# Report on Planning and Development of the GTL-1 Facility and Further Consideration of GTL Facilities 2, 3, and 4

Prepared by a Subcommittee of the
DOE Biological and Environmental Research
Advisory Committee (BERAC)

October 7, 2005

*Overview: The Charge and Response*

A Biological and Environmental Research Advisory Committee (BERAC) Subcommittee met on August 15, 2005, in Chicago, Illinois. This Subcommittee considered the questions in regard to the BER GTL Program and facility-1 (GTL-1) as asked by DOE Office of Science Director, Dr. Raymond Orbach in his charge letter transmitted in August 2005 to Dr. Keith Hodgson, Chairman of BERAC. The members of the Subcommittee are listed at the end of the report and a copy of the charge letter is also included.

The charge letter requested that BERAC provide advice on the value of the proposed Facility for the Production of Proteins and Molecular Tags (GTL-1). In considering this charge, the BERAC Subcommittee felt it was important to consider this question in context of the plans for the other three GTL facilities and thus, some recommendations are also provided about the development of the whole facility program. The following report derives from the deliberations of the BERAC Subcommittee meeting.

After review of the DOE Genomics: GTL Roadmap (DOE Genomics: GTL – Systems Biology for Energy and Environment, July 2005), the Subcommittee strongly endorses both the science and the mission goals of the entire GTL program. The Subcommittee feels that the GTL Program has enormous potential for transforming energy production in this country, as well as for addressing other high priority national needs in the areas of environmental remediation and carbon sequestration. The intellectual and physical infrastructure that will be built as a result of the entire GTL program will be of extraordinary value to science and industry in this country and will contribute to a strong energy security for our Nation. Where relevant to the charge considered by this Subcommittee (August 15, 2005, from Dr. Orbach), the Subcommittee also endorses the earlier conclusions and recommendations made in the December 2002 and December 2004 BERAC reports on GTL. (http://www.sc.doe.gov/ober/berac/Reports.html)

The sections below are organized according to the questions posed in the charge letter from Dr. Orbach to BERAC Chair, Keith Hodgson (August 15, 2005).

***Would the GTL-1 facility have value if it were the only facility built?***

The Subcommittee unequivocally supports the funding and construction of the GTL-1 facility. This facility will be critical in providing the proteins and molecular tags that will fuel the entire GTL research program. The ability to access microbial proteins, both alone and in combination, is the foundation around which the promise of Genomics: GTL is built. The GTL-1 facility will develop new methods for isolating and purifying microbial proteins, apply these new methods in the generation of thousands of protein samples, characterize the proteins, and provide to the scientific community the critical tags and affinity labels that are essential for determining the activities and functions of these proteins both *in vitro* and *in situ*. By accomplishing these objectives, the GTL-1 facility will satisfy the needs for the extensive and distributed GTL research program, as well as for the broader community of scientists involved in microbial systems biology. Integral to the facility is first, basic research focused on the generation of new technologies for accessing and assessing microbial proteins and subsequently, the application of these new technologies to a broad spectrum of microbes that will enable GTL investigators, using experimental approaches, to explore the vast amount of microbial genome information, which is after all, being generated by DOE sequencing efforts. Consequently, the GTL-1 facility will

enable the discovery of new proteins and protein systems with intrinsic potential to impact the suite of GTL-DOE mission goals.

Thus, it is the strong and clear consensus of the Subcommittee that the GTL-1 protein production facility will provide significant value ***even if*** the other facilities are not constructed or delayed. The broad research programs sponsored by BER and related DOE programs will see enormous benefit once the GTL-1 facility is able to provide purified and characterized proteins, with appropriate molecular tags, from organisms that have direct relevance to achieving the DOE GTL mission goals. GTL-1 will be central to the further growth and impact of the GTL research portfolio and science program.

The Subcommittee also notes that in order to achieve the full set of goals associated with the GTL-1 facility, there are aspects of the additional three GTL facilities that are critical. For example, the proteomics capabilities to be located in GTL-3 will be required to attain the comprehensive identification of all the proteins in a microbe or in a microbial community. This capability is particularly important for the low abundance, difficult to isolate proteins. Similarly, the capability of GTL-2 is needed to identify and analyze molecular assemblies of proteins in their fully functional forms. Until these facilities are built, an enhanced, highly robust research program will be essential for bringing the tools – both current and future – of proteomics, imaging and characterization to bear on the products of GTL-1. Sustaining an enhanced, highly robust research program in these areas will be even more critical, and possibly problematic, if the additional three GTL facilities were not to be built.

It is inevitable that a reduction in the size of the GTL-1 facility from that which was originally planned will impact the scientific results that will be produced. The consequences clearly depend on how reductions are executed. Downsizing the protein production aspects of the facility will translate into a smaller number of proteins prepared per year. Reducing the major protein preparation research effort will decrease the breadth or range of microbial genomes that will be characterized. This reduction will result in researchers not being able to access the least abundant, most difficult to produce proteins. Since such proteins are often those most critical for understanding biological function, there will be a concomitant loss in our understanding of the overall microbial environment. Alternatively, a decrease in the scope of the GTL-1 facility may be moderated by increasing the time frame to achieve the goals. Doing so, however, would put into jeopardy the timeline of the whole GTL project, which has been designed to impact pressing critical national energy and environmental needs. It is the belief of the Subcommittee that some of the consequences of a reduction in the facility budget could be recouped through the discovery of new technologies that allow more efficient, more effective genome mining and protein production, but that there is significant risk that such technologies will not be developed in time to impact the achievement of GTL program goals.

As noted above, one of the purposes of the GTL-1 facility is to discover and produce new and unanticipated proteins that could impact DOE missions in exciting and unforeseen ways. The chances of such discoveries are reduced non-proportionally by scaling down the facility since this will limit the effort to the more obvious, incremental, planned research preferentially performed in any environment with a very limited budget. Therefore, in a reduced facility, it will be even more important for the facility to prioritize which proteins it produces and not focus only on “the low hanging fruit.” In particular, care will have to be taken that a significant effort is devoted to the more difficult proteins, such as membrane, regulatory and complex post-translationally modified proteins, proteins of low abundance, and the components of large, transient molecular assemblies.

***The importance of the GTL-2, GTL-3, and GTL-4 facilities to the GTL program and achieving the overall mission goals***

During its deliberations, the Subcommittee also discussed the remaining three facilities, GTL-2, GTL-3, and GTL-4, in the context of GTL-1. These three additional facilities will be absolutely essential for achieving the scientific objectives and long-term mission goals of the GTL program, including producing alternative, secure, and renewable energy sources, bioremediation, and carbon sequestration, in the time frame set out in the DOE Genomics: GTL Systems Biology for Energy and Environment Roadmap. Besides their own capabilities and key contributions, the interactions between these three facilities and GTL-1 will be absolutely essential for full programmatic success and the translation of that success into maximal impact. There will be inestimable benefit initially to the scientific community at large, and eventually to our national economy, from both the new technologies that are developed by these facilities and the enormous wealth of information that will be generated by them.

The Subcommittee recommends that planning for the remaining three facilities should begin immediately. Simultaneously defining, competing, and designing these three additional GTL facilities will provide by far the best opportunity to define and develop the required synergies between these facilities and between these facilities and GTL-1. The Subcommittee also believes that any one or all of these three facilities might be constructed as a distributed but integrated facility, with up to four component sites for each facility. The Subcommittee strongly endorses an open solicitation of proposals for locating these facilities in the academic, industrial, and national laboratory sectors, a concept articulated in earlier BERAC reports on GTL. Doing so will encourage added creativity in the community's response and spawn far-reaching collaborations and synergies in the proposals and their implementation. Indeed, new opportunities will be generated that cannot now be fully anticipated. The review process used by BER would select the **best** proposals, whether single site or distributed, for developing each of these facilities. It is expected that different potential locations and different approaches would, over time, generate a range of commercial developments. The Subcommittee also noted that the timelines for development of GTL-2 and GTL-3 can reasonably be assumed to be shorter than that needed for GTL-4, since, when operative, GTL-4 will depend heavily on the results generated by the other three facilities.

The Subcommittee strongly believes that if a facility is distributed among a number of sites, it is absolutely essential to its mission that the facility be managed in an integrated fashion by a single management team. Furthermore, as clearly articulated in the BERAC report of December 2002, there must be "a single oversight mechanism that oversees all four facilities and coordinates their development … . This oversight group must have real authority to make changes in direction, balance and budget to best optimize the ability of this set of resources to most effectively enable the goals of the GTL science portfolio." Such management is critical to ensure that DOE mission goals are achieved in the appropriate time frame.

If GTL-2, GTL-3, and GTL-4 are reduced in size, there will be commensurate decreases in the ability of these facilities to address the DOE mission goals of GTL. While it is not possible, at this time, to quantify in any way the consequences of reduced size of the facilities, we believe that these consequences will not be linear in their negative effects on the potential for new discoveries from Genomics: GTL. The intent of GTL is to develop a broad new base of microbial scientific knowledge that in turn, will lead to a range of technologies to address the energy, remediation, and carbon sequestration needs of the country, in this century and beyond. Limiting the size of these facilities severely jeopardizes the achievement of DOE mission goals by decreasing the opportunity for new discoveries to occur, to be developed, and to be

commercialized. Of course, as with GTL-1, it is possible that for a modest reduction in size of GTL 2, GTL-3, and GTL-4 - for example, a reduction of up to 25 percent - a somewhat smaller reduction in scope and outcomes might be achieved if improved and radically new technologies were to come into play over the next several years while the facilities are being designed and planned. By contrast, sustaining the scope will allow any technology advances to accelerate and expand upon the opportunities provided by GTL-1.

Since the other three facilities are intended to interact closely with GTL-1, their capabilities and size must be commensurate with GTL-1 if we are to achieve maximal benefit to the GTL program. Also, if these three facilities were constructed as distributed facilities, but under reduced scope, it would be critical that each sub-facility be of sufficient size and scope to allow it to achieve the critical mass necessary for its effective, productive function. Delaying these facilities would significantly delay GTL-generated science and technology outputs that will address the Nation's critical needs.

This Subcommittee remains most enthusiastic and strongly supportive of the GTL program. We feel that this approach will harness systems biology in the context of the microbial world to provide solutions to the most pressing problems in the energy and environmental arena that face us in the coming decades. Moving forward as expediently as possible on the GTL facilities, together with the broad research portfolio supported by DOE-BER, is perhaps the single most important thing that can be done to see that this potential is recognized.

**SUBCOMMITTEE MEMBERS**

**Dr. Jonathan Greer (Chair, Subcommittee)**
Abbott Laboratories

**Dr. Keith O. Hodgson**
Stanford University

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August 15, 2005

**Office of the Director**

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

Dear Dr. Hodgson:

In December 2004, the Biological and Environmental Research Advisory Committee (BERAC) issued a report on the potential scientific impact of the proposed Facility for the Production of Proteins and Molecular Tags (GTL-1). This report was very useful in clarifying the value of this facility to the scientific community. It stated:

"Unequivocally, the GTL-1 facility is essential to meet the scientific goals of the GTL program, which are to empower and transform the world of microbial biology and to enable biological research to further specific missions of the DOE Office of Science in areas of energy, environmental remediation and global climate change. It is only through the use of high-throughput, economical approaches that we can capitalize on the dramatically growing volume of new genome information, enabling and accelerating the essential step of studying and understanding microbial function on the cellular to molecular level. Only then will the potential of utilizing microbial biology as a key strategy in addressing DOE missions be realized. The success of such an endeavor will be far reaching to our Nation's economy and quality of life for decades to come.

The GTL-1 protein production facility is the crucial first step in the process to attain the goals of the GTL program. By providing high-throughput production capabilities to make proteins and related affinity reagents and tags, this GTL-1 facility will enable the scientific community to work at the cutting edge of investigating and understanding protein function."

It was also stated that "the GTL-1 facility is appropriate in scope and goals as developed and described in the most recent documentation that was made available to the Subcommittee for review," i.e., the information contained in the GTL-1 chapter of the GTL Roadmap.

As we prepare to move forward with the next steps in the planning and development of this facility I would like BERAC to provide additional advice on the value of this first GTL facility as a stand-alone facility. Given the uncertainties of out year budgets and the urgency of moving forward with the Genomics: GTL program the question has been

raised about the science that would be enabled if only the first of the four planned Genomics: GTL facilities could be built at the previously described scale and cost. I would also like BERAC's advice on the scientific impact if this first facility was built at a scale that was only 50-75 percent of the originally proposed size and scope.

I request that a draft of this report be provided to me by the end of August and that BERAC report on its findings and recommendations at its December 5-6, 2005, meeting.

Sincerely,

Raymond L. Orbach
Director