for that effort.

The Review Process

- The COV found generally that applications submitted to the LS are assigned to three panel members (one primary and two secondary reviewers) who each prepare a written review prior to the convening of the panel meeting. Written reviews are also obtained on an "as needed basis" if the PM feels that a wider range of expertise is needed than is represented by the panel members. Review panels have been comprised of highly qualified individuals representing an appropriate range of: 1) technical specialties; 2) years of experience; 3) government versus academic affiliations; 4) geographic distribution; and 5) diversity.
- The time to decision appears to be appropriate, but the calendar time of the decision is often not optimal for the start of research projects at universities. That is, the regularities of the academic year are such that new graduate students can only be recruited at certain times in the calendar year. It would be helpful if BER/LS were to make an effort to synchronize the timing of their award cycle with some of the milestone dates in the typical academic year. If such synchronization is not done, then it is possible that an award will be made at a time such that investigators may have to wait nearly a year before they are able to recruit graduate students.
- The COV noted that some decline letters simply indicate that the application did not review well enough to warrant funding. The COV feels that each PI should receive written notification from the PM indicating the rationale for the decision to award or decline funding of his/her application. This has potential benefits both to PIs and to LS Program officers. For example, if the decline letter makes it clear that the decline is due to insufficient Program relevance, then the PI could avoid a futile, time-wasting resubmission.

Communication and Future Planning

- The COV applauds the LS for its efforts to communicate its activities to the broader scientific community. At the same time, the COV notes that, for the most part, DOE support for life sciences research remains a hidden jewel

among U.S. Federal support for research. LS in particular and BER in general should take more steps to inform the general scientific community of the opportunities and resources for life sciences research within the BER and LS.

COV Process

A prior COV, conducted in 2004 for another Division in BER (Environmental Remediation Sciences Division) offered several suggestions regarding the COV process itself. A number of those suggestions are applicable for the Life Sciences Division and so we essentially reiterate them here. We also offer some new suggestions arising from the specifics of this COV review

- BER management should consider formalizing the process for presenting guidelines for non-disclosure (confidentiality) at the beginning of the COV meeting. Non-disclosure is implied in the Conflict of Interest form signed by COV members, and non-disclosure was discussed during the introduction to the COV meeting. Nonetheless, the requirement of non-disclosure should be explicit in the written guidance, and awareness of the need for confidentiality should be acknowledged by signature.
- The COV is a management tool whose value is maximized to the extent that the efforts of the COV are focused on important issues. Because the use of a COV is a process that is still relatively new to DOE, we suggest that DOE review the results of each COV with the goal of revising and improving the implicit charge conveyed by the specific questions provided to the COV. We are quick to note that the DOE has encouraged us to follow any line of inquiry we deem appropriate. But this does not ensure that the COV will address potentially important issues that are not addressed by the specific questions. We encourage DOE staff review the COV report with respect to the utility of the existing set of questions and then consider whether or not additional (or alternative) questions would lead to better assessment of Program effectiveness. It is then critical to ensure that data and documentation relevant to the questions is provided to the COV. For future COV meetings, we recommend that the individual jackets provided to the COV should be examined in advance for completeness of the records; missing documentation (reviews, progress reports, etc.) diminishes the efficiency of the COV members and may preclude useful analysis.
- Detailed statistical data covering aspects such as, for example, the number of applications, average reviewer scores of applications, the success rate for all applications, the number of new investigators funded (or declined) in each round of competition, etc., would be valuable. Similarly valuable would be data as to the number of new (relative to the specific research Program) investigators funded for each solicitation as opposed to the number of investigators who are either the recipient of renewal awards or who have (or had) other projects funded by the Program.

- In the list of grants provided, all of the investigators on any given project should be listed, not just the lead investigator and the lead institution. When this information is not available, it is not possible to assess the extent of funding for specific investigators or groups of investigators.
- We commend BER, as noted above in Program Operations, for initiating a policy to ensure for every file, including those actions involving a National Laboratory, that a written justification for the PM's decision be in the file.

MICROBIAL GENOMICS / GENOMICS: GTL

Overview

This COV subsection reviewed the GTL Program from the 2001 Microbial Cell Project (MCP), into 2002 and 2003 GTL, as well as the 2003 and 2004 Microbial sequencing targets Program, and Poplar Genome Carbon Sequestration Notice 02-23. Since its inception in 1997, the Microbial Genome Sequencing Program has had a tremendous impact on our understanding of the microbial world in general, and our knowledge of microbes relevant to the DOE mission in particular. To date, the DOE microbial sequencing Program has contributed to about 20 percent of all published microbial genomes currently available. Without these efforts, the microbial genomes known and in the relevant database would be largely those microbes of strictly biomedical interest, and both fundamental biology and the DOE applied missions would have been neglected.

The visionary efforts of DOE in capitalizing on developing and implementing genome sequencing technologies in mission strategic areas has been and continues to be remarkably successful. These efforts deserve special notice since they have transformed the field of microbiology, as well as having an immediate impact on the approaches of other disciplines and on our understanding of higher eukaryotes. Among other consequences, the DOE Program led to the recognition of microbiology as a key area for the biological sciences in the 21st century. Continued DOE efforts in microbial genome sequencing will ensure the growth of genomic information about organisms that have a global environmental impact, relevance, and utility in the Nation's energy, environmental and bioremediation needs.

The GTL Program began in 2000, expanded in 2002 with the funding of five large Program grants, and transitioned in 2003 to the current, broader and more inclusive GTL Program. This progression has led to a greater number of projects with increased relevance and more diversity. As part of the progression, an emphasis on data management tools, metabolic analyses, improved understanding of molecular machines, development of real-time expression systems and of new methods for imaging and molecular probing, has pushed the Program's accomplishments and ongoing activities to the current frontiers in science and technology. We applaud the accomplishments to date, and encourage continuation and growth of the effort by DOE.

The high-risk technology development solicited in the 2003 GTL Notice (Request for Applications), as judged by the subsequent awards, is particularly promising. The approach of supporting a number of highly qualified investigators pursuing a diverse set of technological approaches, as opposed to supporting only a few, large center-scale research projects, seems a particularly effective way to leverage investments while meeting the technological challenges of modeling and conducting molecular and cellular measurement in mission relevant areas. The Microbial Genomes and GTL Programs have already reinforced and complemented each other in fundamentally useful and important ways. Thus, the momentum from technological developments supported in

Microbial GTL in 2003 can already be seen in the Microbial Genomes RFA Notice issued in 2004. Given the evidence of synergy, we commend the decision to merge the Microbial Genome Program and GTL, which should increase the efficiency of supported efforts.

We note also that the growing emphasis on analysis of microbial communities shows a dynamic response to improvements in technology and to the high-reward scientific opportunities that have resulted. Strategically, the emphasis of these DOE Programs on microbes and environmental processes is an area uniquely suited to DOE and for which DOE will have stewardship responsibility into perpetuity. Other agencies have limited capacity to make important contributions or even to engage in any significant fashion. These two areas, microbes and environment processes, separately and together, are likely to prove critically important to the relevant DOE missions, such as in the areas of environment, energy and remediation. The basic science resulting from these Programs is having a large impact that extends beyond basic science into practical applications. Thus, Banfield's work on the microbial communities found in acid mine drainage has significant practical importance, while contributing remarkable new insights, strategies and methods for the analysis of natural populations in other settings. Similarly, Lovley's project is developing cutting edge techniques and new biological paradigms for studying metal transformations that are useful in remediation of uranium and other radionuclides at contaminated sites. Both projects demonstrate the real utility of genome sequence information in the prediction and monitoring of environmental activities as well as leveraging the environmental activities of microbes. Finally, the GTL Program is leading the way in the development of proteomics from a technological and scientific standpoint. Proteomics is clearly central to much of 21st century biology, and the DOE effort will open a path for proteomics to contribute directly to the necessary technology and the solutions for numerous energy and environmental questions.

The balance of organisms studied in the GTL to date has appropriately focused on a few microbial systems in mission relevant issues such as radiation damage and DNA repair mechanisms (e.g., Deinococcus), and on the remediation of metal, acid and nuclear contaminated sites (Shewanella and Geobacter). The initial focus has numerous positive benefits in that it allows collaboration and complementarity between labs and investigators and it provides for the focused development of technology platforms likely to be of use. However, as the Program has begun to mature, it will be important in the near term to re-evaluate the focus in order to consider a greater diversity of organisms so that other, possibly more relevant organisms and processes are not overlooked; this is a point we have discussed in other contexts in the COV report. Just as the Microbial Genome Program was able to achieve extraordinary success by assembling the community to ask "which bugs" for genome sequencing and biological research foci, GTL needs to engage a broad community, not just those who have been funded, to explore how to ensure the best representative species and communities in order to accelerate the pace of discovery toward Program, BER, SC and DOE goals.

In this context, increasing the support for microbial community genomic projects is important, not only because it will lead to improved understanding of community processes, but also because it is likely to identify a new cohort of model organisms and

microbial processes that are relevant to advancing progress with respect to energy and the environment. While there is currently a strong focus in this work on terrestrial systems, a greatly enhanced focus on aquatic systems, including in particular, those found in the ocean, is likely to provide a critical knowledge base that is currently lacking. The impact would occur across a wide range of genome enabled science, including studies on gene regulation and functional genomics, proteomics, and metabolomics. The COV recommends and emphasizes – here and elsewhere in the report - the importance of continued growth of the already strong Microbial Genomes and GTL Programs, and most notably and even urgently, an expansion into areas not currently examined in GTL, such as marine systems.

Specific Comments

- The review mechanisms currently in place for both the Sequence Targets and the GTL Programs seem appropriate with respect to balance, parity and diversity of perspective and input. The GTL requires a more diverse and complex set of applications but the system employed works well.
- The panel reviews are consistent with GTL and Sequence Target guidelines and criteria and the reviewers do an excellent job of providing a critical evaluation of the scientific quality, appropriateness of the Principal Investigators, and DOE mission relevance.
- Review panel recommendations and priority scores are well documented. However, the COV recommends that when lower ranked applications are funded in preference to those with higher rankings a more in depth justification for the final decision be included in the application jacket (e.g., for reasons of high risk, programmatic balance, etc.).
- For the data that was available, the time from Notice announcement, to pre-review, to review and award notification was very reasonable – generally more expeditious than the timeframe of other comparable agencies competitions (e.g., NSF, NIH).
- Application review, notification, and award and decline processing are all handled well. For the larger, post award (supplemental) requests, the files should include more documentation on how that decision making process occurs, on what factors were considered. It could be instructive to learn what requests are simply denied in advance versus those that are encouraged; investigators do not generally send in supplemental requests in the same open ended or “blind” mode in which applications are generally submitted. In addition, as for other aspects of Program business and to enhance the DOE Programs, the provision of additional mechanisms for “getting the word out” and doing so effectively and routinely, such as by providing increased travel support for PMs for this purpose, would be useful. In addition to the role of increased travel support to ensure adequate communication to stake holders

for DOE programs, the provision, by the SC, of more support for travel by PMs would ensure that they can stay current with the revolutionary pace of modern biology. A significant amount of this revolution is due to technology and new methods advanced through DOE funding, as well as due to the discoveries themselves. Only by the PMs being engaged in active discussions with the community within scientific settings, and not just within the administrative environment of DOE headquarters at Germantown, Maryland, can they, and DOE SC BER, maximize the contribution of those Programs to the DOE missions.

- The panels have a good balance of expertise, which includes reviewers from National Laboratories, university researchers and often, those outside of the DOE system, that is, those never funded by DOE and not likely to be funded by the Department.
- With regard to the selection of reviewers in order to obtain an outside DOE or external, unbiased perspective, the COV judges that there is a good balance on getting in outside experts who are not necessarily proponents or grantees. Although fewer women than men have applied in many of these Programs, the peer review panels have an excellent representation of women referees. This sensitivity and effort on the part of the PMs may in part act as a form of outreach that in the future will serve to balance the gender ratio of the applicant pool. Overall, the COV is very impressed with the quality and efficiency of the entire review process – especially given the small staff size available for this process.
- **The quality of science supported by the Program is high.** We have reviewed a subset of GTL and Sequence Target folders and overall the quality of research proposed is quite high. These research projects have very good track records to date, with respect to results obtained from supported research. It is too early in the history of the Program to make a very thorough or comprehensive overall assessment of the impact from the completed or near-completed projects. However, all indicators suggest a high level of productivity from those projects currently underway, and from the peer review comments and the specifics of the investigator's plans, we expect the same from the newly approved projects.
- In the early stages of development (GTL 2002), a smaller number of very large awards were made; this was probably appropriate for the early stages of the Program. In the 2003 and 2004 competitions, there appears to be a trend toward a more diverse portfolio of investigators, of systems studied and of technology developed. The COV encourages this trend, commends the Program insight, and recommends strongly that this practice be continued. Increased funding for GTL and expanding the diversity of projects (especially over the range of funded projects from mid-size to large) within the Program should result in an even more robust Program with even higher product and technology return.

- **The balance of high-risk projects seems appropriate.** A very important aspect is the decision by the DOE GTL PMs to invest at the cutting edge of technology development. This type of risk taking is achieved in few other agencies. No other agency would be likely to provide the level of funding needed for such early stages of technology development. This commitment should continue to be fostered and encouraged by BER and SC leadership. The potential impact of these efforts on the entire environmental and microbiology communities is significant; the COV wishes to emphasize that it is clear that no other funding agency would or even could support the diversity and number of such efforts in this key scientific arena. The size and scope of high-risk applications seems about right at the moment. The COV recommends maintaining somewhere around the current ratio of high-risk to more standard projects, as the Program grows.
- There is a tremendous pattern of interdisciplinary research. There are a number of good examples of National Laboratories, who possess cutting edge technology developments, teaming with university investigators, who have specific biological problems and expertise with an organism of interest, to answer critical scientific questions. This sort of cross collaboration and multidisciplinary effort should continue to be encouraged and fostered by the Program. The decision to do so allows the leveraging of technical skills and expertise in large laboratory research resources to address key questions for communities that would otherwise not have adequate access to the requisite technology, and it directly connects them to the scientific community and the broader questions and applications related to energy and the environment.
- This Program is at the cutting edge of microbial proteomics, community genomics, bioinformatics tool development, and other areas of active development for the life sciences. This focus on excellence naturally attracts leaders and innovative thinkers in the field. The great ambition in taking a systems level view of microbes and microbial communities, and the creation of technological platforms for these studies, should continue to be fostered and encouraged. **In sum, this Program's activities are a prime example of innovative science.**
- The Program does have an appropriate balance across disciplines and sub-disciplines of the activity and of emerging opportunities. However there is a great opportunity to apply the approaches and technology platforms developed in GTL to understanding DOE relevant questions related to the oceans, including bioremediation, ocean carbon sequestration and biological energy production. Currently, the GTL Program is fairly tightly focused on a few model systems, but the potential for expanding opportunities in comparative and functional genomics is great with respect to expanding beyond terrestrial systems. **The COV emphasizes the value for GTL to include a clear focus on the ocean and marine microbes.**

- This Program is having tremendous impact on many other fields – in particular environmental microbiology, genomics, and environmental remediation. These are all extremely relevant to understanding and developing new energy sources, carbon dioxide sequestration/capture, and bioremediation. The Program does extremely well in focusing RFAs and funded applications on these important issues, with respect to both technology development and basic science questions. Expanding the Program further, for instance into parallel areas in ocean science, would further increase the relevance and impact of the Program.
- BER and the Life Science Division made a key decision to support innovation around community and environmental genomics through support of The Institute for Biological Energy Alternatives (IBEA). This work has become the exemplar for an exciting branch emerging for 21st century biology, termed metagenomics, community genomics, or environmental genomics. The work includes DNA sequencing of samples isolated from the Sargasso Sea (now published in Science magazine), in which many new microbes and more than a million genes were discovered. The pioneering sequence studies provided a wealth of preliminary information on microbial diversity in the coastal Atlantic Ocean, and also provided the development of the methods for the analysis, through sequencing and subsequent sequence analysis, of diverse samples from the environment. The idea of ecological or community genomics has been extensively discussed by the biological science community, has been identified by the field's major professional society, the American Society of Microbiology (ASM), and now has become an active topic of discussion by the relevant committee of the National Academy of Science; BER's efforts have established the potential and provided a strong basis for further efforts. Such studies will form the basis for efforts downstream in re-engineering microbes for energy production, for example. The environmental genomics studies would also connect well to an enhanced effort on marine microbes and would benefit from a deeper connection to ocean sciences, which could help inform the studies in terms of spatial and temporal variations and ecological, physical and chemical properties of the ocean from which the samples are collected.
- **GTL as whole is one of the most novel scientific research efforts ever undertaken. The development of methods to study natural communities will be among the important, definitive contributions of BER that will stand for all time as a unique role for the Department.**
- The balance at present in terms of large-scale projects with an in-depth focus on specific systems, and more distributed funding among different technologies and investigators, seems quite appropriate. Currently, there is significant, even heavy emphasis on metal cycling microbial systems, from the environmental perspective as well as microbial cell perspective (including Geobacter and Shewanella systems in particular). The COV recommends expansion into other areas related to energy production, bioremediation and

carbon sequestration areas beyond metal reduction, to help expand, diversify, and add further value to the Program and its impact on DOE mission relevant interests. The merging of the Microbial Genome Program with the GTL will aid in this trajectory. In particular, the COV recommends more emphasis on microbial and biological energy production and on carbon sequestration research projects that focus on a variety of mission relevant marine and terrestrial environments and systems. The expansion into new facilities to support this balance, for instance, the establishment of a major protein production facility that would complement the current production sequencing facility (JGI), would seem an excellent direction to head and is to be encouraged. The COV was pleased to learn that such discussions are ongoing.

- **The Program is extremely well managed in terms of planning, implementation and vision.** In particular, given the relatively small number of staff, it is remarkable how efficiently and smoothly the planning, solicitation, and funding process operates. The PMs should be encouraged and commended for initiating, nurturing and maintaining these excellent Programs.
- The responsiveness of the Program to emerging research is, overall, excellent. The management has been very responsive, visionary, and on the cutting edge of new and groundbreaking trends in scientific advances. This GTL Program has, and will continue to have high scientific impact and has enormous potential to lead to new technologies and applications in the context energy generation, remediation and carbon sequestration.
- It is clear that there is visionary and responsive planning in management to incorporate new developments, technologies and opportunities into the Program. In general, the progression of the initial genome effort, to the introduction of the Microbial Genomes and GTL Programs, and recently to the merging of Microbial Genomes and GTL, is visionary, exciting, and already successful. The Roadmap has been evolving steadily from year to year as evidence of this responsiveness. The Roadmap, RFA Notices, and applications funded reflect this responsive planning and prioritization.
- We commend the efforts of the dedicated individuals in the Program. The productivity of the staff is remarkable, especially given the scope and size of the Program. It would be useful as the Program grows to have more technical and scientific staff on board to help with this important and growing flagship Program. Some agencies have created an intermediate level of technical staff, those with strong undergraduate backgrounds in the relevant discipline and certainly in science, who carry out much of the effort that could be termed technical-administrative, where some technical expertise is needed but not an in depth understanding of the field. Such intermediate levels of technical staff at other agencies, for example, help extensively with the preparation for COVs, making sure the files are complete with regard to the scientific justifications for awards and declines, and in general, focus on completeness

in actions, allowing PMs to focus more on science and innovation. More avenues to disseminate information about the goals, RFAs or RFPs, and accomplishments of the Program should be pursued. In this context as well, the COV believes that additional travel support for PMs to attend other workshops and meetings would be very helpful. Further effort to distribute flyers, web advertisements, and other venues to bring the Program to a wider audience is also to be encouraged. It would be useful to have a list of examples of Program achievements and success metrics for outside reviewers, annual review and assessment, future strategic planning, and future COVs. Examples of success metrics could include: (1) new projects and entirely new research areas emerging from the Program; (2) new technology developments; (3) high profile publications; (4) field results; (5) National Laboratory efforts; (6) trainees (graduate students, postdoctoral fellows) and other support for the future work force); (7) abstracts and sessions at meetings; (8) popular press coverage; (9) database contributions; and (10) software contributions.

LOW-DOSE RADIATION

Overview

Since its inception in 1999, the Low Dose Radiation Research Program has supported research that investigates the effects of radiation from doses less than 10 rad (0.1 Gy). This line of research is critical for establishing radiation risk policy for the Nation. Current radiation protection standards are based on epidemiological data involving human exposure at relatively high doses. Without appropriate low-dose studies, radiation-risk policy could be based on artifacts inappropriately extrapolated from high-dose studies. At present, clear linkages have not yet been made between measured responses occurring at low doses and the downstream health occurrences in humans.

The COV confirms that the ongoing research supported by this Program has contributed to its goal of investigating and underpinning radiation risk policy with strong basic science. The portfolio of research projects is diverse. Its success is clearly supported by important discoveries about cellular responses to radiation that highlight the differences in response pathways initiated by high and low dose radiation, and demonstrate that classical data from high dose exposures cannot be extrapolated to the prediction of low dose radiation effects. New data show that cells in isolation respond differently to radiation than cells in the context of complex tissues or in the whole organism.

Research needs have been identified in five interrelated areas: (1) to compare low dose radiation and oxidative damage; (2) to understand the biological responses to radiation and endogenous damage; (3) to determine whether there are thresholds or other nonlinearities for low dose radiation; (4) to determine the genetic factors that affect individual susceptibility to low dose radiation; and (5) to communicate these results to effect appropriate policy and perceptions. The portfolio of research projects is diverse; its success is strongly supported by important discoveries in the areas of cellular responses to radiation that include bystander effects, adaptive responses and genomic instability. Continued Program emphasis will include mechanistic modeling, high throughput screens to examine signaling pathways and biological responses, and the determination of genetic susceptibilities for risk assessment.

The COV applauds the BER staff for doing an excellent job of managing the Low Dose Radiation Program. There is a high quality of research funded, strong and expert peer-review, productive efforts to balance the portfolio, and thoughtful overall direction of the Program, especially considering the scant resources at hand.

The COV strongly recommends that the BER staff for the Low Dose Radiation Program be encouraged and enabled to attend more national scientific meetings annually in order to enhance their contacts with potential reviewers, new ideas and technologies, and to recruit new applicants with fresh perspectives to the Program. It is recommended that BER staff complement their strong portfolio of more conventional research by taking steps to encourage the submission of high-risk projects, and for which to establish open-

minded, expert review. Requests for Applications designed to attract or encourage applications from a larger cohort of multidisciplinary teams would also be helpful.

Specific Comments

Quality and Effectiveness of Merit Review Procedures

- The Low Dose Radiation Program solicits grant applications through open RFAs, and applications are received from a wide swath of the research community. Decisions regarding funding are made in consultation by experts in a well organized and thorough peer review. The BER staff should be commended for following this difficult path, especially given the very small number of BER staff and their other myriad responsibilities. They should also be commended for listening carefully to expert advice regarding scientific quality and for the thoughtful way they blend this advice with considerations of programmatic relevance and balance. The work of recruiting reviewers, organizing peer review meetings, synthesizing the comments of diverse reviewers, and making decisions based on peer input is a very demanding job, but it is vital to the success of this Program. **As a result, the Low Dose Program is strong, vibrant, diverse and productive. Funds are well spent on the very best and most efficient approaches to answering questions regarding low dose exposure.**
- The application solicitation process begins with issuing an RFA and requires a letter of intent from interested applicants. The letter is reviewed by the three Program scientists who have also determined the specifics of the Program announcement and manage the portfolio. There are also informal comments kept in the file, which are noted in some decisions, but are not necessarily communicated to the applicants in a follow-up email. The purpose of the email is to inform the applicant of the initial impression of the proposed work's fit to current programmatic needs, technical relevance, and other issues including overlap with existing grants in the portfolio. These emails are short and somewhat direct in their summation, but they provide valuable feedback to prospective applicants, who may contact Program staff for additional information if desired. Importantly, these responses to the short preapplications give guidance, but do not prohibit the submission of any application from any applicant. This is a positive feature of the process, since applicants are able to revise proposed work to better suit programmatic needs based on this feedback. Complete applications are then submitted and distributed to a team of external, selected expert reviewers. Each application is assigned to three primary reviewers; written evaluations are solicited and discussed in a larger peer group meeting including a diverse review team and Program staff. Every application is discussed and evaluated in a number of categories with participation by the whole team, in some part guided by required questions written by Program staff to elicit comments that are useful for further deliberation at higher level reviews. Ad hoc reviews by technical experts are also solicited for a small number of applications as needed in order

to ensure the appropriate review of each application by three scientists qualified in the area. These ad hoc reviews are valuable additions, and are generally shared in a conference call that is audible for all reviewers who are on the review panel. Site visits are not included in the peer review for these applications.

- The review process is very efficient, although there is a very short time between the posting of the announcements and the time to the submission of the final application. In 2003, the announcement was posted February 19, letters of intent requested for April 4, and applications requested for May 23. In 2004, the announcement was posted June 7, letters of intent requested by July 15, emails from Program staff sent in August, and applications requested for September 15. In 2004, reviews were completed by mid-December. Relative to that for other agencies, this is a very rapid turnaround for the submission and review process. Given the small staff available to manage the reviews, decisions and communications back to applicants, this efficiency is remarkable.
- Reviews are consistent with priorities and criteria stated in the Program's solicitations, announcements and guidelines. This is in part aided by very specific questions that are addressed by the reviewers on their evaluation sheets in order to emphasize the Program announcement points and opinions that might be important for higher level programmatic review.
- The documentation for recommendations is succinct, in that it lists the conclusions as Accepted or Declined for funding. Reviewers' comments are provided for the applicants in all cases. In some cases, where programmatic review is used to change priority of an application, e.g., when an application scoring high for technical merit is not funded due to programmatic decisions, the explanation given to applicants is not made explicit. This generates confusion (and possibly ire) for applicants who receive glowing reviews, but are not funded. It would be helpful if a statement were added to the letter of decline or to the review summary, to make it clear to the applicant that while technical merit was strong, appropriateness of proposed work to the call or decisions based on programmatic focus and balance were not in favor of funding.
- The time line to decision is appropriate. Reviews are completed as soon as 10-12 weeks after submission (e.g., for RFA 04-21, the deadline for the applications was in September, followed by reviews in early December); the dates of decision letters are unknown, however, work plan paperwork to the host institutions seems to be dated on average in April, which suggests a rapid process in submission, review, and release of funds. Again, this is a remarkable efficiency compared with most government reviews in the life sciences and points to the efficiency and dedication of this very lean and very busy staff.

- Overall, the strengths of the review process include excellent streamlining of the review process, the high quality peer review by scientists with overall expertise in the project of each applicant, the official meeting in which this review is presented and discussed, and a fair and communicative Program staff. A weakness is the lack of clear feedback when decisions are made on programmatic grounds, especially since these considerations might well affect the applicant in resubmission choices. It is important to ensure a clear message from staff to the scientists in order to facilitate good decision-making in resubmission or for changing the focus of the application.
- One way to strengthen the review process might be selection of a Chair to serve as a facilitator during the review process in order to maintain the flow of discussions, to resolve differences effectively, and to maintain an appropriate time frame for discussion. The separation of the Program officers from the review process to some degree would permit them to serve better as advocates for the Programs they have worked to establish and direct, by allowing them to learn from the discussion and share these comments with the applicant directly, the applicants in improving their study design or programmatic content. A Chair and Co-Chair could also evaluate each application for its success in addressing specific calls for applications, for example, and ensure this feedback gets back to the applicant. This assistance would make this part of the review easier for Program staff.
- The addition of a specially set-aside call and sub-session for review of “High Risk-High Gain” applications might also increase the number of applications in this category and might help ensure that they are reviewed using appropriate criteria. Often, in review sessions that consider a large number of low risk, traditional applications, it is difficult for reviewers to switch mindsets to consider the different kinds of criteria that should be applied to applications with high risk or technical novelty. Some ways to encourage submission and open-minded review of such applications could enhance this Program dramatically.

Quality and Effectiveness of Selection of Reviewers

- The Program makes use of three reviewers for each application, a primary, a secondary and a discussant. This provides a balanced review. Additionally, following discussion, the entire review panel scores the applications independently which permits later numerical ranking for funding considerations by Program staff.
- The Program makes use of reviewers with appropriate expertise and qualifications, although there do seem to be some biases in the review panel members from year to year, in that many are already funded by the DOE, apply for funding the following year, and return to the review panel repeatedly. Six to ten descriptors for each reviewer’s area of expertise should be included in the list of reviewers. These could include descriptors such as

proteomics, statistical genetics, mouse modeling, radiation biology, or DNA repair in order to maintain a good balance of reviewers, to keep the reviewers informed of their colleagues' expertise, and for COV review.

- The Program has a balance of reviewers with expertise in different areas. Some questions remain about whether there is sufficient expertise in the areas required for review for every application, especially in newer technical areas, such as animal modeling, proteomics, transcriptional profiling, and bioinformatics. Some expertise in human or rodent pathology may be useful. While it is impossible to include experts on every subject in a review team, a stronger presence of technical experts who have not traditionally been involved in radiation biology research could be helpful.
- Conflicts of interest are identified in advance of the review. Reviewers with conflicts are asked to leave the review room during the presentation and discussion of the application in question, and not participate in the scoring. All reviewers are instructed clearly as to confidentiality of any information revealed in applications or during review discussions.
- A strength of the reviewer selection process is that many of the reviewers are very familiar with the field of radiation biology and have been previously funded by the Low Dose Program. This can also be a limitation of the reviewer selection process in that it is likely to lead to the successful evaluation of applications with ideas, immediate aims and goals similar to those that have already been funded. Diversity of approach remains important for ensuring discovery and rapid progress in science. One way of avoiding a tendency toward a more narrow range of award foci than would be desirable is to limit the number of times one individual can serve on the panel, and to establish rotations of reviewers who have different areas of expertise than the “standard” radiation biologists in the field, and to maintain these individuals as a relatively larger component (than currently) of the review panel. Broadening the reviewer base in this way would also present a good opportunity to bring in more junior faculty or scientists into the review process, and add in new reviewers with expertise in different areas. There is a balanced distribution of reviewers from universities and the National Laboratories, but this balance should be carefully maintained in order to ensure appropriate review of submissions from the two sources of institutions.
- One limitation of the reviewing and the reviewer selection process is that the Program staff are charged with making all decisions at all steps in the process, from RFA design to selection of all reviewers to the final choice of awards. Staff could be helped, but also the process might be strengthened, if e.g., a designated chairperson or other advisors could help e.g., by recommending specific reviewers. This would help bring in fresh perspectives and new ideas/expertise to the review process.

- The COV very strongly recommends that Program scientific staff, the PMs, be encouraged and enabled to attend more national or international scientific meetings annually, as they deem necessary, to enhance their contacts with potential reviewers, new ideas and technologies, and to recruit new applicants with fresh perspectives to the Program. As we have observed for all of the other Programs in the Life Sciences Division, a very small amount of additional funding for travel would be an important investment for DOE with the resultant very high payoff in the flexibility, strength and visibility of the scientific Program.

Resulting Portfolio of Awards

- The Low Dose Radiation Program portfolio is comprised of grants managed by well-respected, productive researchers with a long history in the radiation biology field. The quality of the work is therefore generally very high. One measure of this is the fact that many grants funded in the previous three-year cycle (beginning 2001) were continued successfully after stringent and competitive peer review. Most of the projects in this category had changed in scope and adopted new approaches and technologies (and frequently, new titles) to keep their Programs up-to-date, a good sign that the researchers are actively pursuing low-dose related questions with the latest technologies. On the other hand, it is also a good sign for the Program that an almost equal number of funded projects are new starts, by PIs already participating in low-dose research as well as many newcomers. This indicates that new researchers with new ideas are being attracted to the Program.
- Awards are appropriate in size considering proposed goals. The review committees give serious attention to cost issues in their reviews and in a few cases, this attention results in a significant downsizing of awards relative to requests. Most PIs are careful to produce budgets that can withstand this scrutiny.
- **The portfolio does contain a few high-risk applications, but increasing the number of these cutting edge applications would clearly be of benefit to the Low Dose Program.** The relatively small numbers of these is due to many contributing factors. First, many of the researchers applying to the Program (and most reviewers) are long-time experts in this field. This brings many advantages, including deep knowledge of this complex field and its long history. However, these experts are mostly trained to generate and appreciate applications that move in slow, cautious, and incremental steps. Such a cautious approach is not to be criticized, because it does yield results. However, it does not necessarily yield breakthroughs. The COV recommends that the BER staff complement their strong portfolio of conventional research by taking steps to encourage the submission and open-minded review of high-risk projects.

- The first step is to attract high quality applications of this type. **Doing so might be accomplished, for example, by a specially announced call of short term “pilot” studies, akin to the DOD “Idea Awards,” to test new technologies and introduce novel approaches to questions of low dose relevance.** Interest by a larger number of potential, innovative investigators could be encouraged, at a minimum, by a wider advertisement of the Low Dose Program to communities that might otherwise not participate, e.g., computational biologists, genome researchers, and nanotechnologists. A special RFA, broadly announced to scientists who might not normally participate in this Program or even in any DOE activities at all, might be a very rapid, effective way to enhance the visibility and attractiveness of this Program. Since young scientists are often the best source of innovation, another mechanism might be to fund a limited number of competitive awards for postdoctoral researchers or young investigators who bring expertise from other fields. Such awards could be made at relatively low cost, but would bring a very high payoff to the Program. There are many different ways that the profile of the Program might be raised to encourage broader participation by these new communities, and these should be investigated. Fliers distributed at meetings and sent to University departments to post on notice boards would also be a simple and low cost way to start. **The need to achieve broader participation and the establishment in general of proactive, effective outreach by way of enhanced, external involvement for the Program staff is one of many good reasons that travel to a larger number of high quality, national scientific meetings should be encouraged for the BER PMs.**
- The number of multidisciplinary efforts is a strong point that distinguishes the DOE Program. Many teams include physicists, biologists, chemists, and computer scientists working very closely together. More applications of this type would strengthen the Program. RFAs designed to attract or encourage applications from multidisciplinary teams would help increase the participation of such groups.
- The number of awards to National Laboratory and university participants is well balanced.
- From data available, a substantial number of awards are made each funding round to researchers who have not previously participated in this Program. There appear to be very few awards made to young investigators overall, but especially to those from the National Laboratories. Some effort to recruit young scientists, from both universities and National Laboratories, might help to freshen and strengthen the portfolio.
- The Low Dose Radiation Program portfolio includes researchers from all parts of the U.S. The distribution of funded PIs reflects the distribution of PIs submitting applications, especially in the case of university awards. National Laboratory PIs are fairly well distributed among the Laboratories with

significant life sciences research activities.

- Attention to emerging opportunities could be enhanced and increased. As mentioned above, some effort to attract new researchers with different perspectives into this field could be extremely helpful. This effort must be managed with care to assure that the innovation stays on point relative to the goals of the Low Dose Program.
- **The Low Dose Radiation Program tackles an important problem that may become center stage with renewed interest in nuclear energy on the national agenda. Very little scientific data are currently available to answer questions about exposures in the dose range highlighted by this Program. The Program is properly aimed at the most central and relevant questions.**
- In summary, the BER staff have done an excellent job in establishing the portfolio for the Low Dose Radiation Program, especially considering the scant resources at hand. They are to be commended for the high quality of research funded, the strong and expert peer-review, and efforts to balance the portfolio. Low-dose radiation effects are important and complex problems; it will be especially difficult to attract the kind of multidisciplinary talent to this field without additional support to help the management staff with their workload and without financial support and incentive to broaden their scientific horizons and contacts.

Management of the Low Dose Program

- The PM for Low Dose is doing a very good job across the board of the responsibilities; this is especially the case in the light of the limited resources available. The solicitations are well prepared, applications are thoroughly reviewed, and the progress of funded applications is carefully monitored. The Program shows evidence of a balanced portfolio of research, including some high-risk projects; further increase in novel approaches is desirable. There have been highly commendable improvements in recent years in record keeping and documentation in the jackets for successful applications as well as documentation for declined applications.
- The Program has been proactive in identifying relevant emerging areas of research, evolving its successive Program solicitations, encouraging introduction of new techniques and encouraging the entry of investigators with new areas of expertise. The challenge of the low dose research questions dictates that further ongoing innovation is required and additional solicitation mechanisms and publicity should be considered to achieve this (see above). It is essential that the PM be given sufficient resources to maintain and expand close contact with the primary scientific community, but also with promising new areas, by attending meetings, workshops and laboratory visits.

- As mentioned above, it is suggested that more feedback be provided on those applications that are declined on programmatic grounds where these might not be obvious from the reviewers' reports alone.
- The COV could not comment on Program prioritization as not enough information was provided (to the COV) directly regarding Program planning and prioritization. As planning and prioritization advances, guidance (possibly initially in the form of a conventional open letter to the community) would be appreciated on how the scientific community could contribute to the process.
- The COV strongly asserts again that for sustained excellence, it is essential for the PM to be provided with adequate resources to develop and maintain contact with the scientific community and to keep abreast of scientific developments across a broad front inclusive of the opportunities and challenges faced by the Program. Given the heavy burden that is placed on them in designing the solicitations or calls for applications (RFAs), in organizing and managing peer review, and in making decisions on programmatic grounds, it is essential that the PMs be given the tools they need to stay current with the science and familiar with the research community.

STRUCTURAL BIOLOGY

Overview

The Structural Biology (SB) subgroup of Life Sciences supports research resources for scientists at synchrotron and neutron sources, which in turn leads to the determination of three-dimensional structure information. SB, thereby, will play an essential role in the development of a GTL-based understanding of complex biological systems. Currently funded research resources include ones at the National Laboratories of Argonne, Brookhaven, Los Alamos, Lawrence Berkeley, Oak Ridge, and the Stanford Linear Accelerator Center. The early history for the provision by BER of resources for biologists at DOE radiation or light sources began with funds for Brookhaven in the 1980's. A SB Initiative beginning in the early 1990's led to a significant expansion and a focus on the relationships of structure or architecture and biochemical function. This growth reflected the increasing recognition of the value and the increasing emphasis on structural biology, specifically, as an approach within the biological sciences for providing insight into the mechanisms by which macromolecules, cells and organisms function. The DOE SB Initiative, in particular, aimed at understanding the underlying principles of how molecular-level biological systems work, and at doing so by characterizing the dynamic form and function of macromolecules interacting with each other. Toward such goals, the Stanford Synchrotron Radiation Laboratory was subsequently funded in 1992 jointly by BER along with the NIH National Center for Research Resources. Funding for the Protein DataBank began as well, in this case jointly with the NSF. The following year saw funding for research resources within major facilities at several National Laboratories. More beam lines were commissioned and experimental equipment improved to enable the resources to continue to be state-of-the-art and be as productive as then possible. Support has also been provided for efforts that address problems in handling vast quantities of data (the development of better experimental instrumentation and computer technology and programming for measuring, handling and archiving the data), and in improving the capabilities of X-ray detectors. Over these two decades, biologists came to depend on light sources for high resolution crystallography, and SB become an integral part of experimental biology.

DOE's resources played an essential role in this transformation that brought SB into a central role in the future of fundamental biology. The resolutions obtained for typical macromolecular structures as determined in a given year have steadily improved; indeed, many structures are now being measured at better than 1 Å resolution. In addition, neutron diffraction of proteins is now becoming possible for many proteins so that hydrogen/deuterium atoms can be located. The COV commends DOE for its vital role in helping make possible the research leading to the vast number of macromolecular structure determinations now in the scientific literature, and of equal importance, for ensuring that the results from these research projects would be made available to all interested scientists via the Protein Databank.

The experimental Programs in SB, after an earlier period in which more general approaches and technologies were explored, were selected to focus exclusively and very precisely on structural features immediately relevant to the particular DOE goals for biology. Specifically, applications on DNA damage repair and bioremediation were solicited in FY 2000, and 18 projects were funded. These projects were terminated early in FY 2004 for budgetary reasons. This outcome is regrettable for its impact on science output itself, and for the short and longer term consequences of this disruption of the human capital, the highly trained individuals for whom considerable investment had already been made. The outcome undoubtedly caused hardship to many scientists and will mean that SB scientists will be more cautious in engaging in any DOE team effort or responding to future solicitations.

DOE BER, as well as making wise choices in terms of funding quality science that is relevant to DOE missions, has to demonstrate clearly to policymakers that all projects provide unique contributions to American science, ones that would not be typically or even readily supported by any other science funding agency and notably, that the projects are not in the core of biomedical research (for which the potential of significant funding appears to be available). The COV believes that the projects terminated represented excellent science, were highly relevant to DOE missions, and are very unlikely ever to be funded by the NIH. However, as noted above, BER faces considerable challenges and a high level of complexity in setting priorities. The COV does appreciate the sophisticated considerations of priorities that were involved, given such a sudden and severe impact on the budget. Nonetheless, SB at one level or another contributes to all of the goals of DOE life science research, and the severe impact of the funding cuts will interfere with the other Programs achieving their priorities; that is, it will do so both directly, through loss of number of investigators supported across LS, and indirectly, through taking away what could be called a modality of discovery from the collective toolkit of biology supported for DOE missions. As a consequence, today at issue is the role of SB in BER funded research outside of contributions arising from the support of resources at DOE radiation facilities/light sources.

Specific Comments

To meet the goals of BER's mission-centered biological Programs and most notably Genomics: GTL, we believe that there is a strong case for the full integration of SB research within the core experimental biology Programs. We suggest two approaches, which are not mutually exclusive and might together be most effective. One is to be sure the human capital and the expertise already invested in the SB resources, largely at extant DOE major facilities, contribute significantly to the biology supporting the DOE mission. That is, utilizing the talents and intellectual resources of a facility, in a cost effective fashion, requires direct collaborations and the full use of the human scientific and technical workforce that maintains the facility. A balance - between the general expectations along with the requirements from general users, on one hand, and the importance of contributing in optimum ways that meet the goals of BER toward the DOE missions - might be achieved through the discretionary funding to utilize those resources to contribute directly to GTL objectives; a path toward this balance might also be

established, in part, through a partnership with the directors of those research resources, since BER would be allowing them, in effect, to see the future and establish a ground breaking path. The second one is to evaluate how collaborations could be built explicitly into future GTL solicitations (RFAs) to ensure that the essential tools and expertise in SB contribute to needed features of GTL. Certainly, without any active intervention by the Program, the GTL scientists will increasingly recognize the need for SB, and the PMs will respond accordingly. SB would then be increasingly be built into GTL research from a bottoms up approach, that is, by the investigators, in the absence of any high level vision. The pull from the science community will demand this, but if the Program and BER wait for the pull to drive the introduction of the needed push, the technology and intellectual expertise of SB, there will be a lag in ability of the funded research to address the DOE mission goals. **BER can greatly accelerate the introduction of the physical sciences and the methods of SB, and therefore ensure more rapid progress, through immediately integrating SB directly into GTL.**

The COV believes that evaluating the best approach and subsequently, implementing SB science activities within the GTL research is essential and should not wait. The ambitious goals of GTL can not be realized without full consideration of the dynamic form and function of the molecules of life. Every discussion in all of the GTL workshops and reports includes this consideration at least implicitly. From the multi-protein, macromolecular machinery operating in cellular metabolism to the pathways, networks and cascades among protein species that regulate and direct life's many processes, macromolecular recognition is at "the heart" of how living systems function, or, that is, is a phenomena central to biology and the processes of living cells. The specific means by which a biological process governs energy production or might allow a microbe to facilitate bioremediation are enabled by specific architectures, the chemical interactions of macromolecules determined by those architectures and the conformational changes (and other dynamics) needed for biological function. For the longer term goals of GTL, establishing a defined process for modifying microbes and microbial processes, rather than requiring considerable luck and statistical technologies (for example, for selection of cells and cellular properties in screens of mutants). Reengineering microbes for clean up or for "green industrial processes" requires an understanding of the dynamic architecture of macromolecules and the details of the interplay among the components of the macromolecular machinery of cells. Ascertaining these biological aspects is the major goal of SB research, and its core deliverable for progress in the life sciences.

The priority for driving immediate advances in basic biology for the first phase of GTL has been obvious, but the approaches, technologies and fundamental scientific concepts of SB are essential for the next step for GTL. This next stage of GTL – to move to a comprehensive knowledge of microbial systems to enable reengineering - will be very difficult and technically challenging, as well as time-consuming and expensive, but the results for DOE's missions and for society make the stage well worthwhile. In the absence of a robust SB research endeavor within GTL, **reengineering microbes and subcellular systems in microbes or in vitro to address these missions will be very difficult even on an individual or singular basis to yield a reengineered subcellular system. On a systematic and routine basis it would be virtually impossible to do so in the absence of the types of knowledge inherent in the outcomes of SB research.**

As a direct result of our COV analysis of the SB Program of the Life Sciences Division, **the COV committee urges the creation of an activity (presumably as a sub-Program of the overall SB Program, for the ease of management, but lying with Genomics: GTL for its scientific focus) entitled "Structural Proteomics"** (and as outlined below). The sub-Program would grow over some longer term period - depending on funding available and on a careful assessment of the state of the interconnections of the microbiology with SB - to empower continued progress in the application of SB methods to GTL. To appreciate the potential and to validate the recommendation, BER should review and consider the objectives of GTL. To put the matter simply, every GTL workshop and every GTL policy document has spoken about the need to understand the mechanisms by which protein assemblies work, how regulation and the wide and diverse collection of cellular processes are achieved. Along with continued molecular biology and microbiology contributions and those from computational biology, to understand these attributes of living cells requires the involvement of SB research. SB can provide a directed path first toward fully understanding the mechanisms in nature and second toward the achievement of GTL's goals through a directed approach, rather than through selection and serendipity based establishment of new properties for microbes. For example, this is stressed in Section 3.2.2.2.1.1. (page 47) of the DOE Genomics:GTL Roadmap, August 2005 on "Developing methods to define cellular networks and molecular interactions and mechanisms of regulation." The GTL implementation document states: "Providing a comprehensive view of proteome organization and dynamics promises to be a singularly important watershed of whole genome biology for coming decade because it will enable, inform, and enhance virtually all other molecular and cellular investigation."

DOE has a considerable investment in resources and the scientific infrastructure around facilities (as well as in the facilities themselves). Naturally, enhancing the research resources at those facilities leverages the facility success and in turn, is essential for that success. These investments today include the SB infrastructure and will include the planned facility for the large-scale production of protein and their complexes, and future facilities around functional aspects of proteins, in the GTL Program. **What is lacking is the ability to connect all these investigations experimentally with structural information so that we can determine and manipulate function.** Then, we believe, such an effort becomes capable of contributing on a large-scale and of being a natural component of GTL. Since it arises from SB approaches and is closely related to the comprehensive or genome scale research on proteins termed proteomics, we suggest calling the effort "Structural Proteomics" (SP).

In sum, the COV thus suggests an augmentation of DOE's Life Science efforts through the addition of a new focus on SP, which could be a Program or a sub-Program of SB, whichever best suits the administrative needs and activities of BER. Together with the LS Division's Programs on Genomics and Biology, Genomics: GTL, and Low Dose Radiation, the SP Program would provide DOE and the scientific community with the basic interconnection among these DOE Programs aimed at understanding the science and function of all systems. Thus, SP is truly a science at the interface required for the successful continuation of DOE's research mission for the advancement of scientific knowledge. SP would greatly expand the existing concepts and current research

strategies for proteomics by providing the information needed to interpret our current knowledge and to explain the functions of the structures found and their mechanisms of action. The COV believes SP will certainly be another important Program of BER's "Science at the Interface".

SP research, as an interface science within Genomics: GTL, is vastly different from the research being emphasized by conventional structural genomics efforts (that is, research as part of the NIH's Protein Structure Initiative (PSI), as well as related efforts in other countries). The differences are in the specifics of the approach, inclusiveness, and the applications. These novel features, essential for any DOE BER research funding, will be sustained through the full integration of SP research within the extant experimental biology portfolio of BER. For example, in terms of the unique applications, DOE's research interests cover such areas as microbial genomics and environmental management (bioremediation of metals). These are organism-based research subjects. Structure-function relationships of proteins of these organisms are relevant to DOE research mission and scientific community, but they are not of interest to NIH or to the large-scale structural genomics projects underway in other countries, such as Japan, Canada, the United Kingdom and Germany. The NIH's PSI represents an effort to focus structural genomics research to have a maximum ultimate impact in improving the accuracy of the computational prediction of protein structure. In addition, the PSI funding is provided so that researchers will have a comprehensive picture of protein architectural or structural space. Such a picture notably involves finding some examples of each protein family and the completion of our knowledge, by way of multiple examples, of the architecture of each of these protein families (see below) in structural space. As background, an important consideration is that the individual protein families are grouped according to sequence homology (or strictly speaking, molecular isology) rather than according to a particular organism, and the emphasis is to get to mammalian and human proteins, not continue to exploit the advantages of microbes. The PSI does not provide funding for functional studies on individual proteins and/or their multi-protein complexes within an organism. In contrast, functional studies to define cellular networks and molecular interactions, the mechanisms of regulation, and "a comprehensive view of proteome organization and dynamics" are extremely important to DOE's mission and for that reason, are on the GTL roadmap, and require an understanding of dynamic form and its relationship to biochemical and biological function for macromolecules.

Over the past several years, it has become quite clear that the NIH PSI is moving in the exclusive direction of developing and applying "rapid, efficient and dependable methods" for creating high-throughput gene-to-structure pipelines in order to find a few examples of all protein families and to solve their structures. The objective is to provide sufficient number of structural templates of various protein "types" for future homology modeling (another PSI goal in development) of any protein structure with more than 30 percent sequence homology to the template. To facilitate the structure determinations of representative structures, a homologous structure from a different species will be studied, if the structure of a protein from the initially selected species cannot be obtained. While this approach of the PSI and other structural genomics efforts will eventually provide sufficient numbers of representative structural types for the scientific community, the

outcome will not be sufficient when detailed and critical three-dimensional structural information is required to understand the structure-function relationships and dynamics of proteins from organisms that are of importance to the DOE mission. This is because a representative structure, while providing the researcher with the overall structural shape of a molecule, will not routinely provide the level of structural detail that will be necessary for understanding fully the function and mechanisms of action of specific proteins and their macromolecular assemblies, or for their reengineering to optimize the utility of microbes for applications in energy and environmental science.

Furthermore, the software for homology modeling has not yet advanced to the point where the predicted structures are precise enough (and therefore provide enough accurate information) for pathway and protein redesign. Biological issues related to energy, environmental remediation and climate change are of primary importance to the 21st-Century biology of the Nation. Since assembling a comprehensive view of the proteome and its multi protein complexes is a piece of the foundation for systems biology and a cornerstone of GTL, the COV places a high priority in urging the DOE to create a mechanism for the systematical investigation of the structure-function relationships of proteomes and of their individual, multiprotein complexes for organisms of interest to DOE, which we termed SP. For GTL to achieve its objectives, and for research in biology to apply to the energy and environmental missions, will only be possible through inclusion of the essential features of SP. **Without this important "Science at the Interface," GTL will not be able to effectively assemble "a comprehensive view of the proteome and its multi-protein complexes" and build a solid "foundation for systems biology" because an important property, the structure of the proteome and of its complexes as well as its link to function, would be missing from the research portfolio.**

The COV considers that the review process for the existing SB Program is very good and the handling of grants has been appropriate, but beyond the immediate needs for advances in microbiology within GTL, we believe the current organization and practices will limit the potential of GTL. In urging BER to adopt our concept of a "SP" activity, we note the administrative context of implementing SP as an "element" (a sub-Program) of a fully balanced BER research portfolio would permit, in the future, a range of innovative SB research projects to be deeply embedded into the science infrastructure of GTL and accelerate scientific progress. A list of questions was supplied, and the COV SB subcommittee has answered them to a reasonable extent. However, in view of the reduction in funding of SB, the COV had difficulty in commenting on the questions as asked. Approximately half of the projects from 2003 are now eliminated from funding, and those that remain are mainly for research resources, and not explicitly toward research projects (using the facilities) that would deliver on the missions of DOE. While DOE's stewardship responsibilities (in the current situation with severe limitations and an inadequate budget) lead to prioritized funding for research infrastructure, that is, for user resources at state-of-the-art, essential facilities, rather than for individual research projects, several of the discontinued projects have aims that are of continuing high significant importance to the DOE and are not likely ever to be significant for the NIH. Important research has now been delayed into the indefinite future. The COV recognizes the extreme circumstances that led to these actions and appreciates the difficulties of the

decisions and the choices about priorities. Nonetheless, the COV strongly recommends that DOE evaluate the entire history, current environment, and overall implications in order subsequently to find a means for avoiding a repetition of this unfortunate event.

The COV believes it would be ideal for BER to complement its excellent SB resource Program at the light sources, for which the Program is already a world leader, around SP, as we have described above. Coupling SB into the GTL vision in the context of the BER SB resources would provide an opportunity to nucleate and test key ideas and approaches that can be expanded when funding is available. The partnership with the resource efforts should allow BER to define and implement this Program early on, while the Federal science budget is still so severely limited. Despite the current limited funding available, BER leadership and PMs need to work with the relevant scientific community to ensure a strong role for the contemporary physical and chemical sciences to play its potentially powerful role in the interdisciplinary science objectives of GTL through the implementation of our suggested SP sub-Program.

GENOMIC RESEARCH AND BIOLOGY RESEARCH

Overview

In performing its review of LS support for the area of Genomics (the JGI) and exploratory research in biology, a subset of the COV membership reviewed the appropriate Program descriptions, strategic planning documents, grant solicitations, and the websites. In addition, the subcommittee reviewed 21 funding actions that occurred in the period of FY 2002-FY 2004.

This area includes a broad range of activities that are funded and managed through a wide range of management processes. These range from the ELSI Program, a small (\$2M/Yr) Program which was established as part of the human genome project, to the JGI, a major national user facility with a budget in excess of \$50M/year. The ELSI Program solicits, reviews and funds small awards, mostly to academic and non-profit organizations using mechanisms common to a number of other BER Programs that support research. The JGI, also developed as part of the human genome effort, was originally intended to be an efficient, unified sequencing center for the combined human genome sequencing efforts of several National Laboratories. With the successful completion of the human sequence, the JGI has evolved into a national user facility of incredible capability. The JGI has the potential to advance knowledge significantly in a number of areas that include, but are not limited to, the biological sciences. The JGI funding is determined through DOE management decision, supported by an assessment of the quality of science that is being produced at the JGI (details below).

Over the years the SC (formerly, Energy Research) has significantly increased its commitment to using peer review to set priorities for research funding. **The Life Science Division was a leader in that regard; the influence and impact of BER's Life Science Program on the human genome project and its leadership role in microbial genomics (notably, the "which bugs" workshop, among other examples) were possible because of the credibility engendered by community involvement and peer review. The COV commend DOE for moving in this direction.**

We also commend DOE for a leadership role in infrastructure, such as BER's willingness to develop truly outstanding, large-scale facilities like JGI. The overall infrastructure at such resources and facilities allows science to be done that simply could not be accomplished elsewhere. It is important to note that the direct support of large facilities does not mean that their research effort is not subject to prior evaluation. Indeed, the JGI employs a number of review and oversight committees to prioritize the projects undertaken at the JGI.

Specific comments

Ethical Legal and Social Implications

- The COV looked at selected records for approximately 15 applications drawn from among the 40 or so applications reviewed in the last two years of the ELSI Program. Of those we looked at, approximately half were awards. We consider this to be a somewhat small sample size on which to base a programmatic assessment. This is especially true given the wide variety of activities proposed and funded.
- By and large, the COV found the reviewers comments to be useful, and to be consistent with the funding decisions. ELSI represents an essential feature of a modern science research portfolio, and the pioneering efforts of BER are to be commended.
- The regular creation of a written "review analysis" by the PM might help ensure that a balanced review is obtained for each application. This should be retained with other documentation for internal DOE use only. Such an analysis need not be extensive, but could prove helpful, especially where there is significant variance among reviews, or when the reviews themselves do not provide a clear rationale for selection of a particular application for support or decline. In addition, the document could serve as a reminder of any concerns that might be relevant to assessing interim progress.
- In the two ELSI panels we evaluated, there appeared to be no obvious institutional conflicts. However, the documentation did not associate specific panelists with review of specific applications, and so we could not assess this at a fine-grain level.
- The COV noted that the selection of panelists seemed to emphasize the use of reviewers from the Washington-Baltimore area. While this is understandable from a practical standpoint, the Program should strive to emulate the efforts of other agencies in aiming for geographic diversity in reviewer selection.
- The balance of gender and institutional backgrounds of panelists seemed reasonable, with the exception that there appeared to be a disproportionate involvement of government officials. Greater involvement of individuals selected from the non-governmental academic and research community would be desirable. Within this latter group, we would include staff of the DOE National Laboratories.
- Staff should note that involvement in review is a way to stimulate knowledge of and interest in Programs like ELSI. In this regard, **DOE could try to engage staff of the DOE National Laboratories in ELSI review as a way of stimulating interest within the National Laboratory system in the ELSI-relevant aspects of their own activities.**

- With respect to the ELSI portfolio, we were somewhat surprised to note that the relatively low involvement of National Laboratories in ELSI activities (few applications, fewer awards). **Some thought should be given to stimulation of greater National Laboratory involvement in activities addressing ELSI.** These might include novel approaches such as supplements to non-ELSI awards or support of Programs specifically targeted at National Laboratory (and possibly other Federally Funded Research and Development Centers) staff.
- The DOE's original involvement in support for ELSI projects stemmed from its involvement in the HGP. Although DOE's involvement in human sequencing has wound down, the need for greater understanding of ELSI issues by scientists, and by the public, has not. We were informed that, beginning next year, the ELSI Program would expand its scope to cover additional areas (such as nanoscience) supported by SC. The COV applauds this broadened effort.
- The COV encourages DOE senior management to seriously consider a further broadening of the Program to include ELSI aspects of DOE-supported technologies and activities that lie outside the immediate responsibility of BER. The experience gained by BER in addressing this issue (within the context of human genome sequencing) could be an important resource for other parts of DOE in addressing increasing concern within the community of researchers and the public with respect to the ethical, legal and societal impacts of modern technology.

Biology Research

The Biology Research area is currently funding relatively few activities, making difficult a systematic assessment of the Program's operations following the questions provided to the COV by DOE. That is, the sample size was so small that the questions posed could not be answered, except anecdotally. We note that the supported activity in these areas is strong, and that the exploratory contributions have had a history of significant contributions and the current research program shows numerous equally promising examples and should continue to be exciting and productive, and to contribute to the broader goals of BER

Joint Genome Institute

In many ways the JGI is the flagship of this element (or Program) and even of the portfolio of the entire Life Sciences Division. This highly cost effective, high-throughput sequencing facility provides a stunning amount of sequencing capacity to the research community.

The sequencing capacity of the JGI is made available to the community through the Community Sequencing Program (CSP) (and through the microbial sequencing Program reviewed by the GTL subgroup of the COV), a process that allows members of the community to propose sequencing projects. These applications are then reviewed by the

Application Study Panel (PSP) (a panel of qualified scientists selected by JGI). Applications given a high scientific priority by the PSP are then reviewed for appropriateness and technical feasibility by the external JGI Scientific Advisory Committee and the internal JGI Scientific Support Group.

- The current CSP review mechanism for selection of sequencing projects works well. However, we noted that current membership of the PSP emphasizes researchers drawn from the San Francisco Bay area (almost half of the PSP members are physically located within 50 miles of the JGI). Greater geographic diversity among this membership would likely increase knowledge of the availability of the JGI among diverse research communities.
- At present, the CSP review process emphasizes applications that focus on the sequencing of one or a few organisms at a time. The COV suggests that DOE should encourage the JGI advisory bodies to devise ways to encourage *big picture* thinking on a scale commensurate with the capabilities of the JGI. As an example of such thinking, the COV notes that at present there are approximately 5000 named species of culturable bacteria. With an average genome size of 5 megabases, the total aggregate genome size of all known culturable bacteria is 25 billion bases. **Given the present and future³ capacity of the JGI, the production of draft or finished sequences of all 5000 bacterial species is in fact feasible.** Because of the ubiquity of bacteria, the availability of such sequences could not only transform the study of bacteria themselves, but numerous other areas of the biological sciences and other disciplines such as oceanography, earth sciences, and civil engineering. The availability of a full sequence for all known bacteria would transform microbiology (or at least bacteriology) into the first fully “post-genome” science. **The COV offers this as an example of the kind of large-scale transformative thinking that should inform at least some of the allocation process for JGI capacity.** That is, it is important that at least some of this large-scale resource be used for large-scale science. One would not want to use the Hubble Telescope only to look at the moon. It was not clear to the COV who, if anyone, has formal responsibility for this kind of visionary thinking about the use of the JGI. The COV **encourages BER staff and BERAC to think about how this might best be achieved, and does not necessarily expect that our specific recommendation be followed; however, something of this nature would have an exceptional impact and provide incredible recognition for the DOE that could spin off to enabling the funding for many other contributions.**
- Given the flagship role of the JGI for the Life Sciences Division, the COV recommends that the DOE collect and maintain appropriate documentation regarding the details of the JGI allocation process and of JGI scientific operations so that appropriate oversight can be maintained. The COV

³ Current JGI projections indicate that within five years the JGI will be capable of producing more than 100 billion bases of sequence per year.

believes that this is an incredibly valuable resource, one that must be operated in a manner to optimize the value delivered to the scientific community. Because these scientific opportunities are subject to rapid change as new insights become available, it is important that DOE stay involved in the allocation process. The COV notes that DOE is invited to the allocation meetings and the COV encourages DOE to participate as much as possible.

- The COV emphasizes that the scientific application process in place is an excellent approach to resource allocation at a user facility and we are not suggesting that this mechanism be abandoned.
- At present, the JGI guidelines for the allocation of sequencing capacity for any large sequencing project requires that the biology of the organism have some relevance to the DOE mission. **The COV believes that this is short-sighted. The utility of an organism's sequence is not necessarily determined by the organism's known biology.** For example, the sequence of a single known pathogen might not be seen as relevant to the DOE mission, but understanding how bacterial sequence determines bacterial function in energy-relevant bacteria is central to the DOE mission. A general comparative approach relating sequence to biochemical function thus is also central to DOE mission. Gene discovery is a critical part of comparative genomics. Genes are the building blocks of organisms. One cannot understand how genes determine function only by looking at one group of organisms. Data from out-groups is critical for comparative analysis.
- **The COV notes that DOE should recognize its role as a steward in maintaining and operating this facility for the overall research community.** The evolution of this outstanding resource, the JGI, from a dedicated genome-project facility into a general user facility is an excellent example of how a first-rate dedicated facility can be converted to become an even better community resource. DOE should be commended for its willingness to make this excellent resource available to the general community.

ACKNOWLEDGEMENTS

The members of the COV would all like to thank personally the members of the management and staff of the Life Sciences Division and of BER for their courtesy and assistance during the COV meeting. The administrative and scientific staff from the LS Division and from the central office of BER obviously put in a very significant effort preparing for this visit. To facilitate our efforts and provide information whenever needed, they were available to us throughout the visit. Frequently, the COV team asked LS leadership and PMs to join in ad hoc discussions of some aspect of the Programs under consideration. All of these requests were unfailingly met with prompt and pleasant cooperation. We greatly appreciate the assistance of the entire LS team and would like to recognize the excellent administrative assistance provided by the LS staff in so many different ways through the COV.

Drs. David Thomassen and Ari Patrinos provided the COV with basic information about DOE, SC, BER, and specifically, the LS Division. Their comments set the stage for a successful visit and our ability to produce an effective COV. At the completion of the review, Drs. Patrinos and Thomassen entertained all comments from the COV, provided insight and information to allow us to fine tune our considerations, and seriously responded to the issues that were brought before them.

Without the support from Ms. Kim Laing and Dr. Tim Boyle, the task would have been much more difficult. We especially wish to note their energetic engagement in so many small details and required administrative efforts.

We very much appreciate having had the opportunity to provide input into, and suggestions for, the management of these nationally important Programs. We hope that this report will help all four Program elements achieve their full potentials.

APPENDIX A



Department of Energy
Office of Science
Washington, DC 20585

November 18, 2004

Office of the Director

Dr. Keith O. Hodgson
Director, Stanford Synchrotron Radiation Laboratory
Department of Chemistry
Stanford University
Stanford, California 94305

Dear Dr. ^{Keith}Hodgson:

By this letter, I am charging the Biological and Environmental Research Advisory Committee (BERAC) to assemble a Committee of Visitors (COV) to assess some of the research program management processes in the Life Sciences Research Division in BER. The panel should provide an assessment of the processes used to solicit, review, and recommend proposal funding actions. It should also assess the processes used to manage ongoing research programs in the Life Sciences Division, especially the decision-making processes. I would like the panel to consider and provide evaluation of the following two major elements.

1. For both the DOE laboratory projects and university grants, assess the efficacy, fairness, and quality of the processes used to: (a) solicit, review, recommend, and document proposal funding actions, and (b) monitor active projects and programs for progress and outcomes. For example, is the proposal review process rigorous and fair, are funding decisions adequately documented and justified, does the solicitation process for proposals provide sufficient and useful guidance to prospective applicants, and is the progress and outcomes of multi-year projects adequately monitored and evaluated to justify decisions about continued funding?
2. Assess the efficacy and quality of processes used to manage ongoing programs. For example, does the process (a) consider the depth and balance in a research portfolio, (b) solicit and encourage some exploratory, high-risk research, (b) link the research to mission needs of DOE, (b) enable the support of coherent suites of projects that are integrated and collectively of added scientific value to programs, (c) ensure a reasonable and appropriate turnover of funded investigators to enable and foster the support of new projects and scientists by programs, and (d) result in a portfolio of elements and programs that have national and international scientific standing?

The panel should assess the processes and operations used for proposal funding actions and program implementation decisions in the Life Science Division for projects that received funding during FY 2004 or the first part of FY 2005 and provide comments on how they can be improved. It may examine any files of both DOE laboratory projects and university projects that received funding in FY 2004 or FY 2005. It may also examine any documents related to Life Science Division program implementation. The panel is asked to review the aforementioned processes used by all Life Science Division programs and elements. The COV panel will be provided with background material on the processes prior to its first meeting.

A primary requirement is that the COV should have significant expertise across all covered areas, and that this expertise should not rely upon one person alone. A second requirement is that a significant fraction of the committee receives no direct research support from the DOE. A guideline is that approximately 25 percent of the members, including the Committee Chair, receive no support from DOE. It is also important to have representation on the COV from individuals with experience in managing research programs, either at DOE or NSF. There should be an attempt to balance between university principal investigators and national laboratory investigators. A final overlay should also consider a number of other balance factors, including institution, geographic region, etc. In the end, the COV should constitute an exceptional group of internationally recognized researchers, with broad research expertise in the program areas in BER's Life Sciences Division, as well as a deep familiarity with DOE programs.

The COV should take place in the spring of 2005 at the BER/DOE Germantown location at 19901 Germantown Road, Germantown, Maryland. I would like a presentation on the status and progress of the COV to BERAC at either the April or November 2005 meeting. Following acceptance of the full BERAC committee, the COV report with findings and recommendations is to be presented to me, as the Director of the Office of Science.

If you have any questions regarding this charge, please contact David Thomassen, 301-903-5468, or by email at david.thomassen@science.doe.gov.

Sincerely,



Raymond L. Orbach
Director

cc: Ari Patrinos
David Thomassen

APPENDIX B

**COMMITTEE OF VISITORS (COV)
for the
LIFE SCIENCES DIVISION
of the
DEPARTMENT OF ENERGY**

17-19 May 2005

Dr. John C. Wooley, COV Chair
University of California, San Diego
9500 Gilman Drive, MC#0043
University Center, Building 965
La Jolla, CA 92093-0043
Phone: 858-822-3630
Fax: 858-822-4767
Email: jwooley@ucsd.edu

Dr. Edward F. DeLong
Massachusetts Institute of Technology
Department of Civil and Environmental
Engineering & Division of Biological
Engineering, 48-427 MIT
15 Vassar Street
Cambridge, MA 02139
Phone: 617-253-5271
Fax: 617-258-8850
Email: delong@mit.edu

Dr. Jenny Glusker
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111-2497
Phone: 215-728-2220
Fax: 215-728-2863
Email: Jenny.Glusker@fccc.edu

Dr. Dudley T. Goodhead
Radiation & Genome Stability Unit
Medical Research Council
Harwell
Didcot
Oxfordshire England OX11 ORD
United Kingdom
Phone: 44 1235 834393
Email: d.goodhead@har.mrc.ac.uk

Dr. Joanna L. Groden
Department of Molecular Genetics,
Biochemistry & Microbiology
University of Cincinnati
College of Medicine
231 Albert Sabin Way
Cincinnati, Ohio 45267-0524
Phone: 513-558-0088
Fax: 513-558-2794
Email: joanna.groden@uc.edu

Dr. Margo G. Haygood
Professor of Marine Biology
Marine Biology Research Division, 0202
Scripps Institution of Oceanography
University of California, San Diego
9500 Gilman Dr.
La Jolla, CA 92093-0202
Phone: 858-534-5987
Fax: 858-822-5839
Email: mhaygood@popmail.ucsd.edu

Dr. Bernhard Palsson

University of California, San Diego
Bioengineering Department
PFBH, Room 419
9500 Gilman Drive
La Jolla, CA 92093-0412
Phone: 858-534-5668
Fax: 858-534-5722
Email: bpalsson@ucsd.edu

Dr. Robert Robbins

Vice President, Information Technology
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, J4-300
Seattle, Washington 98109
Phone: 206-667-4778
Fax: 206-667-7733
Email: rrobbins@fhcrc.org

Dr. Lisa J. Stubbs

Lawrence Livermore National Laboratory
7000 East Avenue
Livermore, CA 94550
Phone: 925-422-8473
Fax: 925-422-2282
Email: Stubbs5@llnl.gov

Dr. Margaret (Peg) Riley

Department of Biology
University of Massachusetts Amherst
Amherst MA, 01003
Phone: 413-545-2132
Email: riley@bio.umass.edu

Dr. Gerald Selzer

Division of Biological Infrastructure
Room 615N
Biology Directorate
National Science Foundation
4201 Wilson Blvd.
Arlington, VA 22230
Phone: 703-306-1469
Email: gselzer@nsf.gov

Dr. Bi-Cheng Wang

B204A Life Sciences
Department of Biochemistry
& Molecular Biology
Athens, GA 30602-7229
Phone: 706-542-1747
Email: wang@bcl1.bmb.uga.edu

APPENDIX C

**STAFF MEMBERS and COV RESPONSIBILITIES
of the
LIFE SCIENCES DIVISION
of the
DEPARTMENT OF ENERGY**

Jeff Amthor	Carbon sequestration
Dan Drell	Genomics: GTL
Roland Hirsch	Structural biology
John Houghton	Genomics: GTL
Arthur Katz	Low dose radiation research
Noelle Metting	Low dose radiation research
Marvin Stodolsky	Genomics/JGI; Biology
Sharlene Weatherwax	Genomics: GTL
Kim Laing	overall coordination for COV
Tim Boyle	overall coordination for COV
David Thomassen	Chief Scientist, BER
Ari Patrinos	Associate Director, BER

APPENDIX D

DOE BER LS COV AGENDA**MAY 17 (TUE)**

- 8:30 am Welcome to DOE
G-207
- 9:30 am Sub teams move to breakout rooms
various locations
- 12:01 pm Working lunch
G-207
- 1:00 pm Sub teams move to breakout rooms
various locations
- 4:30 pm Executive session to review the findings
G-207
- 6:30 pm Adjourn for the day
G-207

MAY 18 (WED)

- 8:00 am Brief executive session
G-207
- 9:00 am Sub teams move to breakout rooms
various locations
- 12:01 pm Working lunch
G-207
- 1:00 pm Sub teams move to breakout rooms
various locations
- 4:30 pm Executive session to review the findings
G-207
- 6:30 pm Adjourn for the day
G-207

MAY 19 (THU)

- 8:30 am Full Executive Session to Review Reports
G-207
- 10:30 am Preliminary Report Briefing to BER Leadership and Staff
G-207
- 12:30 pm COV Adjourns

APPENDIX E

Responses to Questions

Microbial Genomics / Genomics: GTL

Date of COV: May 17-19, 2005
Program: GTL and Microbial Genome Sequencing
Number of actions reviewed by COV: Awards: Declinations: Other:
Total number of actions within Program during period being reviewed by COV: Awards: Declinations: Other:
Manner in which reviewed actions were selected:

A. Questions about the quality and effectiveness of the Program's use of merit review procedures. Provide comments in the space below the question. Discuss areas of concern in the space provided.

QUALITY AND EFFECTIVENESS OF MERIT REVIEW PROCEDURES	YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE
<p>1. Is the review mechanism appropriate? (Panels, ad hoc reviews, site visits) Comments: The review mechanisms currently in place for both the Sequence Targets and the GTL Programs seems appropriate with respect to balance, parity and diversity of perspective and input. The GTL requires a more diverse and complex set of applications but the system employed works well.</p>	YES
<p>2. Is the review process efficient and effective? Comments: The process works very well for the entire activity.</p>	YES
<p>3. Are reviews consistent with priorities and criteria stated in the Program's solicitations, announcements, and guidelines? Comments: The panel reviews are consistent with GTL and Sequence Target guidelines and criteria and the reviewers do an excellent job of providing a critical evaluation of the scientific quality, appropriateness of the PIs, and DOE mission relevance.</p>	YES

<p>4. Is the documentation for recommendations complete, and does the Program Manager provide sufficient information and justification for her/his recommendation?</p> <p>Comments: Review panel recommendations and priority scores are well documented. However, the COV recommends that when lower ranked applications are funded in preference to those with higher rankings, a more in depth justification for the final decision be included in the application jacket (e.g., for reasons of high risk, Program balance, and so on).</p>	YES
<p>5. Is the time to decision appropriate?</p> <p>Comments: For the data that was available, the time from Notice announcement, to pre-review, to review and award notification was very reasonable – generally more expeditious than the timeframe of other comparable agencies competitions (e.g NSF, NIH).</p>	YES
<p>6. Discuss any issues identified by the COV concerning the quality and effectiveness of the Programs use of merit review procedures:</p> <p>Applications in response to solicitations are handled well. For large supplemental requests it would be useful to provide more documentation on how that decision making process occurs.</p> <p>More mechanisms for “getting the word out,” such as internal travel support for Program Managers for this purpose, would be useful.</p>	

B. Questions concerning the selection of reviewers. Provide comments in the space below the question. Discuss issues or concerns in the space provided.

QUALITY AND EFFECTIVENESS OF SELECTION OF REVIEWERS	YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE
<p>1. Did the Program make use of an adequate number of reviewers for a balanced review? YES</p> <p>Comments: Excellent in terms of the ratio of reviewers to applications. Great job.</p>	YES
<p>2. Did the Program make use of reviewers having appropriate expertise and/or qualifications? YES</p> <p>Comments: The panels have a good balance of expertise, which includes reviewers from national labs, university researchers and often outsiders to the DOE.</p>	YES
<p>3. Did the Program make appropriate use of reviewers to reflect balance?</p> <p>Comments: The reviewer pool is well balanced in the important ways essential to provide a sense of equity in a DOE context; namely, in terms of</p>	YES

intellectual disciplines and institutional considerations.	
4. Did the Program recognize and resolve conflicts of interest when appropriate? Comments: NO DATA so we can not answer this; no conflicts were observed by the COV.	NO DATA AVAILABLE

<p>5. Discuss any concerns identified that are relevant to selection of reviewers</p> <p>Good balance on getting in outside experts who are not necessarily proponents or fundees for outside, unbiased perspective. Although fewer women than men have applied in many of these programs, the review panels have excellent representation of women referees. This may in part act as a form of outreach to balance the gender ratio of the applicant pool in the future.</p> <p>Overall, the COV is very impressed with the quality and efficiency of the entire review process – especially given the small staff size available for this process.</p>
--

C. Questions concerning the resulting portfolio of awards under review. Provide comments in the space below the question. Discuss areas of concern in the space provided.

RESULTING PORTFOLIO OF AWARDS	APPROPRIATE, NOT APPROPRIATE, OR DATA NOT AVAILABLE
<p>1. Overall quality of the research projects supported by the Program. Comments: We have reviewed a subset of GTL and Sequence Target folders and overall the quality of research proposed is quite high. These Programs have very good track records to date, with respect to results obtained from supported research. It is early in the Program with respect to making a thorough overall assessment of impact from completed or near-completed projects. However, All indicators suggest a high level of productivity from approved Programs and currently underway projects.</p>	YES
<p>2. Are awards appropriate in size and duration for the scope of the projects? Comments: In the early stages of development (GTL 2002), a smaller number of very large awards were made; this was probably appropriate for the early stages of the Program. In the 2003 and 2004 competitions there appears to be a trend toward a more diverse portfolio of investigators, of systems studied and of technology developed. This is commended and recommended. Increased funding and expanding the diversity of projects (mid-size to large) within the Program should result in an</p>	YES

<p>even more robust Program with even higher product and technology return. The COV encourages this trend.</p>	
<p>3. Does the Program portfolio have an appropriate balance of high-risk applications? Comments: The balance of high-risk projects seems appropriate. A very important aspect is the DOE GTL is the decision to invest at the cutting edge of technology development. This type of risk taking is achieved in few other agencies, and should continue to be fostered and encouraged. The potential impact of these efforts on the entire environmental and microbiology communities is significant and it is clear that few or no other funding agencies could support the diversity and number of such efforts. The size and scope of high-risk applications seems about right at the moment. The COV recommends maintaining somewhere around the current ratio of high-risk to more standard projects, as the Program grows.</p>	YES
<p>4. Does the Program portfolio have an appropriate balance of multidisciplinary applications? Comments: There is a good pattern of interdisciplinary research. There are a number of good examples of national labs with cutting edge technology developments, teaming with university investigators to answer critical scientific questions. This sort of cross collaboration and multidisciplinary effort should continue to be encouraged and fostered. This decision allows the leveraging of technical skills and expertise in large lab research resources, often around National facilities, and it directly connects them to the scientific community and the broader questions and applications related to energy and the environment.</p>	YES
<p>5. Does the Program portfolio have an appropriate balance of innovative applications? YES Comments This Program is at the cutting edge of microbial proteomics, community genomics, bioinformatics tool development, etc. This focus naturally attracts leaders and innovative thinkers in the field. The great ambitions in taking a systems level view of microbes and microbial communities, and the creation of technological platforms for these studies should continue to be fostered and encouraged. This Program is a prime example of innovative science.</p>	YES
<p>6. Does the Program portfolio have an appropriate balance of funding for awards to individuals and the national laboratories? Comments: A careful examination of the portfolio supports a strong affirmation of their efforts.</p>	YES
<p>7. Does the Program portfolio have an appropriate balance of awards to new investigators?</p>	YES

<p>Comments: The Program does bring in new investigators and is sensitive to their requirements and special considerations.</p>	
<p>8. Does the Program portfolio have an appropriate balance of geographical distribution of Principal Investigators? Comments: Insufficient data is available. However, from what data we have or can infer, this does not seem problematic and there appears to be a good balance in the distribution of PIs, and also maps well onto the distribution of national laboratories.</p>	<p>INADEQUATE DATA AVAILABLE</p>
<p>9. Does the Program portfolio have an appropriate balance across disciplines and sub-disciplines of the activity and of emerging opportunities? Comments: The Program does have an appropriate balance across disciplines and sub-disciplines of the activity and of emerging opportunities. However there is a great opportunity to apply the approaches and technology platforms developed in GTL to understanding DOE relevant questions related to the oceans, including bioremediation, ocean carbon sequestration and biological energy production. Currently, the GTL Program is fairly tightly focused on a few model systems, but the potential for expanding opportunities in comparative and functional genomics is great with respect to expanding beyond terrestrial systems. (We encourage the Program to expand in this way.)</p>	<p>YES</p>
<p>10. Is the Program relevant to national priorities, agency mission, relevant fields and other customer needs? Comments: This Program is having tremendous impact on many other fields, including, in particular, environmental microbiology, genomics, and environmental remediation. These are all extremely relevant to understanding and developing new energy sources, carbon dioxide sequestration/capture, and bioremediation. The Program does extremely well in focusing RFAs and funded application on these important issues, with respect to both technology development and basic science questions. Expanding the Program further, for instance into parallel areas in ocean science, would further increase the relevance and impact of the Program.</p>	<p>YES</p>
<p>11. Discuss any concerns identified that are relevant to the quality of the projects or the balance of the portfolio. The balance in terms of large-scale projects with in-depth focus on specific systems, and more distributed funding among different technologies and investigators, at present seems quite appropriate. Currently, there is significant and heavy emphasis on metal cycling microbial systems, from the environmental perspective as well as microbial cell perspective (including <i>Geobacter</i> and <i>Shewanella</i> systems in particular). The COV recommends expansion into other areas related to energy production, bioremediation and</p>	

carbon sequestration areas beyond metal reduction, to help expand, diversity, and add further value to the Program and its impact on DOE mission relevant interests. The merging of the Microbial Genome Program with the GTL will aid in this trajectory. In particular, the COV recommends more emphasis on microbial and biological energy production and carbon sequestration projects that focus on a variety of mission relevant marine and terrestrial environments and systems. The expansion into new facilities to support this balance, for instance a protein production facility that would complement the current production sequencing facility (JGI), would seem an excellent direction to head and is to be encouraged.

D. Management of the Program under review. Please comment on:

1. Management of the Program.

The Program is extremely well managed in terms of planning, implementation and vision. In particular, given the relatively small number of staff, it is remarkable how efficiently and smoothly the planning, solicitation, and funding process operates. The Program managers should be encouraged and commended for initiating, nurturing and maintaining these excellent Programs.

2. Responsiveness of the Program to emerging research.

The responsiveness of the Program to emerging research is, overall, excellent. The Program management has been very responsive, visionary, and on the cutting edge of new and ground-breaking trends in scientific advances. This GTL Program has, and will continue to have high scientific impact and has enormous potential to lead to new technologies and applications in the context energy generation, remediation and carbon sequestration.

3. Program planning and prioritization process (internal and external) that guided the development of the portfolio under review.

It is clear that there is visionary and responsive planning in management to incorporate new developments, technologies and opportunities into the Program. In general, the progression of the initial genome effort, to the Microbial Genomes and GTL Programs, to the merging of Microbial Genomes and GTL, is exciting, successful and visionary. The road map has been evolving steadily from year to year as evidence of this responsiveness. The Roadmap, RFA Notices, and applications funded reflect this responsive planning and prioritization.

4. Concerns identified that are relevant to the management of the Program.

A. The productivity of the staff is remarkable, given the scope and size of the Program. It would probably be useful as the Program grows have more technical and scientific staff on board to help with this important and growing flagship Program.

B. More avenues to disseminate information about the goals, RFAs, and

accomplishments of the Program. In this context, additional travel support for Program managers to attend other workshops and meetings represents one approach. Further effort to distribute flyers, web advertisements, and other venues to bring the Program to a wider audience is also to be encouraged.

- C. It would be useful to have a list of examples of Program achievements and success metrics for outside reviewers, annual review and assessment, future strategic planning, and future COVs.

Examples of success metrics could include:

- New Programs and research areas emerging from the Program
- New technology developments
- High profile publications
- Field results
- National laboratory efforts
- Trainees (graduate students & postdoc fellows; support of future work force)
- Abstracts and sessions at meetings
- Popular press coverage
- Database contributions
- Software contributions

Low-Dose Radiation

Date of COV: May 17-19, 2005
Program: Low-dose Radiation
Number of actions reviewed by COV: Awards: Declinations: Other:
Total number of actions within Program during period being reviewed by COV: Awards: Declinations: Other:
Manner in which reviewed actions were selected:

A. Questions about the quality and effectiveness of the Program's use of merit review procedures. Provide comments in the space below the question. Discuss areas of concern in the space provided.

QUALITY AND EFFECTIVENESS OF MERIT REVIEW PROCEDURES	YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE
<p>1. Is the review mechanism appropriate? (Panels, ad hoc reviews, site visits) Comments:</p> <p>The Low Dose Radiation Program solicits grant applications through open RFAs, and applications are received from a wide swath of the research community. Decisions regarding funding are made in consultation by experts in a well organized and thorough peer review. The BER staff should be commended for following this difficult path, especially given the very small number of BER staff and their other myriad responsibilities. They should also be commended for listening carefully to expert advice regarding scientific quality and for the thoughtful way they blend this advice with considerations of Program relevance and balance. The work of recruiting reviewers, organizing peer review meetings, synthesizing the comments of diverse reviewers, and making decisions based on peer input is a very demanding job but it is vital to the success of this Program. As a result, the Low Dose Program is strong, vibrant, diverse and productive. Funds are well spent on the very best and most efficient approaches to answering questions regarding low-dose exposure.</p> <p>The application solicitation process begins with an RFA and then, a submission of a letter of intent from interested applicants, which is reviewed by three Program scientists who have also determined the specifics of the Program announcement and manage the portfolio. There are informal comments kept in the file that are noted but not necessarily communicated in a follow-up email. The purpose of the email is to inform the applicant of the initial impression of the proposed work's fit to current</p>	YES

<p>programmatic needs, technical relevance, and other issues including overlap with existing grants in the portfolio. These emails are short and somewhat direct in their summation but provide valuable feedback to prospective applicants, who may contact Program staff for additional information if desired. Importantly, these responses to the short preapplications give guidance, but do not prohibit the submission of any application from any applicant. This is a positive feature of the process, since applicants are able to revise proposed work to better suit programmatic needs based on this feedback. Complete applications are then submitted and distributed to a team of external, selected expert reviewers. Each application is assigned to three primary reviewers; written evaluations are solicited and discussed in a larger peer group meeting including a diverse review team and Program staff. Every application is discussed and evaluated in a number of categories with participation by the whole team, in some part guided by required questions written by Program staff to elicit comments that are useful for further deliberation at higher level reviews. Ad hoc reviews by technical experts are also solicited for a small number of applications as needed in order to ensure the appropriate review of each application by three scientists qualified in the area. These ad hoc reviews are valuable additions, and are generally shared in a conference call that is audible for all reviewers who are on the review panel. Site visits are not included in the peer review for these applications.</p>	
<p>2. Is the review process efficient and effective? Comments: The review process is very efficient, although there is a very short time between the posting of the announcements and the time to the submission of the final application. In 2003, the announcement was posted February 19, letters of intent requested for April 4, and applications requested for May 23. In 2004, the announcement was posted June 7, letters of intent requested by July 15, emails from Program staff sent in August, and applications requested for September 15. In 2004, reviews were completed by mid-December. This is a very rapid turn-around for the submission and review process relative to other agencies. Given the small staff available to manage the reviews, decisions and communications back to applicants, this efficiency is remarkable.</p>	<p>YES</p>
<p>3. Are reviews consistent with priorities and criteria stated in the Program’s solicitations, announcements, and guidelines? Comments: Reviews are consistent with priorities and criteria stated in the Program’s solicitations, announcements and guidelines. This is in part aided by very specific questions that are addressed by the reviewers on their evaluation sheets in order to emphasize the Program announcement points and opinions that might be important for higher level, programmatic review.</p>	<p>YES</p>

<p>4. Is the documentation for recommendations complete, and does the Program Manager provide sufficient information and justification for her/his recommendation?</p> <p>Comments: The documentation for recommendations is succinct, in that it lists the conclusions as Accepted or Declined for funding. Reviewers' comments are provided for the applicants in all cases. In some cases, where programmatic review, or a higher level consideration, is used to change priority of an application, e.g. when an application scoring high for technical merit is not funded due to programmatic decisions, the explanation given to applicants is not made explicit. This generates confusion (and possibly ire) for applicants who receive glowing reviews, but are not funded. It would be helpful if a statement were added to the letter of decline or to the review summary, to make it clear to the applicant that while technical merit was strong, appropriateness of proposed work to the call or decisions based on Program focus and balance were not in favor of funding.</p>	YES
<p>5. Is the time to decision appropriate?</p> <p>Comments: The time line to decision is appropriate. Reviews are completed as soon as 10-12 weeks of submission (e.g. for RFA 04-21, the deadline for the applications was in September, followed by reviews in early December); the dates of decision letters are unknown, however work plan paperwork to the host institutions seems to be dated on average in April, which suggests a rapid process in submission, review, and release of funds. Again, this is a remarkable efficiency compared with most government reviews in biology and points to the efficiency and dedication of this very lean and very busy staff.</p>	YES
<p>6. Discuss any issues identified by the COV concerning the quality and effectiveness of the Programs use of merit review procedures. Comments: Overall, the strengths of the review process include excellent streamlining of the review process, high quality peer review by scientists with overall expertise in the Program of each applicant, a meeting in which this review is presented and discussed, and a fair and communicative Program staff. Weaknesses include the lack of clear feedback when decisions are made on programmatic grounds, especially since these might affect the applicant in resubmission choices. It is important to maintain one message from scientists and staff in order to facilitate good decision-making in resubmission or for changing the focus of the application.</p> <p>One way to strengthen the review process might be selection of a chair or possibly a facilitator during the review process to maintain a flow of discussion, to resolve differences effectively and to maintain an appropriate time-frame for discussion. The separation of the Program Managers from the review process to some degree would</p>	

permit them to serve better as advocates for the Programs they have worked to establish and direct, by allowing them to learn from the discussion and share these comments with the applicant directly, the applicants in improving their study design or programmatic content. A Chair and Co-Chair could also evaluate each application for its success in addressing specific calls for applications, for example, and ensure this feedback gets back to the applicant. This assistance would make this part of the review easier for Program staff.

The addition of a specially set-aside call and sub-session for review of “High Risk-High Gain” applications might also increase the number of applications in this category and might help ensure that they are reviewed using appropriate criteria. Often, in review sessions that consider a large number of low risk, traditional applications, it is difficult for reviewers to switch mindsets to consider the different kinds of criteria that should be applied to applications with high risk or technical novelty. Some ways to encourage submission and open-minded review of such applications could enhance this Program dramatically.

B. Questions concerning the selection of reviewers. Provide comments in the space below the question. Discuss issues or concerns in the space provided.

QUALITY AND EFFECTIVENESS OF SELECTION OF REVIEWERS	YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE
<p>1. Did the Program make use of an adequate number of reviewers for a balanced review? Comments:</p> <p>The Program makes use of three reviewers for each application, a primary, a secondary and a discussant. This provided a balanced review. Additionally, following discussion, the entire review panel scores the applications independently which permits later numerical ranking for funding considerations by Program staff.</p>	
<p>2. Did the Program make use of reviewers having appropriate expertise and/or qualifications? Comments:</p> <p>The Program makes use of reviewers with appropriate expertise and qualifications, although there do seem to be some biases in the review panel members from year to year, in that many are already funded by the DOE, apply for funding the following year, and return to the review panel repeatedly. Six to ten descriptors for each reviewer’s area of expertise should be included in the list of reviewers. These could include descriptors such as proteomics, statistical genetics, mouse</p>	

<p>modeling, radiation biology, or DNA repair in order to maintain a good balance of reviewers, to keep the reviewers informed of their colleagues' expertise, and for COV review.</p>	
<p>3. Did the Program make appropriate use of reviewers to reflect balance? Comments:</p> <p>The Program has a balance of reviewers with expertise in different areas. Some questions remain about whether there is sufficient expertise in all of the areas required for review for every application, especially in the newer technical areas, such as animal modeling, proteomics, transcriptional profiling, and bioinformatics. Some expertise in human or rodent pathology may be useful. While it is impossible to include experts on every subject in a review team, a stronger presence of technical experts who have not traditionally been involved in radiation biology research, while not absolutely essential, could be helpful.</p>	
<p>4. Did the Program recognize and resolve conflicts of interest when appropriate? Comments:</p> <p>Conflicts of interest are identified in advance of the review. Reviewers with conflicts are asked to leave the review room during the presentation and discussion of the application in question, and not participate in the scoring. All reviewers are instructed clearly as to confidentiality of any information revealed in applications or during review discussions.</p>	
<p>5. Discuss any concerns identified that are relevant to selection of reviewers.</p> <p>A strength of the reviewer selection process is that many of the reviewers are very familiar with the field of radiation biology and have been previously funded by the Low Dose Program. This can also be a limitation of the reviewer selection process in that it leads to the successful evaluation similar kinds of applications that have already been funded. One way of avoiding this repetition is to limit the number of times one individual can serve on the panel, and to establish rotations of reviewers with different areas of expertise than the standard radiation biologists have, and to maintain this as a larger component of the review panel. This would also be a good opportunity to bring in more junior faculty or scientists into the review process, and add in new reviewers with expertise in different areas. There seems to be a balanced distribution of reviewers from universities and the National Laboratories, but this should be maintained equitably in order to ensure appropriate review of submissions from the two sources of institutions.</p> <p>One limitation of the reviewing and the reviewer selection process is that the Program</p>	

staff members are charged with making all decisions at all steps in the process, from RFA design to selection of all reviewers to the final choice of awards. Staff could be helped, but also the process might be strengthened, if e.g. a designated chairperson or other advisors could help e.g. by recommending specific reviewers. This would help bring in fresh perspectives and new ideas/expertise to the review process.

It is strongly recommended that Program staff be encouraged and enabled to attend more national or international scientific meetings annually, as they deem necessary, to enhance their contacts with potential reviewers, new ideas and technologies, and to recruit new applicants with fresh perspectives to the Program. A very small amount of additional funding for travel would be an important investment for DOE with very high payoff in strength of the scientific Program.

C. Questions concerning the resulting portfolio of awards under review. Provide comments in the space below the question. Discuss areas of concern in the space provided.

RESULTING PORTFOLIO OF AWARDS	APPROPRIATE, NOT APPROPRIATE, OR DATA NOT AVAILABLE
<p>1. Overall quality of the research projects supported by the Program. Comments:</p> <p>The Low Dose Radiation Program portfolio is comprised of grants managed by well-respected, productive researchers with a long history in the radiation biology field. The quality of the work is therefore generally very high. One measure of this is the fact that many grants funded in the previous 3-year cycle (beginning 2001) were continued successfully after stringent and competitive peer review. Most of the projects in this category had changed in scope and adopted new approaches and technologies (and frequently, new titles) to keep their Programs up-to-date, a good sign that the researchers are actively pursuing low-dose related questions with the latest technologies. On the other hand, it is also a good sign for the Program that an almost equal number of funded projects are new starts, by PIs already participating in low-dose research as well as many newcomers. This indicates that new researchers with new ideas are being attracted to the Program.</p>	<p>YES</p>
<p>2. Are awards appropriate in size and duration for the scope of the projects? Comments:</p>	<p>YES</p>

<p>Awards are appropriate in size considering proposed goals. The review committees give serious attention to cost issues in their reviews and in a few cases, doing so results in a significant downsizing of awards relative to requests. Most PIs are careful to produce budgets that can withstand this scrutiny.</p>	
<p>3. Does the Program portfolio have an appropriate balance of high-risk applications? Comments:</p> <p>The portfolio does contain a few high-risk applications, but increasing the number of these cutting edge applications would clearly be of benefit to the Low Dose Program. The relatively small numbers of these is due to many contributing factors. First, many of the researchers applying to the Program (and most reviewers) are long-time experts in this field. This brings many advantages, including deep knowledge of this complex field and its long history. However, these experts are mostly trained to generate and appreciate applications that move in slow, cautious, and incremental steps. The cautious approach, per se, should not be criticized, because it does yield results. However, it does not necessarily yield breakthroughs. It is recommended that the BER staff complement their strong portfolio of conventional research by taking steps to encourage the submission and open-minded review of high-risk projects.</p> <p>The first step is to attract high quality applications of this type. This might be accomplished, for example, by a specially announced call of short term “pilot” studies akin to the DOD “Idea Awards”, to test new technologies and novel approaches to questions of low-dose relevance. A special RFA, broadly announced to scientists who might not normally participate in this Program, might be one way to draw increased attention to this Program. Another mechanism might be to fund a limited number of competitive awards for postdoctoral researchers or young investigators (often the best source of innovation) who bring expertise from other fields. Such awards could be made at relatively low cost, but bring very high payoff to the Program. It could be encouraged by a wider advertisement of the Low Dose Program to communities that might otherwise not participate, e.g. computational biologists, genome researchers, and nanotechnologists. There are many different ways that the profile of the Program might be raised to encourage broader participation by these new communities, and these should be investigated. This is one of many good reasons that travel to more high quality national scientific meetings should be encouraged for BER staff. But fliers distributed at meetings and sent to University departments to post on notice boards would also be a simple/low cost way to start.</p>	<p>NO, but with clarifications</p>

<p>4. Does the Program portfolio have an appropriate balance of multidisciplinary applications? Comments:</p> <p>The number of multidisciplinary efforts, along with interdisciplinary efforts – those where the various efforts are fully integrated, is a very strong point that distinguishes the DOE Program from those run by any other agency. Many of the DOE funded teams in this Program include physicists, biologists, chemists, and computer scientists working very closely together. Encouraging even more applications of this type would strengthen the Program. RFAs designed to attract or encourage applications from multidisciplinary teams would help increase the participation of such groups.</p>	<p>YES</p>
<p>5. Does the Program portfolio have an appropriate balance of innovative applications? Comments:</p> <p>The initial question should be are awards for innovative applications being made in a reasonable proportion of the portfolio. The answer is that there are indeed awards for innovative work; recognizing particularly innovative work can often require Program Manager engagement, since the peer review process can be quite conservative. However, the other point is that this question is not phrased properly. So in the more general case, the response to the first question posed by the COV here would be: If yes, fine; if not, then why? The why might be a failure to attract enough innovative applications, and this requires more outreach on the part of Program Managers. As far as we could ascertain, the Program Managers are quite capable of recognizing and encouraging innovation but do not have enough opportunities for going to meetings and participating with the community in science events; nor do DOE, the SC, BER or the Life Sciences Division communicate adequately to the public and the science community the successes in biology and the opportunities at DOE. This alone will set a limit on how many innovative applications any Program at DOE would receive.</p>	<p>YES</p>
<p>6. Does the Program portfolio have an appropriate balance of funding for awards to individuals and the national laboratories? Comments:</p> <p>The number of awards to National Labs and University participants is well balanced. It is clear the Program has thought very carefully about balance and how to attract and fund the best science, with careful analysis rather than any rote or arbitrary boundaries about site</p>	<p>YES</p>

of performance of the work.	
<p>7. Does the Program portfolio have an appropriate balance of awards to new investigators? Comments:</p> <p>From the data available, a substantial number of awards are made each funding round to researchers who have not previously participated in this Program. There appear to be relatively very few awards made to young investigators, as opposed to new investigators to the DOE system, overall; this is especially the case for those from National Labs. Some effort to recruit more young scientists, from both Universities and National Labs, as applicants might help to enlarge and strengthen the portfolio.</p>	YES, up to a point
<p>8. Does the Program portfolio have an appropriate balance of geographical distribution of Principal Investigators? Comments:</p> <p>The Low Dose Radiation Program portfolio includes researchers from all parts of the US. The distribution of funded PIs reflects the distribution of PIs submitting applications, especially in the case of University awards. National Lab PIs are fairly well distributed among the Laboratories that have significant biology Programs.</p>	YES
<p>9. Does the Program portfolio have an appropriate balance across disciplines and sub-disciplines of the activity and of emerging opportunities? Comments:</p> <p>Attention to emerging opportunities could be enhanced and increased. As mentioned above, some effort to attract new researchers with different perspectives into this field could be extremely helpful. This effort must be managed with care to assure that the innovation stays on point relative to the goals of the low-dose Program.</p>	YES but with concerns
<p>10. Is the Program relevant to national priorities, agency mission, relevant fields and other customer needs? Comments:</p> <p>The Low Dose Radiation Program tackles an important problem that may become center stage with renewed interest in nuclear energy on the national agenda. Very little scientific data are currently available to answer questions about exposures in the dose range highlighted by this Program. The Program is properly aimed at the most central and relevant questions.</p>	YES
<p>11. Discuss any concerns identified that are relevant to the quality of the projects or the balance of the portfolio.</p>	

In summary, BER staff members do an excellent job of managing the Low Dose Radiation Program especially considering the scant resources at hand. They are to be commended for the high quality of research funded, the strong and expert peer-review, and efforts to balance the portfolio. Low-dose radiation effects are important and complex problems; it will be especially difficult to attract the kind of multidisciplinary talent to this field without additional support to help the management staff with their workload and without financial support and incentive to broaden their scientific horizons and contacts.

D. Management of the Program under review. Please comment on:

1. Management of the Program.

In general, the Program manager is doing a very good job, especially in the light of the limited resources available. Solicitations are well prepared, applications are thoroughly reviewed and progress of funded applications is monitored. The Program shows evidence of a balanced portfolio of research, including some high-risk projects; further increase in novel approaches is desirable. There have been highly commendable improvements in recent years in record keeping and documentation in the jackets for successful applications as well as documentation for declined applications.

2. Responsiveness of the Program to emerging research.

The Program has been proactive in identifying relevant emerging areas of research, evolving its successive Program solicitations, encouraging introduction of new techniques and encouraging the entry of investigators with new areas of expertise. The challenge of the low-dose research questions dictates that further ongoing innovation is required and additional solicitation mechanisms and publicity should be considered to achieve this (see above). It is essential that the PM be given sufficient resources to maintain and expand close contact with the primary scientific community, but also with promising new areas, by attending meetings, workshops and laboratory visits.

3. Program planning and prioritization process (internal and external) that guided the development of the portfolio under review.

No information was provided to the COV regarding Program planning and prioritization. Guidance would be appreciated on how the scientific community could contribute to the process.

4. Concerns identified that are relevant to the management of the Program.

As stated above, it is essential for the PM to be provided with adequate resources to maintain and develop contact with the scientific community and keep abreast of scientific developments across a broad front. Given the heavy burden that is placed on Program

managers in designing calls for applications, organizing and managing peer review, and making decisions on programmatic grounds, it is essential that they be given the tools they need to stay current with the science and familiar with the research community.

Structural Biology

Date of COV: May 17-19, 2005
Program: Structural Biology
Number of actions reviewed by COV: Awards: Declinations: Other:
Total number of actions within Program during period being reviewed by COV: Awards: Declinations: Other:
Manner in which reviewed actions were selected: total actions were considered, program small enough that all actions were reviewed.

A. Questions about the quality and effectiveness of the Program's use of merit review procedures. Provide comments in the space below the question. Discuss areas of concern in the space provided.

QUALITY AND EFFECTIVENESS OF MERIT REVIEW PROCEDURES	YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE
1. Is the review mechanism appropriate? (Panels, ad hoc reviews, site visits) Comments: Yes, it follows the methods of other granting agencies.	YES
2. Is the review process efficient and effective? Comments: It appears excellent and informed.	YES
3. Are reviews consistent with priorities and criteria stated in the Program's solicitations, announcements, and guidelines? Comments: The reviews reflect the solicitations and the requirements for funding.	YES
4. Is the documentation for recommendations complete, and does the Program officer provide sufficient information and justification for her/his recommendation? Comments: The Program officer did a good job.	YES
5. Is the time to decision appropriate: Comments: The time generally seemed fine, very few took any longer than their standards	YES

6. Discuss any issues identified by the COV concerning the quality and effectiveness of the Programs use of merit review procedures:

The COV deeply regret the elimination of approved projects and the entire experimental component of the Program, while we fully understand, recognize and appreciate the priorities that made this action necessary. Nonetheless, all of the projects terminated represented excellent science, were of high impact and important to be conducted, and were precisely and specifically fully relevant to DOE missions; no other agency will pick these projects up, and the science will be delayed, at a detriment to the goals of BER

B. Questions concerning the selection of reviewers. Provide comments in the space below the question. Discuss issues or concerns in the space provided.

QUALITY AND EFFECTIVENESS OF SELECTION OF REVIEWERS	YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE
1. Did the Program make use of an adequate number of reviewers for a balanced review? Comments: Yes, an appropriate number of reviews were found for each of the applications we examined..	YES
2. Did the Program make use of reviewers having appropriate expertise and/or qualifications? Comments: Where the identity of the reviewer was obvious a good choice had been made.	YES
3. Did the Program make appropriate use of reviewers to reflect balance? Comments: This seemed fine.	YES
4. Did the Program recognize and resolve conflicts of interest when appropriate? Comments: No information on this.	DATA NOT AVAILABLE
5. Discuss any concerns identified that are relevant to selection of reviewers. There are none.	

C. Questions concerning the resulting portfolio of awards under review. Provide comments in the space below the question. Discuss areas of concern in the space provided.

RESULTING PORTFOLIO OF AWARDS	APPROPRIATE, NOT APPROPRIATE, OR DATA NOT AVAILABLE
<p>1. Overall quality of the research projects supported by the Program. Comments: The quality is excellent.</p>	HIGHLY APPROPRIATE
<p>2. Are awards appropriate in size and duration for the scope of the projects? Comments: Yes, except for the projects that were cut. Also, some excellent grants were approved, but not funded. Given what happened, this is not significant.</p>	NOT APPROPRIATE;
<p>3. Does the Program portfolio have an appropriate balance of high-risk applications? Comments: Yes, very good, until all of the high-risk programs were cut.</p>	NO
<p>4. Does the Program portfolio have an appropriate balance of multidisciplinary applications? Comments: After it was originally reviewed the balance was fine, but later, after the Program was cut, it was not.</p>	NO (after funding cut)
<p>5. Does the Program portfolio have an appropriate balance of innovative applications? Comments: Originally, it did, but after the budget was cut the balance was not so good.</p>	NOT ENOUGH DATA, NOT APPROPRIATE QUESTION (under circumstances)
<p>6. Does the Program portfolio have an appropriate balance of funding for awards to individuals and the national laboratories? Comments: Originally, the balance was certainly fine, but after the budget cut, largely only the National Labs were left as the Institutions for awards, since seven of the ten research resources are a National Labs.</p>	NO, NOT APPROPRIATE
<p>7. Does the Program portfolio have an appropriate balance of awards to new investigators? Comments: As far as we can tell, there have not been enough awards to new investigators. However, given that there could be only one round of awards and the experimental Program was terminated, there was also</p>	NO, NOT APPROPRIATE

no real chance to develop balance. Although we do not much information on access to new investigators at the research resources, we would naturally expect the lead investigators for the research resources to be more senior.	
<p>8. Does the Program portfolio have an appropriate balance of geographical distribution of Principal Investigators?</p> <p>Comments: The Program is quite small and we do not have enough information to say very much. With the termination of the experimental Program, the distribution now is inherently limited; that is, the research resources are largely at the National Labs.</p>	NOT ENOUGH INFORMATION
<p>9. Does the Program portfolio have an appropriate balance across disciplines and sub-disciplines of the activity and of emerging opportunities?</p> <p>Comments: It was good initially, but cuts forced upon the Program made it poor.</p>	NO
<p>10. Is the Program relevant to national priorities, agency mission, relevant fields and other customer needs?</p> <p>Comments: Relevant to DOE and national objectives.</p>	YES
<p>11. Discuss any concerns identified that are relevant to the quality of the projects or the balance of the portfolio.</p> <p>Comments: See the details in the attached report. Originally, until the imposed budget cuts, this was a well-managed Program.</p>	

D. Management of the Program under review. Please comment on:

<p>1. Management of the Program.</p> <p>The Program management has been quite good. From the internal side and given the breadth of the research resources activities and the range of core research, it took a substantive effort to maintain the Program. The facility effort benefits large Programs and other users, as well as individual scientists doing projects within the rest of the Life Sciences Division.</p>
<p>2. Responsiveness of the Program to emerging research.</p> <p>The Program was responsive to emerging research over an earlier history. This responsiveness inevitably disappeared when the Program disappeared; that is to say, since the grants terminated represented cutting edge research themes and</p>

echoed the emerging research goals of the office as a whole, in this area the Program's response to emerging research would be said to be poor.

3. Program planning and prioritization process (internal and external) that guided the development of the portfolio under review.

The planning and prioritization process that led to the creation of the Program was quite good, and the early decisions were compelling. Of course, this careful process of selecting highest priority goals for structural biology was greatly affected by the budget cut. The budget cut resulted in the termination of Programs that are clear deliverables within structural biology, that is, of projects that whose continuing advances would have facilitated the delivery of DOE mission goals.

4. Concerns identified that are relevant to the management of the Program.

See attached report. We note that the Program officer for structural biology, Roland Hirsch, plans to retire in a few years' time and, in view of his great contributions, suggest that an assistant be selected (during Dr. Hirsch's tenure) who can "learn the ropes," help with actions subject to Dr. Hirsch's approval, and eventually take the position.

Genomic Research and Biology Research

Date of COV: May 17-19, 2005
Program: Genome/Biology (ELSI)
Number of actions reviewed by COV: Awards: 8 Declinations: 6 Other:
Total number of actions within Program during period being reviewed by COV: Awards: Declinations: Other:
Manner in which reviewed actions were selected:

A. Questions about the quality and effectiveness of the Program's use of merit review procedures. Provide comments in the space below the question. Discuss areas of concern in the space provided.

QUALITY AND EFFECTIVENESS OF MERIT REVIEW PROCEDURES	YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE
<p>1. Is the review mechanism appropriate? (Panels, ad hoc reviews, site visits) Comments:</p> <p>A section of synthetic summary comments by panelists themselves (if rules allow it) could be a useful addition to current approach.</p>	YES
<p>2. Is the review process efficient and effective? Comments:</p> <p>Of necessity, the diverse nature of ELSI applications requires a wide participation of reviewers.</p>	YES
<p>3. Are reviews consistent with priorities and criteria stated in the Program's solicitations, announcements, and guidelines? Comments:</p> <p>We note that in come cases reviewers explicitly cited the announcement in their reviews.</p>	YES
<p>4. Is the documentation for recommendations complete, and does the Program officer provide sufficient information and justification for her/his recommendation? Comments:</p> <p>We understand that as part of a response to a prior COV this aspect of the review process will be strengthened. We concur with that strengthening</p>	YES
<p>5. Is the time to decision appropriate:</p>	YES

<p>Comments: The time to decision is consistent with overall SC expectations and is similar or better than that for other agencies.</p>	
<p>6. Discuss any issues identified by the COV concerning the quality and effectiveness of the Program’s use of merit review procedures:</p> <p>We note that older jackets (as we were advised by DOE) do not document reviews. The newer jackets do provide documentation. We commend DOE on this change in their procedures.</p> <p>We also note that, if DOE wishes to continue with the COV approach to assessing the quality of review on a periodic basis, DOE may wish to create a set of meta-data related to the review process and then explicitly collect data into that set to facilitate future COV analysis.</p>	

B. Questions concerning the selection of reviewers. Provide comments in the space below the question. Discuss issues or concerns in the space provided.

<p>QUALITY AND EFFECTIVENESS OF SELECTION OF REVIEWERS</p>	<p>YES, NO, DATA NOT AVAILABLE, or NOT APPLICABLE</p>
<p>1. Did the Program make use of an adequate number of reviewers for a balanced review? Comments: The regular creation of a “review analysis” by the Program officer can help ensure that a balanced review is obtained for each application.</p>	<p>YES</p>
<p>2. Did the Program make use of reviewers having appropriate expertise and/or qualifications? Comments: The reviewers all have the right expertise and experience.</p>	<p>YES</p>
<p>3. Did the Program make appropriate use of reviewers to reflect balance? Comments: Geographic balance was not good. Too many reviewers were taken from the local area, that is, they work near the Washington DC metro area. Balance across institutions seemed reasonable. However, less involvement from government officials and a greater involvement from the research community itself would also be desirable.</p>	<p>NO, needs improvement</p>
<p>4. Did the Program recognize and resolve conflicts of interest when appropriate? Comments: We could not tell which reviewers reviewed which applications, so</p>	<p>YES</p>

could not assess this at a fine-grain level, but as far as we could tell, there were no problems	
--	--

<p>5. Discuss any concerns identified that are relevant to selection of reviewers.</p> <p>Program should get more researchers and use fewer government officials involved in review. Similarly, Program should get more reviewers from outside the Wash DC area.</p> <p>DOE should note that involvement in review is a way to stimulate interest in the Programs. In this regard, DOE could try to engage National Lab staff in ELSI review, as a way of stimulating interest in ELSI work at the Labs</p>

C. Questions concerning the resulting portfolio of awards under review. Provide comments in the space below the question. Discuss areas of concern in the space provided.

RESULTING PORTFOLIO OF AWARDS	APPROPRIATE, NOT APPROPRIATE, OR DATA NOT AVAILABLE
<p>1. Overall quality of the research projects supported by the Program.</p> <p>Comments: Projects should have an impact.</p>	YES, APPROPRIATE
<p>2. Are awards appropriate in size and duration for the scope of the projects?</p> <p>Comments: These are relatively smaller projects.</p>	YES APPROPRIATE
<p>3. Does the Program portfolio have an appropriate balance of high-risk applications?</p> <p>Comments: We note that “risk” in the field of ELSI research is not the same as risk in original bench research.</p>	YES, APPROPRAITE
<p>4. Does the Program portfolio have an appropriate balance of multidisciplinary applications?</p> <p>Comments: Numerous interdisciplinary and multidisciplinary awards have been made; indeed, by and large the entire portfolio is multidisciplinary, as is appropriate.</p>	YES, APPROPRIATE
<p>5. Does the Program portfolio have an appropriate balance of innovative applications?</p> <p>Comments: Innovative applications are among funded projects.</p>	YES, APPROPRIATE
<p>6. Does the Program portfolio have an appropriate balance of</p>	NO, NOT

funding for awards to individuals and the national laboratories? Comments: The National Labs seem under-represented (in applications submitted as well as in awards).	APPROPRIATE
---	-------------

7. Does the Program portfolio have an appropriate balance of awards to new investigators? Comments: Numerous new investigators have been brought into the Program.	YES
--	-----

8. Does the Program portfolio have an appropriate balance of geographical distribution of Principal Investigators? Comments:	YES
---	-----

9. Does the Program portfolio have an appropriate balance across disciplines and sub-disciplines of the activity and of emerging opportunities? Comments: The balance is excellent.	YES
---	-----

10. Is the Program relevant to national priorities, agency mission, relevant fields and other customer needs? Comments: The relevance is very high to all of the above.	YES
---	-----

11. Discuss any concerns identified that are relevant to the quality of the projects or the balance of the portfolio. As the DOE involvement in the original human genome project winds down, DOE should broaden the scope of ELSI projects to include other areas of research relevant to the Life Sciences Division, and to BER as a whole; given adequate funding, the Program should consider the other research of the SC. There is no comparable Program any where in government; the NIH activities are very narrowly focused on a limited subset of biomedical ethics and the implications of science and technology far exceed this exceptionally narrow activity with the NIH National Institute for Human Genome Research. What support exists at NSF is for more academic considerations and doesn't reflect the practical consequences for society in a direct way.

D. Management of the Program under review. Please comment on:

1. Management of the Program. See narrative in body of COV report.

2. Responsiveness of the Program to emerging research. See narrative.
--

3. Program planning and prioritization process (internal and external) that guided the development of the portfolio under review.
See narrative.
4. Concerns identified that are relevant to the management of the Program.
See narrative.

APPENDIX F LIST OF ACRONYMS USED IN THIS REPORT:

ASM	American Society for Microbiology
BER	Office of Biological and Environmental Research
BERAC	Biological and Environmental Research Advisory Committee
COV	Committee of Visitors
CSP	Community Sequencing Program
DNA	Deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
ELSI	Ethical, Legal, and Social Implications
ERSD	Environmental Research Sciences Division
FY	Fiscal Year
GTL	Genomes to Life
GPRA	Government Performance Results Act of 1993
IBEA	Institute for Biological Energy Alternatives
JGI	Joint Genome Institute
LS	Life Sciences Division
MCP	Microbial Cell Project
NIH	National Institutes of Health
NSF	National Science Foundation
PART	Program Assessment and Rating Tool
PI	Principal Investigator
PM	Program Manager
PSI	Protein Structure Initiative
PSP	Application Study Panel
RFA/RFP	Request for Applications/Request for Applications (by definition, DOE refers to application for Universities, and proposal for DOE National Laboratories)
SB	Structural Biology Program
SC	Office of Science
SP	Structural Proteomics