Creating a World Leading Multiscale Bio-imaging Facility on Long Island

Vision

Many recent advances in medicine, drug development, and biotechnology have been made possible by our ability to study processes at the molecular level. For example, resolving the structure of proteins enabled fundamental insights into the cause of a range of diseases. X-ray diffraction and electron microscopy will continue to be the key techniques for deepening our knowledge.

Since the mid-20th century, scientists working at Brookhaven National Laboratory's (BNL) National Synchrotron Light Source (NSLS) have used x-ray crystallography to determine the structure of proteins and deduce their internal workings. Recent advances in cryo-electron microscopy (cryo-EM) have opened up the possibility of resolving the structure of the large multi-protein complexes that perform vital functions within cells. In the future, scientists will combine both techniques in their studies. A complete picture of these complexes is needed to fully understand the vital processes they perform and forms the basis for the development of novel drugs or biotechnology. The transformative opportunities offered by the cryo-EM revolution have been recognized by the U.S. National Institutes of Health (NIH) and the U.S. Department of Energy (DOE). Both of these agencies are working to establish, in the near future, funding opportunities for regional cryo-EM user facilities. To provide maximum impact, we plan to combine BNL's NSLS-II and its world-leading capabilities in protein structure analysis with a new cryo-EM facility. An investment in cryo-EM would elevate Long Island and NY State to world-leading prominence in the field of biomolecular science, positioning the region for additional NIH and DOE investments.

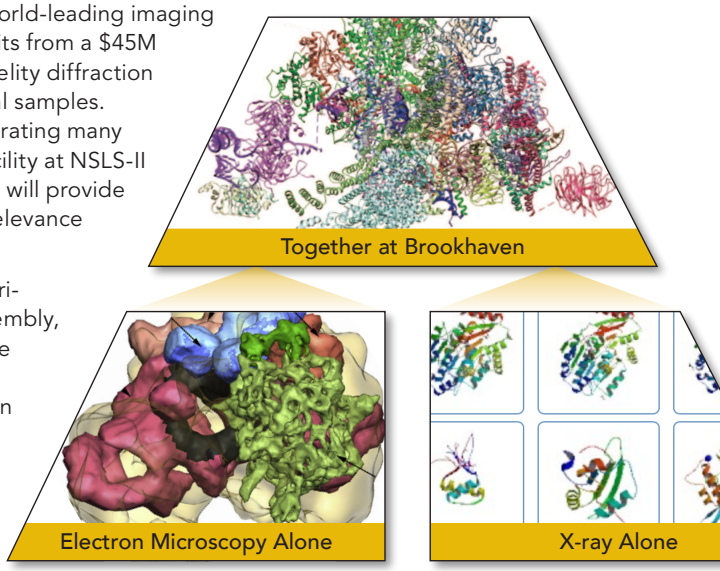
We propose that BNL establishes a Laboratory for Bio-Molecular Structure (LBMS), giving researchers access to the complementary tools of state-of-the-art cryo-EM and x-ray diffraction in the same institute for the first time, creating a major national user facility with tremendous impact in bioscience research. BNL's facility operation experience will enable access to both the world's leading light source—NSLS-II, a $912 million (M) facility completed in 2015—and to the cryo-EM. The cryo-EM suite will require an initial investment of $15M to fund two complementary instruments and sample preparation lab space. This facility would provide a significant boost to the competitiveness of NY State's bioscience and biotechnology communities and, through close collaboration with Cold Spring Harbor Laboratory and Stony Brook University, to Long Island in particular.

The Benefit of an Investment at BNL

There would be several advantages to establishing a bio-imaging facility at BNL.

First, NSLS-II is the world's brightest synchrotron light source, enabling world-leading imaging performance for samples of nanometer to millimeter size. BNL also benefits from a $45M investment from NIH in a suite of experimental facilities enabling high-fidelity diffraction data to be obtained from the smallest, most fragile macromolecule crystal samples. Placing biological molecules in their cellular context also requires incorporating many layers of data – this is where the creation of a state-of-the-art cryo-EM facility at NSLS-II is compelling. The combination of world-class x-ray and cryo-EM facilities will provide unique opportunities to understand biological systems of physiological relevance and generate breakthroughs in biotechnology.

Second, BNL's national nanocenter—the Center for Functional Nanomaterials—has world-leading programs in electron microscopy and protein assembly, further enhancing the impact of LBMS through tight integration with these sample preparation and handling programs. Third, BNL's computation capabilities are key to managing the data volume, analysis, and integration challenges associated with these microscopes . Fourth, BNL has a strong program in novel electron-detection devices, enabling us to push the state-of-the-art in cryo-EM beyond what is available anywhere in the world today. Fifth, BNL has long experience in operating user facilities and the support infrastructure necessary for the LBMS.



Academia, biotechnology companies, and the pharmaceutical industry will all benefit from our approach. Cryo-EM, when combined with x-ray crystallography, fits well in the drug-discovery and drug-development workflow. The models resulting from the combined investigations can deliver essential information for the next steps of chemical refinement for drug molecule candidates.

Implementation

We will employ a phased approach to develop the bio-imaging facility.

In the first phase, two electron microscopes will be purchased and installed on the NSLS-II experimental floor—where they will benefit from vibration isolation, temperature regulation, and close proximity to the x-ray diffraction and imaging infrastructure. The first microscope will be optimized for high-resolution 3D imaging of proteins and macromolecular assemblies. This microscope will be the "first port of call" for users to study their samples. Access to this instrument will be possible for scientists physically at BNL and for others through remote access from their home institutions. The second microscope will include an automated cryogenic sample exchange system for bio-sample handling at liquid nitrogen temperatures. This microscope will be primarily dedicated to high-resolution 3D imaging of proteins and macromolecular assemblies, but can also perform 3D cellular reconstructions. In the second phase we will develop a suite of laboratories to house the microscopes and provide sample preparation facilities.

Brookhaven National Laboratory Cryo-EM Facility	
Instrumentation	
Item	Cost (millions)
High-end	$7
Mid-level	$3.8
Total Instrumentation	$10.8
BNL Laboratory Upgrade	
Item	Cost (millions)
Microscope labs with vibration and temperature control	$4
Sample preparation lab	$0.2
Total BNL Laboratory Upgrade	$4.2
Total BNL Facility	$15

Leverage and Impact

The proposed investment in a cryo-EM would leverage several BNL resources. BNL would support operation and access to the cryo-EM, at a cost of ~$2M/year. The investment in the first microscope would also provide leverage for developing a fully equipped multi-user cryo-EM facility with DOE/NIH as likely sources for further investment; we anticipate it will house at least two additional instruments. The annual cost of a BNL national cryo-EM facility will be approximately $10M/year, supporting 500 visiting scientists and proprietary research programs.

To ensure transparent access, we will develop a program based on our experience running a national user facility capable of supporting 4,000 scientific visitors per year. We have the infrastructure in place for the administrative overhead of running such a facility, and expect that the cryo-EM facility will draw scientists from across the nation. We will be able to support more than 500 academic and industrial visitors each year. Approximately 50 FTE staff will support and operate the National Cryo-EM User Facility and the LBMS. Prior economic impact studies have shown that for every 50 jobs created at BNL, another 50-plus jobs are created in the community. The investment is also expected to serve several hundred visiting scientists annually, conducting both academic and proprietary research that is likely to attract additional funding and investment to NY State.

The electron microscopes installed in the NSLS-II experiment hall, sitting between the scattering beamline (LiX, right) and the x-ray diffraction beamline (AMX, left)

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