Department of Energy's Role in Advancing Biomedical Sciences

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Chairwoman Kaptur and Members of the Subcommittee, thank you for the opportunity to provide my perspective on the value and impact of Department of Energy scientific-user facilities on advances in biomedical sciences and new drug discovery to address the many health-related issues facing the Nation. My perspective is based on many years as a visiting scientist at the Department of Energy's Brookhaven National Laboratory and other Department of Energy-supported facilities, and for the past 15 years as Professor of Proteomics and Bioinformatics at Case Western Reserve University.

I would sum up my testimony as follows: Department of Energy facilities are essential to the nation's medical research agenda and to saving thousands of patients' lives every year. One piece of key evidence: Over 90% of new Food and Drug Administration drug-approvals from 2010-2016 used the Department of Energy supported facilities as an essential part of drug development.

Slide 1

The Department of Energy is responsible for building and operating large scientific facilities for the benefit of the entire national science effort. A national community of scientists visit the facilities to conduct research across virtually all the important areas of our Nation's science.

Thus, the Department of Energy must be – and is – sensitive to many disciplines beyond its core areas of focus of energy sciences to maximize the potential of—and investment in—such facilities. To attract a wide range of users across many disciplines to these facilities, the Department of Energy plans for and constructs a facility or storage ring with configurations and capability needed by communities, ranging from material science and physics to chemistry and biology. In this way, a costly and complex facility be leveraged by hundreds of projects simultaneously and cost effectively achieve very high productivity for the nation's science enterprise.

The Department of Energy supports 5 light source facilities, these very large machines supply very intense x-ray beams to users serving over 12,000 scientists from 49 states. The facilities reported 1200 papers published in 2019 with 30% of this activity in biomedical research. In particular for the biomedical sciences, synchrotron beams are used to investigate biological processes and understand the three-dimensional structure of proteins (called targets), which are molecules in the cell that can be manipulated to fight disease. 42 beamlines at the five facilities are entirely dedicated to biological and biomedical studies.

Synchrotron data relevant to structural biology and drug development are made publicly available through a resource called the Protein Data Bank, funded by a partnership of the Department of Energy, the National Science Foundation and the National Institutes of Health.

Slide 2

In the next slide, I introduce the Case Western Reserve University's Center for Synchrotron Biosciences, (https://case.edu/medicine/csb/), which I established in 1994 to use synchrotron technologies and light beams to study the structures of proteins and other biomolecules. The Center has been partners in 10 "beamline" projects at Brookhaven Laboratory's synchrotron facilities over this time. The Center's share of the funding for building and operating costs of these 10 instruments at Brookhaven, including University staff embedded full-time at the

facilities, has come from the National Institutes of Health and the National Science Foundation in the form of grants to the university. With this support, Center for Synchrotron Biosciences users solved nearly 3,000 protein structures and published over 2,500 papers across dozens of biology and chemistry disciplines relevant to many important areas of fundamental biology and medicine. In the process, the Center for Synchrotron Biosciences has trained and supported thousands of scientists from hundreds of institutions, helping them solve protein structures important for cancer drug discovery, examine the structures of deadly viruses, and see how metals and nutrients are transported between cells, to name a few novel discoveries.

Early on in the development of the Center for Synchrotron Biosciences, we saw an opportunity to expand the partnering between the National Institutes of Health and the Department of Energy to establish protein-production and structure-solution centers at the U.S. synchrotron facilities. This idea, in fact, was so powerful that dozens of centers popped up worldwide to collaborate on this initiative. Thus in 2000, the Protein Structure Initiative (https://www.nigms.nih.gov/research/specificareas/PSI) was established with three main goals: 1) To define the protein structures that corresponded to the rapidly emerging gene sequences arising from the human genome project and other initiatives; 2) To revolutionize structure determination at Department of Energy facilities to make the process faster and cheaper, and 3) To make sure that knowledge was disseminated widely and used for biomedical discovery and drug development through a public database called the Protein Data Bank (https://www.rcsb.org/).

The results have been nothing short of spectacular: In the 30 years up to 2000, less than 10,000 structures were solved. Today, there are more than 160,000. Over 90% of these structures have been determined by synchrotron-related methods. This is an incredible example of successful Department of Energy and National Institute of Health collaboration to enable biomedical science.

Slide 3

What's the impact of this interagency partnership for patients today? With the courtesy of data provided by Dr. Stephen Burley, Director of the Protein Data Bank, we can look at the period from 2010- 2016, and see there were 210 new drugs approved by the Food and Drug Administration, covering a wide range of diseases. These include anti-infectives, anti-cancer agents and central nervous system agents as just over half of the total. The drugs are mostly small molecules – pills, or biologics – injectables. 184, or 93% of these had relevant protein structural data collected at Department of Energy supported synchrotrons and deposited in the Protein Data Bank meaning it was fully accessible to the community. This high % reflects the tremendous importance of understanding the structure for drug development.

In particular, for cancer there have been 59 new medications approved; 55 of which have accurate structures of the protein targets available in the Protein Data Bank. 26 include the structure of the drug and target together, reflecting the value of structure-aided drug design to the drug development process, where the detailed interactions of the drug with the target can be verified and optimized.

One example includes the structure and visualization of a specific mutant form of one protein, called BRAF, bound to its target drug, vemurafenib. BRAF is a well studied protein kinase,

which is found to be mutated in half of metastatic melanoma patients. These structural biology data permitted scientists at both drug companies and in the academic world to confirm the details of how the drug interacts with the mutant form of the protein found in patients. This level of detailed analysis is essential to producing effective medicines. This is also an example of the National Institutes of Health-supported vison of Precision Medicine, where genomics and gene-sequencing in patients can identify a particular mutation and a specific drug is developed for those patients. For a moment, let's think of what if this project hadn't happened? What if Department of Energy and National Institutes of Health had failed in this protein-structure initiative? From this one example alone, thousands of patients each year would not have lifesaving medicines. The impact is really remarkable and wide ranging.

Slide 4

To set the stage for the next generation of experiments, the Center for Synchrotron Biosciences received National Science Foundation funding and completed a new beamline instrument for the biomedical sciences at a new Department of Energy-supported facility, the National Synchrotron Light Source-II, to solve the next generation of structural biology problems.

As examples this is being used to:

1. Solve structures of proteins that have eluded existing methods by integrating novel synchrotron data sets from multiple beamlines funded by National Institutes of Health and the Department of Energy. The illustrated case is the human estrogen receptor structure solved by our group. This project has developed new drug candidates that are needed to treat tamoxifen-resistant breast cancers.

2. Determine structures of pathogenic proteins significant to the development of treatments for Creutzfeldt-Jakob's (Mad Cow disease) and Alzheimer's disease.

3. Investigate the dynamics of protein reactions, adding a time dimension to our understanding of biology.

The efforts at this beamline and at this new facility are embedded larger ecosystem of Department of Energy facilities including nanocenters, and other instruments such as cryo-electron microscopes etc., that will enable tackling these large and important challenges.

In summary, the Department of Energy's scientific facilities are critical to conducting the nation's biomedical research. They have been invaluable in my own research sponsored by National Institutes of Health, National Science Foundation, the Department of Defense and other sponsors including industry. Dozens of drugs have been developed by Case Western Reserve and its Center for Synchrotron Biosciences collaborators alone through access to the unique facilities at Brookhaven. Your continued support for operation of current facilities and planned upgrades to maintain our nation's leadership in synchrotron science and biomedical research is paying off. I will be glad to answer any questions.

APPENDIX

Slide 1 National Synchrotron Light Source II
https://www.bnl.gov/ps/

Slide 2 Center for Synchrotron Biosciences
https://case.edu/medicine/csb/

Slide 3 Protein Structure Initiative
https://www.nigms.nih.gov/research/specificareas/PSI
Protein Data Bank
https://www.rcsb.org/

Publications:

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Slide 4 **Publications:**

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