Testimony of

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House Committee on Science, Space, and Technology

Subcommittee on Investigations and Oversight

COVID-19 Variants and Evolving Research Needs

May 12, 2021

Chairman Foster, Ranking Member Obernolte, and Members of the Subcommittee, thank you for the invitation to testify before you today about the critical role of the U.S. Department of Energy (DOE) national laboratories in combatting the COVID-19 pandemic and the virus' emerging variants. My name is Stephen Streiffer and I serve as Argonne National Laboratory's deputy laboratory director for science and technology, as well as the director of the lab's Advanced Photon Source.

For the last 15 months I have also had the honor of serving as the co-director of the DOE's National Virtual Biotechnology Laboratory (NVBL). The NVBL is truly one of the unsung heroes in the nation's fight against this disease. It was formed at the beginning of the pandemic to put the broad capabilities of the DOE complex to the task of fighting COVID-19, including the expertise and facilities of all 17 DOE national laboratories. Our labs are home to scientists and researchers that lead the world in their areas of expertise. We also house unique and powerful "user facilities": experimental and computational tools used by researchers from universities, government laboratories, and companies from across the country and around the world.

The national laboratories have a long history of putting our groundbreaking discoveries and innovations to work responding to national and international emergencies. From the 2005 Hurricane Katrina disaster, to the 2010 Deepwater Horizon oil spill, to the 2011 Fukushima nuclear accident, we have been on the front lines, helping with immediate response and developing long-term technical solutions. When the COVID-19 pandemic hit, we were prepared, ready, and willing to support an whole-of-government effort to fight the disease.

ACCOMPLISHMENTS OF THE NVBL IN FIGHTING COVID-19

The creation of the NVBL allowed the laboratories' collective capabilities to be almost immediately transformed into key assets in the world's fight against COVID-19. With funding from the CARES Act, all 17 national laboratories, through the NVBL, addressed medical supply shortages, discovered potential drugs to fight the virus, developed and verified COVID-19 testing methods, modeled disease spread and impact locally and nationally, and helped officials understand virus transport in buildings and the environment. Although NVBL CARES Act funding has been fully expended, this work sets the stage for ongoing work to identify, understand, track, and treat variants.

The national laboratory resources leveraged for this effort include a suite of world-leading facilities that are used by scientists from universities, industry, and other laboratories across the country and around the world:

- Light and neutron sources
- Nanoscale science research centers
- Sequencing and biocharacterization facilities
- High-performance computing centers
- Advanced manufacturing research facilities

Here are a few of the many contributions that the NVBL has made to the fight against COVID-19, through both the labs' discoveries and innovations and the support of their user facilities to the international scientific community.

Molecular Design for Medical Therapeutics

DOE's high-performance computers and light and neutron sources were used to identify promising candidates for antibodies and antivirals that universities and drug companies are now evaluating. These efforts were led by Oak Ridge, Lawrence Berkeley, and Lawrence Livermore National Laboratories with participation from six other laboratories. Specific examples include:

- Used artificial intelligence methods to screen 10^{40} (over a thousand-trillion-trillion-trillion) possible antibody variations, identifying the best matches against the SARS-CoV-2 spike protein.
- Computationally screened tens of millions of small molecules against SARS-CoV-2 viral proteins and then experimentally evaluated top contenders, greatly accelerating the search for new antiviral therapeutics.

Development and Evaluation of COVID-19 Testing

NVBL researchers developed new diagnostic targets and sample collection approaches and supported U.S. Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and Department of Defense (DoD) efforts to establish national guidelines used in administering hundreds of millions of COVID-19 tests. Led by Los Alamos, Sandia, and Lawrence Livermore National Laboratories, with significant contributions from eight other laboratories, projects included:

- Collaborated with DoD, CDC, and FDA to provide experimental data in support of national testing guidelines, assessing potential contamination in commercial kits, evaluating protocols such as for pooled samples, examining test kit viral transport media and protocols, and evaluating virus inactivation and extraction methods. These projects helped ensure that the nation was using effective tests and protocols and protecting frontline health care workers.
- Developed tools to analyze and assess how variants of the SARS-CoV-2 virus may affect the reliability of COVID-19 tests.

Epidemiological and Transportation Modeling

Researchers used artificial intelligence and high-performance computing to produce near real-time analysis of data to forecast disease transmission, stress on public health infrastructure, and impacts to the economy and transportation networks, supporting decision-makers at the local, state, and national levels. This work informed pandemic response with respect to underserved communities in Illinois, New Mexico, and Tennessee. Led by Oak Ridge National Laboratory with participation from six other laboratories (Argonne, Lawrence Berkeley, Livermore, Los Alamos, National Renewable Energy Laboratory, and Sandia), specific projects include:

- Created an approach to forecast COVID-19 case counts at state, county, and metropolitan scales using data-driven statistical models, enabling short-term planning of contact tracing, healthcare staffing, testing capacity, and vaccination strategies.
- Performed longer-term, scenario-based analysis and mitigation planning to support decision makers with information on effects of nonmedical interventions such as social distancing, masking, stay-at-home policies, and school closures before they are implemented.
- Collected and curated disease data, which created a unique national data resource to support epidemiological and pandemic modeling, including assessment of the impact of human behavior on infection spread and location and the availability of critical infrastructure.
- Developed an approach using cellular phone- and vehicle-derived data to reveal transportation patterns across industries, including bars and restaurants, as well as passenger, fleet, and heavy-duty vehicles.

Viral Fate and Transport

NVBL teams studied how to control indoor virus movement to minimize uptake and protect human health, designed materials to deactivate the virus, and developed models to track it in wastewater. This effort was led by Pacific Northwest National Laboratory with strong participation from Lawrence Berkeley, Livermore, and eight other laboratories. Examples include:

- Provided critical information about how behavioral, environmental, and operational conditions affect the risk of airborne virus transmission indoors, such as in classrooms, offices, and conference rooms, to mitigate viral spread in enclosed spaces.
- Designed new antiviral materials that can deactivate the virus.
- Produced and validated models for SARS-CoV-2 fate and transport in wastewater, enabling wastewater sampling as a means to provide early warning and hot-spot detection of localized COVID-19 outbreaks.

Advanced Manufacturing

Within just a few months, NVBL teams produced innovations in materials and advanced manufacturing that mitigated shortages in test kit components and personal protective equipment (PPE), creating over 1,000 new jobs. All 17 national laboratories contributed, and specific partnerships with industry include:

- Designed a system for mass producing N95 filter media, enabling Cummins Filtration (Nashville, TN) to produce material for more than 3 million masks per day, and worked with DemeTech (Miami Lakes, FL) to convert the N95 material to masks and respirators.

- Worked with the U.S. Department of Health and Human Services and Coca-Cola (Atlanta, GA), which produces 2 billion bottle preforms per week, to evaluate the use of these preforms to alleviate shortages of test tubes used to collect nasal swab samples.
- Developed an approach to 3D print the tooling needed to produce over 8 million sample collection tubes weekly by Thermo Fisher Scientific, Inc. (Lenexa, KS).
- Developed a new low-cost ventilator with BioMedInnovations (Denver, NC) that received FDA Emergency Use Authorization approval.

These accomplishments, made possible through the NVBL, demonstrate the game-changing resource represented by DOE's 17 national laboratories working together virtually, with a single focus on alleviating pandemic challenges. Going forward, the NVBL can bring these resources to bear on future national and international needs and emergencies.

BASIC RESEARCH UNDERLIES COVID-19 VACCINES

The speed with which effective COVID-19 vaccines were developed and disseminated has been unprecedented—and it wouldn't have happened without decades of investment in scientific research involving the national laboratories. I share two examples below.

First, the science behind the production of messenger RNA, or mRNA, that is used in the Pfizer/BioNTech and Moderna vaccines, is based on the building blocks of innovation that started at Brookhaven National Laboratory in the 1980s. At that time, a team led by F. William Studier was studying a virus that attacks *E. coli* bacteria. They created the first complete sequence of that virus' genome, which allowed them to understand how it produced many copies of itself. Studier and his team learned how to direct this copying capability toward making other things: specifically, copious amounts of RNA. This RNA could be delivered to the ribosomes in cells to be translated into proteins—or used directly in mRNA-based vaccines. Thus, Studier's pivotal discovery almost four decades ago enabled the production of today's life-saving treatments.

Second, five of the vaccines now in use—including those developed by Pfizer/BioNTech, Moderna, and Johnson & Johnson—leverage a technique developed from more than a decade of research at Argonne's Advanced Photon Source (APS). This technique, which increases the effectiveness of the vaccines, was developed by researchers now at the University of Texas at Austin and the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (NIH). Their current work on COVID-19 vaccines is based on their research into an entirely different disease: respiratory syncytial virus (RSV), which affects thousands of individuals per year. In their work to develop a vaccine for RSV, they used data from the APS to design a version of an RSV viral protein that would provide an effective target for the immune system, helping it build immunity against the virus. They realized that the technique could be applied to coronaviruses as well, and in 2013 began work on a vaccine for the Middle East Respiratory Syndrome coronavirus (MERS-CoV). They reported success in 2017, which again was supported by their use of the APS. When SARS-CoV-2 emerged, they joined with other researchers to successfully apply the same technique to vaccines against it.

COVID-19 VARIANTS: STRATEGY AND CHALLENGES

Having made great strides in combatting the original SARS-CoV-2 virus, the U.S. and the world is in the midst of a race between human ingenuity and the evolving coronavirus. The growing number of vaccines that have received the FDA's Emergency Use Authorization offer real hope for increasing rates of immunity. However, community prevalence of COVID-19 conversely enables the rise of new virus variants, such as the B.1.1.7 variant first identified in the UK or the B.1.351 variant first identified in South Africa. The DOE national laboratories can build on previously mentioned contributions and continue to drive innovation and information for the sustained, multi-pronged approach necessary to stay ahead in the race against coronavirus mutation.

The SARS-CoV-2 virus, as with any biological entity, is essentially a moving target. As the virus replicates within its host, it will frequently make mistakes – spelling errors – as it copies its genetic code, creating new variants. Many of these mistakes are inconsequential, akin to spelling differences between American English and British English (e.g., "color" versus "colour"). You can still understand the underlying meaning of the word. Most mutations are benign, although occasionally a spelling mistake is made that is more profound (e.g., "fowl" to "foul"). Thus, some mutations can compound and create a situation where not only has the word's meaning changed but that of the entire sentence as well. At this stage, the virus might not be "readable" by diagnostic tests, and, in the worst case scenario, the vaccine target and therapeutic target might no longer be recognizable.

Protecting our communities from COVID-19 variants can be summarized in four steps. Each of these steps is a complex, research- and technology-intensive process that requires a whole-of-government approach to succeed.

1. Sequence the genome of the virus collected from as many samples as possible, with testing distributed equally across the country.
2. Provide a centralized inventory of collected viral sequences and build a "family tree" that represents how they relate to each other. This large-scale analysis enables us to understand what variants are arising, where they are arising, and when they are arising.
3. Use computational modeling and experimental assessments to identify which variants may escape detection through currently available tests, can evade current vaccines, may be more dangerous, or resist current medical therapeutics.
4. Design new tests, vaccines, and treatments that target and work against variants as they continue to emerge.

Through the NVBL, DOE national laboratories are leveraging their resources to provide solutions to all four of these critical steps.

Sequencing and Monitoring Viral Variants

What helps us monitor and identify variants that evade vaccines and therapies is to sequence as many samples of the virus as we can from as many communities as possible, either from testing or from wastewater – in a broad and consistent effort – that allows us to effectively track these changes. We can make our specialized scientific facilities available to our partners at the NIH, CDC and other agencies to improve and speed up current virus sequencing. We also have expertise in large-scale sampling that can be put to work to support testing across the country.

Analyzing the Virus' "Family Tree"

A framework for comparing, classifying, and analyzing the genome sequences of all of these variants is crucial. This framework is already in place by using phylogenetic trees ("family trees") to represent how the variants are related to one another. Each leaf on the tree represents a variant. Leaves attached to the same twig are very similar, whereas leaves on different branches are less similar. Having this framework in place allows us to understand how certain variants arise and what series of mutations create the path to a certain outcome, such as increased virulence. Although this analogy appears quite simple, the underlying calculations for representing these relationships when considering all of the leaves in the tree is extremely complex. DOE supercomputing resources have historically been a critical component for this type of large-scale bioinformatic analytical work, and they will continue to support this work moving forward. An NIH-funded Bioinformatics Resource Center supported by supercomputing at Argonne provides an ongoing analysis of all emerging variants based on available SARS-CoV-2 genome sequences. As these sequences become available, specific variants of concern are tracked, as are the corresponding discrete changes in their genome sequence that differentiate them.

Identifying Variants of Concern

The DOE national laboratories also play a major role in identifying variants that may escape detection or be resistant to vaccines or treatment. Having the above framework in place in order to identify, classify, and track variants of SARS-CoV-2 also means that this information can be used to understand the implications of these changes on the human body.

We have unique, large-scale scientific facilities – such as the aforementioned light sources – and the corresponding expertise for structural biology work that can identify the actual physical changes in the shape of variant components. If the virus is considered as a set of LEGO bricks, we have the tools to literally manufacture and then inspect each individual brick at the scale of its individual atoms. These bricks are viral proteins. Any change in shape of one of those bricks means that we can predict how it interacts with other bricks, including those that stick to surfaces of human cells. Visualizing the changes in shapes of viral proteins provides insight into how they interact with and function in the human body.

Once we can predict how the changed viral proteins interact in the body, our large-scale computing and data management facilities can quickly assess if existing tests, vaccines, and therapeutics might fail against a new variant.

Mitigating Impacts of New Variants

For the fourth step, designing new testing, protocols, and treatment, the DOE laboratories collectively bring significant resources and expertise to the table. We support computational modeling, data analysis, and artificial intelligence techniques that accelerate the discovery of drugs that can successfully treat COVID variants. Our structural and experimental biology expertise and facilities can help national laboratory and university researchers refine or, if necessary, completely redesign therapeutic antibodies and small molecules in response to variations in the virus.

We can develop new tests for rapid detection of variants in clinical and environmental samples. We can also help decision-makers understand how the virus is transported, so that physical and administrative protocols can be developed and implemented that protect people against variants.

We can provide epidemiological modeling for near real-time forecasts and predictions. These forecasts help officials at all levels plan for different intervention options to prevent COVID variants from spreading, allowing them to make the best decisions regarding how to use their resources to keep our communities healthy. At Argonne, we have supported elected officials from the City of Chicago and the State of Illinois with forecasts and predictions since the start of the COVID pandemic, and stand ready to continue this support for COVID variants.

Lastly, to support both the ongoing response to the pandemic caused by the original SARS-CoV-2 virus, and the new variants, we will continue to develop innovative materials and manufacturing processes that address critical supply chain issues and support domestic production of key supplies.

CHALLENGES AND HURDLES

We have come a long way in the last year but we still have far to go both in confronting the current pandemic and preparing the nation for the next one. DOE and the NVBL can play a leading role addressing key concerns including virus sequencing, vaccine hesitancy, speed of drug design, testing and diagnostic development, enhancing epidemiology models, and real-time data sharing.

1. *Virus sequencing.* The U.S. has not performed much in the way of systematic sequencing of the virus in the country's population to identify and track the emergence of variants, and what we have conducted has predominately been done on a regional basis. A national, uniform sequencing of the virus across the whole country is needed to track these emerging variants. Fortunately, the NIH is putting resources into this effort, but more is needed.

2. *Vaccine hesitancy.* Improved public education about the efficacy of vaccines and the pivotal role they play in curtailing the extent and length of the pandemic would go a long way towards instilling confidence among the American people and decrease their skepticism about taking the vaccine. The DOE plays an important role in building scientific literacy among the American public, and the laboratories are actively engaged in STEM outreach across communities, including the most underserved. In addition, vaccine uptake/hesitancy is one variable the labs' epidemiological models can address, helping government and public health leaders better understand the likely evolution of the pandemic.

3. *Computational modeling and drug design.* The national laboratories' computational and artificial intelligence tools can accelerate the process of drug and vaccine development, and narrow the field of effective existing treatments. NVBL sponsored projects built computational discovery platforms that leveraged investments from multiple agencies and had demonstrable success in finding potential therapeutics that can enable faster response to future variations.

4. *Testing and diagnostic tool development.* DOE has the capabilities to further evaluate and validate existing or experimental tools for testing and diagnostics. DOE has a long history of experience in large-scale sampling and DNA sequencing and can deploy efforts to lower the cost and introduce simpler diagnostics.

5. *Continued epidemiology work.* Artificial intelligence inspired new ways of thinking about data inputs into pandemic models, including data on mobility, health, behavior, and demographics.

Future work can incorporate the emergence of vaccine-resistant variants, the analysis of societal impacts, the effects of international travel, and the potential benefits of vaccination to inform long-term planning efforts to mitigate effects of COVID-19.

6. *Standards and data sharing.* Metropolitan and state-level models of COVID-19 variant-penetration, immunity, transmission, and morbidity/mortality—broken down by geography and demographics—will continue to enhance the nation's ability to proactively plan and near real-time respond to the evolving landscape. These efforts would build on multiple agency investments for a dynamic, accurate, and multi-modal operational picture and provide web-based tools and actionable information for a whole of government approach.

CONCLUSION

For these reasons, Congress should consider continuing to strongly support the DOE complex and the NVBL as part of the nation's continued response to COVID-19 and future pandemics. At the national laboratories, we have infrastructure, networks, and teams of experts ready to deploy. Together, our national labs were able to develop vaccines, mitigation strategies, and solutions in record time due to Congress's robust and consistent support for the past several decades. Our all-hands approach—marshalling the talent and resources of the national laboratories, other government agencies, pharmaceutical industries, and universities from across the country—was instrumental to the impact we've demonstrated.

We were fortunate that we had a head start on research and modeling of coronaviruses. We were able to develop potential vaccines within weeks of the release of the original virus genomic code (most of the time to the authorization of the vaccines was taken up by Phase 1, 2, and 3 clinical testing). This will not always be the case. In the future, we may be confronted with more complex, less understood, more deadly viruses—diseases that can spread from different species and more effectively evade current treatments.

I am proud of the accomplishments of the NVBL and the national laboratories in responding to the COVID-19 pandemic, and feel confident these resources will be available to respond to future national challenges.

At Argonne, as we celebrate our 75th year as a national lab, we look forward to confronting the next 75 years of complex challenges facing society like the current pandemic. The scale of our facilities, the depth of our experience, and our collaborative approach, which are hallmarks of our national laboratories, match the scale of the pandemic we collectively face, and whatever the future holds.

Thank you to the Subcommittee for your time and consideration. I am happy to answer any questions.

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The APS is the brightest source of high-energy X-rays in the Western Hemisphere and is used to study the structures of materials and processes at the atomic scale. It is also one of the largest scientific user facility in the North America, with more than 5,500 users visiting each year.

He has also served as interim director of Argonne's Center for Nanoscale Materials, a national user facility that provides capabilities explicitly tailored to the creation and characterization of new functional materials on the nanoscale. The center's portfolio includes research on electronic and magnetic materials and devices, nanobio interfaces, nanofabrication, nanophotonics, theory and modeling, and X-ray microscopy.

Streiffer's scientific expertise is in structural characterization of materials particularly using transmission electron microscopy and X-ray scattering techniques. He has authored or co-authored more than 150 scientific publications and holds one patent.

He is one of the founding co-chairs of the National Virtual Biotechnology Laboratory (NVBL). The NVBL is a consortium of all seventeen Department of Energy National Laboratories founded in March 2020 to address key challenges associated with the COVID-19 crisis. The NVBL brought together the broad scientific and technical expertise and resources of the National Laboratories to address medical supply shortages, discover potential drugs to fight the virus, develop and verify COVID-19 testing methods, model disease spread and impact across the nation, and understand virus transport in buildings and the environment.

Streiffer holds a PhD degree in materials science and engineering from Stanford University and a BS degree in materials science and engineering from Rice University.