Report of the Subcommittee on the BERAC Charge in Regard to Synchrotron Structural Biology Resources

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

October 2005

A Biological and Environmental Research Advisory Committee (BERAC) Subcommittee, chaired by Dr. Jonathan Greer (full membership of this subcommittee is listed at the end of this letter report) met in Chicago, Illinois, on August 15, 2005, and considered the following two questions posed in the charge letter from Dr. Raymond Orbach, Director of the Office of Science, U.S. Department of Energy, to Dr. Keith Hodgson, BERAC Chair, on January 14, 2005.

Question 1: What would be the advantages and disadvantages of establishing more than one program in a particular technology at one of the Department's light sources? What priority should the BER program give to duplicating existing, well-developed technologies at a light source relative to supporting research in light source techniques that are in an earlier stage of development?

It was the general sense of the Subcommittee that beamlines and instrumentation at the DOE synchrotron light sources were relatively well matched to the current demand and that the balance of programs across the light sources was a reasonable one. It was strongly felt that duplication/creation of additional capacity was justified only in cases of clear saturation and demonstrated need. While the only way to accurately assess this would be to do a new detailed facility survey, based on personal experience and that of scientific colleagues, additional capacity was not believed to be necessary for the more conventional beamlines for macromolecular crystallography (in particular those on bending magnets).

An exception appears in the area of crystallography studies of the most demanding and complex problems (e.g., large molecular machines that are typically characterized by large unit cells, weakly diffracting crystals, and microcrystals) where the demands for brightness are the greatest. Those beamlines and instrumentation on the highest brightness wiggler and undulator synchrotron sources supported by DOE-BER do not meet existing demand. Moreover, the GTL program which calls for production and characterization of molecular machines is very likely to result in more of these frontier crystallographic problems, which require advanced beamline design and instrumentation. It was strongly felt that duplication/creation of additional capacity was justified only in this last case, but even then a careful study should be performed before embarking on such a venture given that there are several high brightness undulator beamlines still in construction/commissioning phases at APS and SSRL and their impact is yet to be felt. Furthermore, there is still much to be gained in throughput and technical capability for existing beamlines through developments such as enhanced robotics, automation, and advanced detectors (such as pixel array detectors) and these avenues should be given highest priority. Such developments have greater potential for payoff and leverage the already significant investment by DOE-BER in building and operating its valuable component of structural biology beamlines.

One area of special note for macromolecular crystallography is the need for beamlines/instrumentation optimized for microcrystal and microbeam studies. Beamlines

in Europe (especially at ESRF) have proven essential in tackling the most challenging problems in high resolution crystallography of large complexes (such as the molecular machines and membrane-bound protein complexes, and microcrystalline complexes) and such capability in the U.S. is under-represented. Efforts should be made to foster, develop and effectively support beamlines for microcrystal studies. This capability and capacity is also likely to deliver significant dividends for the GTL program as the production pipeline produces an increasingly large number of interesting complexes that require structural characterization. It is certainly clear that the only approach that is currently viable for achieving the needed high resolution structural information on large assemblies for GTL is synchrotron-based macromolecular crystallography. It was noted by the Subcommittee that progress toward automation and robotics needed for optimized facilities for this type of investigation has already been made through BER funding and in partnership with NIH-funded investment (through NIGMS [the PSI initiative] and NIH-NCRR), and that at least three commercial automation systems are now on the market.

The Subcommittee considered other "less well developed" synchrotron-based techniques that have relevance to structural biology. These include x-ray microscopy, small angle x-ray scattering and x-ray absorption spectroscopy (other spectroscopies such as IR and CD have potential, but were not discussed). Each of these three x-ray based techniques offer benefits that are complementary to crystallography and can provide valuable answers to important structural biology questions when appropriate experiments are carried out. X-ray absorption and scattering techniques, for example, lend themselves to solution studies, including those done in a time-resolved domain. X-ray microscopy is complementary to EM and has potential benefits that include study of hydrated, thick samples. It was generally felt that the BER support for these other techniques was relatively well matched to the current needs and demand. The area of small angle scattering is finding some resurgence because of its ability to determine solution structure (at low resolution), but it remains to be seen just how large an impact comes from this area and how the demand grows. Further investment is certainly not warranted at this time. Small angle scattering and x-ray absorption do both have potential developing roles in GTL from the perspectives of characterization and structure/function studies. X-ray microscopy has potential as an important new imaging modality that could also be important to GTL in the future. Thus, it is felt that the current level of investment in these technologies is well justified. However, there may be a growth in future potential for GTL for these x-ray methods, and this should be monitored and evaluated as GTL evolves.

Question 2: In discussing this issue, I would like BERAC to specifically comment on the potential rationale for supporting the further development of the X4A and X4B beamlines at the NSLS within the BER structural biology portfolio.

As stated above in the answer to Question 1, it was felt that there is currently not a significant over demand for lower intensity beamlines of the type represented by X4A and X4B (in contrast to a shortage of instrumentation on high intensity and undulator beamlines). While such beamlines can still find productive use for less challenging

crystallography problems, can serve regional user groups and can serve useful purposes in areas like crystal screening, it is the strong sense of the Subcommittee that funds should not be devoted to significant upgrades/improvements of such bending magnets beamlines. This is especially the case if they are not multiwavelength (MAD) capable. Rather, to the degree possible, available funds should instead be devoted to upgrading the highest brightness wiggler/undulator beamlines with enhanced robotics, tools for remote access and other means to improve their throughput and technical capabilities (like next generation detectors).

NOTE:

- During the discussion, Dr. Hodgson clearly identified his potential conflict of interest in those cases where facilities at his home institution stood to benefit directly from future investments that could derive from implementation of these recommendations. His comments were focused on the more scientific points and providing factual input.

SUBCOMMITTEE MEMBERS

Dr. Jonathan Greer (Chair, Subcommittee)
Abbott Laboratories

Dr. Keith O. Hodgson
Stanford University

Dr. James Tiedje
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Dr. Michelle Broido
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CHARGE LETTER:

Department of Energy
Office of Science
Washington, DC 20585

Office of the Director

January 14, 2005

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

Dear Dr ~~Hodgson~~ Keith:

The Biological and Environmental Research (BER) program provides substantial funding for each of the DOE's four synchrotron light sources to support access to the most advanced light source capabilities by the national structural molecular biology community. In Fiscal Year 2005, a total of more than $14 million is being provided for operation of beam lines and research into new technologies. This support provides access to instrumentation for crystallography, spectroscopy, microscopy and small-angle scattering using x-rays, as well as for spectroscopy in the ultraviolet region of the electromagnetic spectrum and spectromicroscopy in the infrared region.

BER, in general, supports only one program in a given technology at each light source. However, there is the potential for establishing more than one program in the more widely used technologies, such as crystallography or x-ray spectroscopy, as many beamlines at the DOE light sources are suitable for experiments using these techniques.

I am asking the Biological and Environmental Research Advisory Committee (BERAC) to establish a subcommittee with broad expertise in the application of light source-based technologies in structural molecular biology and am charging BERAC to provide me with advice on the following:

- What would be the advantages and disadvantages of establishing more than one program in a particular technology at one of the Department's light sources? What priority should the BER program give to duplicating existing well-developed technologies at a light source relative to supporting research in light source techniques that are in earlier stages of development?

- In discussing this issue, I would like BERAC to specifically comment on the potential rationale for supporting the further development of the X4A and X4C beam lines at the National Synchrotron Light Source within the BER structural biology portfolio.

I request that BERAC report on its findings and recommendations at the April 20-21, 2005, meeting of BERAC.

Sincerely,

Raymond L. Orbach
Director

cc: Ari Patrinos, BER