Building on DOE’s Science and Technology Leadership for National Biopreparedness

In a quick and impactful response to the COVID-19 pandemic—an event that has forever changed our perspective on biopreparedness—the U.S. Department of Energy (DOE) Office of Science established the National Virtual Biotechnology Laboratory (NVBL) in March 2020. Harnessing capabilities across all 17 DOE national laboratories, NVBL made critical advances by leveraging decades of DOE investments in basic science and experimental user facilities—including x-ray and neutron sources, leadership computing facilities, nanoscale science research centers, and biological characterization laboratories. This foundational research delivered the expertise and capabilities necessary to meet some of the greatest scientific challenges facing the community during the pandemic.1

Given the inevitability of future biological crises, the nation must be prepared to respond. This preparedness requires forward-leaning investments in the relevant science and technology. Addressing future impacts on human, animal, and plant systems requires (1) building technologies that support surveillance and new diagnostics, (2) understanding the molecular mechanisms that lead to pathogenesis, (3) developing models that define disease transmission through our population and environment, and (4) exploring new materials that will make personal protective equipment and other countermeasures readily available and resistant to viral and bacterial contamination. Basic research focused on these topics, coupled with DOE’s expertise and capabilities, will significantly improve our ability to quickly respond to future biological threats.

To identify the most important biopreparedness research areas, DOE’s Office of Science convened a roundtable of participants from across the national laboratories, along with representatives from other governmental agencies and industry. Held in March 2022, the roundtable focused on understanding DOE’s unique role in addressing future biological crises. Participants identified five priority research opportunities and the specialized cross-cutting capabilities needed to support biopreparedness studies at DOE national user facilities. These research opportunities will drive a transformative research agenda to achieve the underlying science and technology advances needed for ensuring the nation’s biopreparedness.

Priority Research Opportunities

1. Decode Pathogen Emergence, Evolution, and Host-Pathogen Dynamics in Real Time

Key Question: How do complex and dynamic biological systems interact with a host?

DNA and RNA sequencing capabilities in humans, plants, animals, and microbes have advanced significantly over the past three decades, but the ability to interpret these sequences has not kept pace. We also lack a complete understanding of the complex physical, chemical, and biological dynamics that occur when a pathogenic microbe interacts with a susceptible host. We therefore must transform biological science by discovering novel principles and phenomena that will underpin the development of high-throughput analytical approaches capable of measuring and determining the networks that define pathogen-environment interactions, pathogen evolution, and host-pathogen interactions. Innovations are needed to enable real-time measurements that will enhance understanding of complex biological system interactions in situ. Such an understanding will accelerate the ability to continuously monitor systems and identify anomalies that can alert us to a developing crisis and help guide our response.

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Cover image: Molecular representation of delta SARS-CoV-2 spike proteins (cyan) surrounded by respiratory mucins (red) and calcium ions (yellow) within an aerosol. Viral membrane is depicted in purple. [Courtesy University of California, San Diego]
2. **Build a Multiscale Understanding of Biomolecular Interactions to Catalyze Design of Targeted Interventions**

*Key Question: How do molecular interactions and vast biological networks give rise to cellular functions on physiological scales and co-evolution on ecological scales?*

Preparing for the next biological crisis requires moving beyond understanding individual biomolecules, organelles, and microbes to understanding the interactions of complex biological networks that drive cellular functions on physiological scales and co-evolution of microbes on ecological scales. Attaining this advanced knowledge will require unraveling interactions across vast numbers of molecules, with outcomes that manifest across many orders of magnitude of spatiotemporal scales. In turn, wholly new approaches are needed to characterize molecules within the cell and understand their interactions with cell states, host physiology, and environmental factors. Success on this front will yield a massive reward: the technology to design and deliver new drugs, vaccines, and diagnostic prototypes in weeks. In short, these developments would transform the nation’s ability to prepare for, prevent, detect, respond to, and recover from biological incidents. Importantly, this undertaking would also provide broader insights into microbial evolution and function, which in turn would advance efforts to address climate challenges and support biomanufacturing and the bioeconomy.

3. **Elucidate Multiscale Ecosystem Complexities for Robust Epidemiological Modeling**

*Key Question: How can complex and dynamic ecosystem interactions be captured in a framework of multiscale models?*

Accurate representations of human-environment interconnections, particularly among the four key ecosystem components—human, animal, microbial, and Earth systems—are necessary to successfully model and quantify disease impact. Traditionally, epidemiological models have focused only on modeling disease dynamics within individual ecosystem components. Addressing this gap requires integrating validated models across space, time, and disciplines, as well as assimilating real-time heterogeneous data streams to capture behavioral responses to environmental changes and interventions. Flexible, scalable, and disease-agnostic modeling frameworks will dramatically improve the ability to prepare for, and quickly respond to, emerging biological threats. Creating multiscale ecosystem approaches that leverage DOE computational facilities will help anticipate and reduce impacts to health, society, the environment, the economy, and infrastructure.

4. **Exploit Biotic-Abiotic Interfaces to Accelerate Design, Discovery, and Manufacturing of Materials for Biopreparedness**

*Key Question: How do we understand, predict, and control biotic-abiotic interfaces in ambient conditions and across time scales?*

The molecular details of pathogen-material interfaces are critical for understanding the environmental transmission of biological threats and, consequently, for protecting human health. Pathogen-surface interactions are extremely complex, and understanding them requires new characterization and modeling capabilities, under ambient conditions and across time scales. Further, a fundamental understanding of biotic-abiotic interfaces is the foundation for developing the transformative technologies that will strengthen the nation’s biopreparedness. Gaining such an understanding would enable, for example, the design of materials that control pathogen transport and leverage new antiviral and antimicrobial properties. This knowledge would also underpin creation of next-generation smart and wearable sensors to provide real-time pathogen detection. Finally, modular and distributed manufacturing will be critical for addressing supply chain issues during a biological event.
5. Accelerate Biopreparedness by Integrating Experimentation, Computing, and Globally Distributed Data

Key Question: How do we support innovative scientific research with integrated experimental, computational, and data capabilities?

The innovative research needed to accelerate scientific discoveries for biopreparedness requires a new paradigm that integrates experimental, computational, and data techniques. A systems approach is needed that combines complex heterogeneous data with autonomous experiments and real-time simulations. This approach would support efficient experiment-compute iterative processes and provide tools for data-to-knowledge transformations. Enabling scientific advances will also require new computational frameworks for model development, along with secure and privacy-preserving data and metadata access, curation, and quality management. These foundational capabilities intersect with each of the priority research opportunities and, if realized, will accelerate breakthroughs in bioscience and biopreparedness.

Outlook

The five priority research opportunities outlined here target specific scientific gaps identified during the national COVID-19 response. Achieving these research objectives would revolutionize our understanding of the science underlying a range of potential biological events and transform the nation’s ability to prepare for, and respond to, future biological threats. NVBL’s COVID-19 accomplishments demonstrated that DOE is uniquely positioned to lead these research opportunities through its capabilities and facilities in physical, computational, and life sciences and its integrative, cross-disciplinary, and collaborative tradition across experiments, models, and analyses.

Strengthening the nation’s ability to prepare for and respond to future biological threats requires innovative, integrative, and collaborative research that intersects with multiple disciplines and draws on diverse capabilities.

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