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"Biological Research at the Department of Energy: Leveraging DOE's Unique Capabilities to Respond to the COVID-19 Pandemic"

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Chairman Fletcher, Ranking Member Weber, and Members of the Subcommittee, thank you for the opportunity to participate in today's discussion about Biological Research at the Department of Energy: Leveraging DOE's Unique Capabilities to Respond to the COVID-19 Pandemic.

I am Glenn Randall, a Professor of Microbiology and Chair of the Committee on Microbiology at The University of Chicago, where I have studied emerging RNA viruses for the past 15 years. I am also the Director of Emerging Infections at the Howard Taylor Ricketts Regional Biocontainment Laboratory. This is one of thirteen National Institutes of Health-funded Regional Biocontainment Laboratories built to sustain research with pathogens that require enhanced biosafety (Biosafety Level 3), such as SARS-CoV-2, the causative agent of the COVID-19 pandemic. This facility is operated by the University of Chicago. There are a limited number of Biosafety Level 3 facilities in the United States. I direct a COVID-19 research core at this facility. The purpose of this core is to facilitate the COVID-19 research of other scientists, who need us to do experiments with live virus under enhanced safety conditions that they cannot do themselves due to a lack of expertise or facilities. This research is primarily focused on evaluating potential treatments and vaccines for SARS-CoV-2. It is in this capacity that I have gained an appreciation of the value of COVID-19 research performed in the Department of Energy. In particular, I have enjoyed multiple productive COVID-19-related collaborations with scientists at the DOE Argonne National Laboratory.

The U.S. Department of Energy Office of Science's Biological and Environmental Research (BER) program has a storied history. Decades ahead of the curve, it embraced inter-disciplinary science. It integrated biologists, physicists, computer scientists and engineers to address some of the most important questions of today and tomorrow. It is specifically designed to answer questions larger than one field can answer, such as our current pandemic. The needs are vast: effective drugs (both against the virus and to treat

the symptoms), a vaccine (both effective initially and likely better generations of vaccines in the future that provide long-lasting protection), and drugs and vaccines that will also protect against coronaviruses that will emerge in the future. Additional issues include more and better personal protective equipment (PPE) for our front-line health care workers. Moreover, coronaviruses are not our only pandemic threat. Influenza virus, as one example, will almost certainly cause a new pandemic in the not too distant future.

Many of the extraordinary capabilities that BER has nurtured have been foundational to a specific response to COVID-19: The U.S. Department of Energy National Virtual Biotechnology Laboratory (NVBL), which is a consortium of all 17 DOE National laboratories, each with core capabilities relevant to the threats posed by COVID-19. They leverage expertise and technology that synergistically interact with each other, academia and industry to advance our fight against COVID-19. This effort capitalizes on long-held expertise in unequaled strengths, such as discovering the structure of proteins (what they look like and how to target them) and supercomputing to simulate billions of potential drug-target interactions that amplify our current pharmaceutical capabilities by orders of magnitude.

The NVBL effort focuses on the following areas: https://science.osti.gov/nvbl[1]

Molecular structural determination: X-ray sources and neutron sources at DOE user facilities provide protein crystal structures needed for both computational modeling and experimental studies related to drug and vaccine development. These include the Advanced Photon Source (APS) at Argonne, Advanced Light Source (ALS) at Lawrence Berkeley, Stanford Synchrotron Radiation Light Source (SSRL) at SLAC, the Linac Coherent Light Source at SLAC, National Synchrotron Light Source II (NSLS II) at Brookhaven, and Spallation Neutron Source (SNS) at Oak Ridge National Laboratories. In addition, cryo-electron microscopes can be used to provide high resolution structures of virus particles and their interactions with antibodies and other drugs. DOE's Nanoscale Research Science Centers provide additional capabilities for imaging and characterization, as well as materials synthesis and nanofabrication capabilities to support study of biomolecules.

The DOE X-ray and neutron sources are a long-held treasure for the biological sciences, in addition to many other disciplines. We mostly study proteins blindly, not knowing what they look like or how to target them with drugs. These groups provide us with a detailed picture of the target. Many structures of SARS-CoV-2's 30 proteins have been solved at these facilities, many by DOE staff. These protein structures allow predictions as to what types of drugs may be effective against SARS-CoV-2. Structures of SARS-CoV-2 proteins bound by drugs are also being solved to give us important clues as to how we can modify the drugs to be more effective. Similarly, the structure of antibodies bound to the viral Spike protein are solved to better understand how they neutralize infection. Every submitted SARS-CoV-2 manuscript thus far involving my group relies on this invaluable capability.

Computational modeling and simulation: High performance computing resources at DOE user facilities, employing artificial intelligence, molecular dynamics simulations, and

modeling tools, combined with input from protein structure data, provide information to support research related to rapid survey of existing drugs and development of anti-viral agents and vaccines.

Most pharmaceutical companies have a library of 1-3 million compounds to screen against a disease target of interest. The supercomputers of multiple DOE National Laboratories have collaborated to generate a virtual library of every known chemical (~5 billion) and then screen them by molecular docking computer simulations of potential drugs bound to the SARS-CoV-2 protein structures described above. This is done over multiple iterations using artificial intelligence and machine learning to identify the best drug candidates. Now that candidates have been identified computationally, we are currently helping this consortium experimentally screen ~1000 potential drugs for anti-SARS-CoV-2 activity.

Genomic sequencing: Genomic resources at DOE's Joint Genome Institute and other facilities can sequence large numbers of patient samples to identify constrained regions, compare COVID-19 with other genomes to identify candidate regions for immuno-targeting, and construct models of individual susceptibility.

This capability is important for tracking how SARS-CoV-2 evolves. We have already witnessed an example where a SARS-CoV-2 variant emerged in Europe and overtook most of the world, including the United States (D614G in Spike). This capability will prove more valuable as we track drug and vaccine resistant emergence in the months to some.

The NVBL also works in areas that don't currently involve me, but are no less important such as:

Epidemiological and logistics support: Proven capabilities based on data analytics, artificial intelligence, and other decision tools have previously supported many national emergencies including oil spills, hurricanes, DOD supply chains and epidemiology. These capabilities have been deployed for government agencies, such as DOE, FEMA, and DOD. Such tools can yield information for health care providers and government groups on modeling disease spread, collecting/analyzing information and data from open sources world-wide, and providing tools for real-time decision making, risk analysis and prioritization for patient care and supply chain logistics.

Knowledge Discovery Infrastructure / Scalable Protected Data (KDI/SPI): Specialized facilities consisting of a multi-tier architecture facilitating a private cloud environment are available to host protected health data for research and analysis. These facilities meet NIST 800.66 and 800.53 control sets that meet Federal Information System Management Act (FISMA) requirements for a classification of moderate with enhanced controls. These capabilities are currently being used by Veteran's Affairs, Center for Medicare & Medicaid Services, and the National Cancer Institute's Surveillance, Epidemiology, and End Results programs.

Supply Chain Bottlenecks: Extensive manufacturing capabilities across the DOE laboratory complex are addressing supply chain bottlenecks associated with COVID-19.

Guided by input from both public and private stakeholders (government, health care providers), three health care supply chain bottlenecks have been identified: surgical masks and face shields, ventilator systems, and consumables (swabs, test kits components) used in COVID testing. These DOE teams have capabilities to rapidly reverse engineer/design and manufacture prototype parts, dies, and molds for industrial scaling.

Testing of clinical and non-clinical samples: DOE laboratories have established deep capabilities in high throughput preparation and analysis of biological samples using PCR-based protocols. While currently used to support DOE's mission in energy science, these facilities and trained personnel can be deployed to help address the rising surge in clinical samples. In addition, many labs have expertise in sampling and analysis of surfaces for biological materials developed in support of DOE programs.

NVBL has also recently started a new project on understanding *SARS-CoV-2 viral fate and transport*. This research effort leverages capabilities in computational modeling, data science, chemistry, environmental science, material science, aerosol chemistry and modeling, indoor air quality science and bioaerosol facilities, genomics and biodefense and makes extensive use of DOE user facilities, biosafety level 3 (BSL 3) facilities, environment research facilities, and the computational infrastructure across the national laboratory complex, to address the open questions around mechnisms of SARS-CoV-2 transmission. Enhancing the potential to predict SARS-CoV-2 viability and transmission in built and natural environments will help inform approaches to interrupt the chain infections, as well as inform strategies that guide society's resumption of normal activities.

I thought the best way for me to discuss DOE's impact on COVID-19 is to describe four of my personal experiences working with them. The first two studies I will describe used the strategy of drug repurposing, which was the topic of a prior subcommittee hearing. The basic idea is that drug development is a lengthy process, beginning with biochemistry, virology, animal studies, and finally clinical trials. By repurposing already approved drugs, you can greatly accelerate this process. In the first study[2], DOE scientists at Argonne National Lab first described the structure of the SARS-CoV-2 protein Nsp15. They then developed biochemical assays to assess the activity of the protein. Based on structural similarities, they predicted that the FDA-approved drug Tipiracil would inhibit the activity of the protein, which it did. Although Tipiracil had limited antiviral activity in our assays, co-structures of the drug bound to Nsp15 suggest modifications to improve its antiviral activity.

In the second study[3], colleagues of ours at The University of Chicago screened a library of ~1900 FDA-approved drugs against the related coronavirus OC43, a cause of the common cold that can be worked with under standard biosafety conditions (BSL 2). We when tested the top 30 hits in their screen for anti-SARS-CoV-2 activity and identified 20 drugs, ~ half of which were not previously identified in the literature. Collaborators at The University of Chicago and Duke University tested the 20 drugs for activity against the major viral protease, 3CLpro. One drug in particular, Masitinib completely blocked 3CLpro and virus replication. Our colleagues at Argonne solved the structure of Masitinib bound to the active site of 3CLpro. You can think of it as a key that perfectly fits in a lock, inactivating the

protein and preventing infection. Two potential clinical trials have emerged from this study. One involves the manufacturer of Masitinib (AB Science). The second trial would be run out of the University of Chicago and examine the potential use of a nasal spray Azelastine as a preventative against COVID-19. As these drugs show activity against multiple coronaviruses, there is potential for stock-piling them for future pandemics.

The third study[4] included many of the same collaborators. A major drug target of SARS-CoV-2 is another protease called PLpro. Proteases are attractive, in part, because they have been successfully targeted by drugs to treat HIV and hepatitis C virus. Our collaborators at Argonne solved the structure of PLpro, while colleagues at The University of Chicago designed inhibitors against the protein and biochemical assays to test the potential drugs. They confirmed activity against PLpro and for some of the compounds, we showed activity against the virus. Finally, our Argonne colleagues solved structures of the drugs bound to PLpro, suggesting strategies to further improve them.

I have already described the final study, which is testing potential drugs identified by the NVBL Molecular Design for Medical Therapeutics project. The work is a little less developed on the biology side, as we have begun testing compounds in the past two weeks (it is quite advanced on the computing side). There are already clearly potential antiviral compounds in this group.

In the past few months, I have enjoyed my collaborations with the DOE labs at Argonne. The unique skill sets that they bring to COVID-19 research are valuable and impressive. My interactions have been with just a fraction of the capabilities that DOE brings to combat COVID-19. DOE work in epidemiology, patient databases, manufacturing to address supply chain bottlenecks in PPE and ventilators, and clinical sample testing address important complementary challenges present by the pandemic.

Thank you for the invitation to testify to the Subcommittee on Energy. I would be happy to answer any questions you or other members of the committee may have.

References

1. https://science.osti.gov/nvbl

2. Kim Y, J Wower, NI Maltsev, C Chang, Robert Jedrzejczak, M Wilamowski, G Randall, K Michalska and A Joachimiak. Tipiracil binds to uridine site and inhibits Nsp15 endoribonuclease NendoU from SARS-CoV-2. bioRxiv 2020.06.26.173872; doi: https://doi.org/10.1101/2020.06.26.173872

3. Drayman, N, KA Jones, SA Azizi, HM Froggatt, K Tan, NI Maltseva, S Chen, V Nicolaescu, S Dvorkin, K Furlong, , RS Kathayat, MR Firpo, EA Bruce, MM Schmidt, R Jedrzejczak, MA Muñoz-Alía, B Schuster, V Nair, JW Botten, CB Brooke, SC Baker, BC Mounce, NS Heaton, B Dickinson, A Jaochimiak, G Randall and Savaş Tay. Drug repurposing screen identifies masitinib

as a 3CLpro inhibitor that blocks replication of SARS-CoV-2 and other viruses. bioRxiv. doi:https://doi.org/10.1101/2020.08.31.274639

4. Osipiuk, J, SA Azizi, S Dvorkin, M Endres, R Jedrzejczak, KA Jones, S Kang, RS Kathayat, Y Kim, VG Lisnyak, SL Maki, V Nicolaescu, CA Taylor, C Tesar, YA Zhang, Z Zhou, G Randall, K Michalska, SA Snyder, BC Dickinson, A Joachimiak. Structure of papain-like protease from SARS-CoV-2 and its complexes with non-covalent inhibitors. doi: https://doi.org/10.1101/2020.08.06.240192