HOUSE APPROPRIATIONS SUBCOMMITTEE ON ENERGY AND WATER

The US Department of Energy's role in advancing the biomedical sciences

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Chairwoman Kaptur, Ranking Member Simpson:

Thank you for the opportunity to provide a summary of my views about the importance of research supported by the Department of Energy for progress in biology and medicine.

Background

History teaches us that major advances in health care---and advances in our basic understanding of living organisms and diseases---often depend on the physical sciences, not just the life sciences. Xrays, radioisotopes, and nuclear magnetic resonance help us see tissues and monitor their functions inside living organisms; electrocardiograms and electro-encephalograms assess the vitality of critical organs, like the heart and the brain; and the identification of chemical components of blood precisely measure the metabolic and other actions of our bodies. These are just a small sampling of ways in which physics, chemistry, and engineering have shaped modern medicine. When we add more recent, complex computational methods to those historical developments, it is even more obvious how the disciplines championed by the DoE--the physical sciences, engineering, and computation--- contribute to biology and medicine.

I am speaking here today in part because I have observed some of these contributions from a front row seat, especially when I was Director of the National Institutes of Health (NIH) from 1993 to 1999 and Director of the National Cancer Institute (NCI) from 2010 to 2015. I have also seen what the DoE does for the life sciences when I served as a co-chair of the President's Council of Advisors on Science and Technology (PCAST; 2009-2010), as a member of the Secretary of Energy's Advisory Board (SEAB; 2015-2017), and as President of Memorial Sloan Kettering Cancer Center (MSKCC; 2000-2010). All of these experiences have contributed to my appreciation of the close relationship between DoE and the NIH, built on shared interests and complementary skills in a wide range of disciplines.

Previous NIH-DoE collaborations

Let me offer two specific examples of this productive relationship. During my tenure as NIH Director in the 1990's, the international Human Genome Project (HGP) was in its most active phase. (slide #1) The deciphered map of the human genome, with its nearly three billion elements (https://www.nature.com/articles/35057157), is now the foundation for a vast array of studies of human biology and disease. The HGP was initiated at the DoE National Laboratory in Los Alamos in the 1980's, and the sequence of most of the human genome was determined by a small number of centers, one of which was a laboratory directed by DoE scientists. These shared interests in the genomes of humans and many other organisms persist through projects that are often conducted collaboratively by the DoE and the NIH, catalyzed by faster and cheaper sequencing methods and by advanced computational methods for storing and analyzing vast sets of data.

In the same decade, the 1990's, the field of structural biology was expanding rapidly, in part due to an agreement between the DoE and the NIH to support so-called "beam lines," generated at cyclotrons at several DoE National Labs, for the elucidation of the three-dimension structures of proteins, the essential building blocks of cells. (slide #2) This collaboration helped to generate detailed structures of many of the molecular machines responsible for life--- the ribosome for protein synthesis; complex enzymes to copy DNA into RNA; and membrane proteins to transport important molecules, such as water and electrolytes, into and out of cells or to mediate the effects of hormones and the drugs that interfere with them. These shared interests persist, with new collaborative work on cryo-electron microscopy and on neutron beams to probe molecular structures more accurately, in great detail, and in more natural settings. (Blank slide #3)

The 2016 SEAB Report

After I left the NCI in 2015, then-DoE Secretary Ernest Moniz asked me and another SEAB member, Steve Koonin, to co-chair a SEAB working group to assess opportunities to promote biomedical sciences with DoE-supported technologies and facilities and to strengthen the relationships between investigators funded by the two agencies. The study group conducted workshops at which historical and current relationships between the agencies were described and future collaborations were envisioned by scientists representing a wide range of scientific disciplines, including materials science, fabrication, nanotechnology, development of sensors, radiobiology, imaging, and (especially) advanced computation and simulations. These technologies were considered in the context of existing initiatives in the biomedical sciences, such as Precision Medicine, the Cancer Moonshot, the BRAIN program, and microbial drug resistance.

Our SEAB study group also learned about important differences in the scientific cultures of the two agencies. The NIH traditionally depends on the imaginations of

many individual investigators, working in small laboratory groups, to explore the normal and abnormal functions of organisms. In contrast, the DoE devotes much of its scientific resources to National Laboratories, where large multi-disciplinary teams of scientists are assembled to pursue specifically defined national goals. This so-called "mission-driven" science at DoE is often focused on the development of new technologies that can accelerate work done in many scientific disciplines by many funding agencies.

Stimulated by the presentations we heard at the workshops, we wrote a report in the fall of 2016 (https://www.energy.gov/seab/downloads/final-report-seab-task-force-biomedical-sciences) that emphasized several important medical areas---such as oncology, neurosciences, microbiology, imaging, and biodefense--- in which collaborative research involving the two agencies should be expanded, by taking advantage of progress in instrumentation, data sciences, DNA technologies, material sciences, and modeling and simulation.

The report concluded with a few over-arching recommendations that are especially important for today's discussion:

(1) Convene panels of experts to identify opportunities for research programs that could be usefully pursued jointly by the two agencies;

(2) Share the cultures of the two agencies through joint training programs, workshops, and other events;

(3) Establish facilities for large scale, mission-driven collaborative research in the national interest, modeled on existing programs; and

(4) Report more often to the Administration, Congress, and the public about the virtues of inter-agency collaborations. (Happily, we are doing that today.)

Consequences of the SEAB Report and Interagency Collaborations

Prompted by an invitation to testify at this hearing, I have recently consulted with several officials at the NIH and the DOE, as well as others in the academic sector, to learn how these recommendations have fared. I am pleased to say that both the spirit and the letter of the report are thriving at both agencies; that most of the goals we advocated are being actively pursued through joint projects; that extensive consultations are occurring between the agencies; and that many individual scientists are engaged with both agencies. As one measure, the DoE Office of Science reports that nearly 3000 scientists with NIH support are working on over 1200 projects at DoE facilities.

I would like to conclude my testimony by describing two joint DoE-NIH programs---one a current initiative promoted by our report and one that I suggest as a future topic for expert evaluation.

(i) Among the many projects now being pursued jointly by the DoE and a number of Institutes at the NIH, several involve the NCI. Three are pilot projects that employ the DoE's tools for advanced computing (slide #4) to pursue three new goals in modern cancer research:

(a) making better predictions about the outcomes of treatment, based on characterization of each patient's cancer when grown in mice or tissue culture;
(b) learning how a set of common drivers of cancerous growth, the RAS proteins, interact with cell membranes and other proteins to distort cell behavior; and
(c) adding more sophisticated genetic and clinical data to the annual national epidemiological survey of cancer incidence and mortality.

(These plans have been discussed at multiple trans-agency meetings in last year and in a paper published in October (Bhattacharya et al, AI meets exascale computing: Advancing cancer research with large-scale high performance computing. *Frontiers in Oncology*, October 2, 2019; doi: 10:3389/fonc.2019.00984).

The second of these three pilots is of special interest today because the DoE-NCI collaboration is being conducted at the Frederick National Laboratory for Cancer Research (FNLCR) in Frederick, Maryland ---a contract program modeled on DoE's National Labs---and within the so-called "RAS Initiative," a mission-driven program that harnesses the talents of both the staff of the FNLCR and many individual labs supported by NCI grants. The initiative was created because RAS genes are mutated in as many as one-third of all human cancers, but unusual properties of RAS proteins have made them refractory to drug development.

To try to understand how these proteins work, DoE's computer scientists are working with NCI's RAS experts to solve a difficult problem: how to envision the relatively fast interactions of proteins that interpret the malignant signal from RAS proteins, in the context of much slower changes occurring in the cell membrane (slide #5). With the help of machine-learning methods provided by the DoE, it is now possible to simulate the location of RAS proteins on the inner surface of cell membranes (slide #6).

The kinds of interactions occurring between NCI and DoE have been expanded to include academic and pharmaceutic partners. One notable example is the ATOM consortium (slide #7) that includes both the University of California, San Francisco, and Glaxo Smith Kline in an effort to combine multiple types of expertise, large libraries of chemical compounds, and well-equipped facilities at the NCI's FNLCR

and the DoE's Lawrence Livermore National Laboratory to speed development of new therapeutics.

(ii) Before concluding my testimony, I would like to propose that the DoE and the NIH consult with experts, as recommended in the SEAB report, to consider a new, joint, mission-driven effort, centralized in a National Laboratory. The frequent emergence of antibiotic-resistant pathogens, especially gram-negative bacteria, and the retreat of many pharmaceutical companies from development of new antibiotics have created an international crisis (*The New York Times*, "Crisis looms in antibiotics as drug makers go bankrupt, December 25, 2019). This dire situation presents an immediate need to identify molecular targets in such bacteria and to seek novel chemicals to inhibit them. NIH-funded microbiologists and DoE-funded engineers and chemists could work together towards these common goals in a flexible, esteemed facility, such as the Molecular Foundry at the DoE's Lawrence Berkeley Laboratory (slide #8). Furthermore, the National Institute of Allergy and Infectious Diseases at NIH already supports grants to many laboratories working on this problem; those infectious disease experts could be assembled into a dispersed network of NIAID-supported investigators, like the network of NCI-supported investigators who enrich the RAS Initiative at the FNLCR. The benefits of a joint initiative to produce new antibiotics could be profound.

Conclusion

Federal support of the largely mission-driven science and development of technologies at DoE's National Labs and of the individual investigator-initiated research programs funded by NIH grants has made the US the world's leader in medical research. The agencies should be congratulated for their past and present collaborative efforts and encouraged to expand them to address many unsolved problems in the life sciences and medicine.

Thank you for holding this important hearing. I would be pleased to answer any questions you might have.