

Structural Biology Research Center (SBRC) Science Advisory Committee Summary February 14, 2020

Advisor:

Alexander Wlodawer, Ph.D.
Chief, Macromolecular Crystallography Laboratory,
National Cancer Institute (NCI),
Frederick, MD, USA

Based on the presentations by staff members of SBRC, as well as on the written activity report covering the years 2014-2019, I would like to answer the following questions raised during the first meeting of the KEK-SAC.

(https://www.kek.jp/ja/About/OrganizationOverview/Assessment/Roadmap/1st_KEKSAC.pdf)

1. There is clear scientific excellence across the materials science and structural biology portfolio, as well as strong examples of industrial relevance. At the next meeting, we would like KEK to clarify where believes it holds, or could hold, a leadership position in materials science or structural biology.

It is my understanding that SBRC is principally responsible for the structural biology portfolio of KEK. SBRC plays a double role – it is responsible for the management of the structural biology pipeline for the university-based scientific community, as well as conducting its own research projects. With the scientific staff of ~40, supported by 5 administrators, the SBRC is tasked with providing access to the state-of-the-art protein expression and purification facility, operation of five Photon Factory (PF) synchrotron beamlines devoted to protein crystallography (MX), as well as two beamlines for biological small-angle scattering (SAXS). Additionally, for the last two years SBRC has been operating a Talos Arctica cryo-electron microscope.

Answers to KEK-SAC (cont.):

Historically PF has been the first MX facility in Japan and one of the first ones anywhere in the world. Although by now not among the most powerful X-ray sources, it is still competitive with the best synchrotrons, to a large extent due to its high level of automation, allowing operation with comparatively very small staff. Its macromolecular crystallization facility is unique in academic environment, since it is completely automated, allowing setting up the experiments and monitoring their outcome in a manner that requires only minimal staffing. Some of the beamline facilities are unique in their capabilities. For example, beamline BL-1A is optimized for collecting data using long-wavelength radiation that maximizes the anomalous scattering of the sulfur atoms present in native proteins. The samples and the detector are enclosed in a helium-filled chamber, thus avoiding air scattering. This uncommon facility has been successfully used to determine a number of *de novo* protein structures without the need to derivatize the samples with heavy atoms. Another unique facility available in SBRC is the anaerobic chamber for crystallization of proteins while excluding oxygen.

The facilities operated by SBRC are extensively utilized by about 200 groups of academic and industrial scientists from a number of different institutions, as documented by the publication record that varies between ~150 and ~175 publications per year. Additionally, about 20 publications are published each year by the SBRC staff, a significant fraction of which are in leading journals. About 300 sets of coordinates and structure factors are deposited each year in the Protein Data Bank. These are clear indications of the value of the resources provided by SBRC.

Answers to KEK-SAC (cont.):

2. The KEK-SAC would also like to hear about KEK's current and future leadership roles in structural biology.

It is very clear that SBRC has been playing a leadership role in Japan by enabling access to high-quality instrumentation for academic researchers, as well as by conducting very high-quality in-house projects. The latter activities are very important, since they set a very high standard of performance for the facility users and for scientific collaborators. Although attached to the Photon Factory, SBRC provides leadership not only in synchrotron-related aspects of structural biology, but also in biochemistry and imaging. Of particular importance is the recent addition of a cryo-EM instrument. However, the currently available 200 kV microscope is not sufficient to maintain the leadership role for the future and since cryo-EM is rapidly becoming the principal technique in studies of macromolecular complexes, it is absolutely necessary to expand the range of available instrumentation, preferably by adding both a 300 kV microscope, as well as a smaller microscope for sample evaluation. It is also clear that in the long range it will be necessary to upgrade the flux of the synchrotron X-ray source and continue upgrading the beamline instrumentation if the future leadership roles are to be maintained.

Answers to specific questions:

1. How does SBRC-SAC evaluate the leadership of SBRC in the field of structural biology? Has SBRC been a core academic research hub?

It is clear that SBRC has been a leader in the field of structural biology. Staff of SBRC has been involved in a number of high-importance scientific investigations, mostly through their involvement in national projects, first PDIS and then BINDS. Of particular interest is the project of investigating GTP metabolism that resulted in identification of a cellular GTP sensor. Glycobiology is another very interesting area of investigations, with extensive research on glycosyltransferases and lectins. Research on infective diseases resulted in structural studies of multidrug resistance transporters and *H. pylori* effector proteins. Studies of transcription initiation factors and redox enzymes have been also conducted on very high level. There is no doubt in my mind that SBRC is a go-to laboratory for cutting edge collaborative projects.

2. Have SBRC users in addition to in-house scientists been making outstanding contributions to structural biology and interdisciplinary scientific fields?

The users of both the MX and BioSAXS instruments have been very successful in obtaining high-quality results and in publishing them. Examples include structural investigations of Toll- like receptors, LHC-II, autophagy related protein complexes, and onco-protein from *Helicobacter pylori*, among others. Structural analysis of VDR that combined the use of methods such as MX, BioSAXS, and molecular dynamics showed the power of merging results obtained by complementary techniques.

Answers to specific questions (cont.):

3. Does SBRC play a role of an international academic research center?

SBRC has been engaged in a number of successful international collaborative efforts on projects in the area of infectious disease, studies of the process of gene transcription, as well as GTP metabolism. Based on an agreement with the Swiss Light Source (SLS), several of their scientists have been visiting PF every year, principally to use the unique capabilities of the beamline BL-1A that allow direct phasing based on anomalous scattering of sulfur atoms. Other foreign users have been utilizing the crystal-shaping instrument (moved from Spring-8). These projects provided a basis of a workshop during the 69th annual meeting of the American Crystallographic Association that took place in Covington, KY in 2019. SBRC staff were able to use the facilities of SLS during summer periods when no MX beamlines are operational in Japan. Foreign visitors have been coming to SBRC, some for extended period of time, and SBRC staff has travelled abroad and presented their results in international conferences.

Answers to specific questions (cont.):

4. Does SBRC provide appropriate support for researchers/visitors from abroad?

Foreign visitors to SBRC need English-language support from the scientific and administrative staff. Whereas it is assumed that the scientists and engineers should be reasonably fluent in the language, this might not always be true for the administrative staff. However, as I found myself, administrators were able to make all the arrangements for my travel and stay in Tsukuba without having to involve the scientific staff. I assume that the same acceptable level of support is available to all foreign visitors to SBRC. Thus, in my opinion, the facility makes it easy for the foreigners to obtain necessary information and guidance.

Answers to specific questions (cont.):

5. How does SBRC-SAC evaluate the effort of expanding the research fields by SBRC? Does SBRC create networks for scientific collaboration and discuss reorganization with different research organizations or fields?

Considering the relatively small size of the staff of SBRC it is difficult to recommend a significant expansion of the covered areas of interest. The existing extensive networks already prove that SBRC is very helpful to the scientific community, but further expansion of projects may dilute the efforts due to the lack of resources, mainly human.

6. How does SBRC-SAC evaluate contributions to education in Academia?

Presentations at national and international meetings are very helpful in making the scientific community, including students and postdocs, aware of the results obtained by SBRC staff. A large number of workshops and seminars also contribute to the success of educational efforts.

Answers to specific questions (cont.):

7. How does SBRC-SAC evaluate the PR activities?

The presence of many visitors, including foreign, is very helpful in making SBRC better known in the scientific community. The PR activities seem to be adequate.

8. How does the SBRC-SAC evaluate the present status of the SBRC?

SBRC is a vibrant organization with well thought-through research program. It provides very important service to the structural biology community in Japan. Some of the services offered by SBRC are unique and important.

9. How does the SBRC-SAC evaluate research projects in SBRC? Are these research outputs adequate?

As already mentioned above, the research projects conducted in SBRC are generally well chosen, important, and carried to completion. A number of manuscripts published in high-impact journals provide an evidence of the quality of science. The research output is certainly adequate considering the relatively small size of the scientific staff and the need to share the human resources between service and in-house research.

Answers to specific questions (cont.):

10. How does the SBRC-SAC evaluate the recent developments of facilities in SBRC?

The level of automation for protein expression, crystallization, and data collection is quite impressive. Of course, there is a limitation of what can be accomplished on the beamlines due to the fact that the synchrotron itself is rather old and SBRC has to live with the photon fluxes that they cannot control. Addition of more cryo-EM instrumentation would be very helpful in keeping SBRC at the forefront of modern structural biology.

11. How does the SBRC-SAC evaluate the funding situation of SBRC?

It is my understanding that the core funding of SBRC from the KEK provides only a small fraction of the total budget and a more stable institutional support would certainly be helpful. Since a large part of the efforts are directed to helping outside academic organizations, relying principally on grants might not be the most efficient way to secure proper funding. Current funding does not allow hiring more staff that could support outside users that conduct research on the MX and SAXS beamlines – for example, a similar organization in the United States is the Structural Biology Center/Midwest Center for Structural Genomics at Argonne. In that case about 12 staff support only 2 beamlines, whereas SBRC operates 7 beamlines with fewer than 20 support staff. Similarly, SER-CAT operates two beamlines at Argonne with a dozen staff. Thus it appears that improvement in the funding, in particular by making it more predictable year-to-year might be very helpful for assuring continuing future success of SBRC.

Answers to specific questions (cont.):

12. How does the SBRC-SAC evaluate the relationship with industries?

SBRC provides services to industrial partners for a fee, and these additional funds are clearly helpful in maintaining a healthy level of funding. With not much material provided in the reports (written or oral presentations), it is difficult for me to provide more detailed evaluation of this subject.

13. Is SBRC moving in the right direction? Are the future development items adequate?

I consider SBRC to be a mature organization that is doing very well now and that is likely to continue its high level of productivity well into the future. In the long term some of the developments will be affected by plans to upgrade the capabilities of synchrotrons and the provision of more cryo-EM instrumentation.



Alexander Wlodawer, Ph.D.
Chief, Macromolecular Crystallography Laboratory, NCI
Foreign Member, Polish Academy of Sciences
Fellow, American Crystallographic Association