BRaVE: Biopreparedness Research Virtual Environment Initiative

Summary of BER-supported projects awarded in 2023 under DOE National Laboratory Program Announcement LAB-23-2955

Projects

- Decoding Host–Pathogen Dynamics with 4D (Epi)Genomics
- Enhancing Biopreparedness Through a Model System to Understand the Molecular Mechanisms that Lead to Pathogenesis and Disease Transmission
- Phage Foundry: A High-Throughput Platform for Rapid Design and Development of Countermeasures to Combat Emerging Drug-Resistant Pathogens
- Unlocking the Molecular Basis of Plant–Pathogen Interactions to Create Resilient Bioenergy Crops

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Websites

BRaVE
science.osti.gov/Initiatives/Biopreparedness

DOE Office of Science
energy.gov/science

DOE Biological and Environmental Research Program
science.osti.gov/ber

BER Genomic Science Program
genomicscience.energy.gov

In September 2023, the U.S. Department of Energy (DOE) announced $112.4 million in funding over 3 years for 10 research projects as part of a new Biopreparedness Research Virtual Environment (BRaVE) initiative. The projects are designed to leverage DOE's distinctive national laboratory capabilities to support U.S. preparedness and response to future potential biological crises. The multidisciplinary and collaborative initiative will provide insights into host–pathogen interactions that lead to new methods for disease detection, design of targeted therapies, and understanding of crop pathogens central to DOE bioenergy programs. Advances in the fundamental understanding of biological processes at molecular levels will complement research across federal agencies.

To provide the underpinning science that will enable DOE's strategy for biopreparedness and response, BRaVE projects focus on five priority research areas that take advantage of DOE's capabilities and facilities in physical, computational, and biological sciences.

1. Decipher host–pathogen dynamics in real time for new mitigation strategies.
2. Reveal molecular interactions across biological scales for design of targeted interventions.
3. Elucidate multiscale ecosystem complexities for robust epidemiological modeling.
4. Realize understanding to accelerate design, discovery, and manufacturing of materials.
5. Advance innovations in user facility instrumentation, experimental techniques, and data analytics.

The 10 multidisciplinary projects are supported by DOE Office of Science programs in Advanced Scientific Computing Research (ASCR), Basic Energy Sciences (BES), and Biological and Environmental Research (BER). The projects include multi-institutional teams, led by individual national laboratories with partners from other national laboratories and universities, including historically Black colleges and universities and minority-serving institutions.

Of the 10 projects, BER supports four. These projects (detailed below) focus on developing innovative multidisciplinary experimental and computational technologies to understand molecular mechanisms underlying host–pathogen interactions. These technologies will be used to develop new approaches for disease detection and targeted intervention design. The ASCR and BES projects focus on developing more complete models of how epidemics spread, designing novel anti-pathogen materials, and providing innovations in DOE user facilities.

Decoding Host–Pathogen Dynamics with 4D (Epi)Genomics

Principal Investigator: Shawn Starkenburg (Los Alamos National Laboratory)

Co-Principal Investigator: Christina Steadman (Los Alamos National Laboratory)

Co-Investigators: Karissa Sanbonmatsu, David Rogers, Cullen Roth, John Watt, Shounak Banerjee, and Jessica Kubicek-Sutherland (Los Alamos National Laboratory); Frank Alexander, Paul Freimuth, and Qun Liu (Brookhaven National Laboratory); Daniel Jacobson (Oak Ridge National Laboratory); Judy Brown (University of Arizona); Anna Lappala (Harvard University)

The ability to counter biological threats is limited given the enormous lack of knowledge of host resiliency mechanisms in the face of pervasive pathogens. The resilience of multicellular hosts (e.g., plants, animals, and humans) is predicated on the susceptibility of individual cells and effective defense mechanisms to halt the spread of infection for pathogen elimination. Recent work in the field of epigenomics suggests that epigenetics plays a key role in host defense. Epigenetic mechanisms collectively function to open or close regions of chromosomes to control gene expression. The resulting dynamic structural changes in the genome underpin most biological functions, including responses to infection. Conversely, genome structure can be altered by pathogens to reorient host cellular function to enhance pathogen replication or to establish latent or persistent infections. In response, hosts employ epigenetic modifications to counter infection, thereby altering the expression and 3D spatial configuration of their own genomes. The investigators hypothesize that epigenetic modifications vary between resilient versus susceptible host cells and that underlying changes to the epigenome and genome are characteristic of pathogen classes. Although recent progress has been made, scientists and decision-makers lack methods to quickly compare and identify these pathogen-induced changes to host genomes to understand susceptibility and resiliency.

The research team is addressing this gap by taking a holistic, "one-health" approach to (1) develop an experimental workflow to characterize and survey early-onset molecular signatures of infection found in the genome and epigenome; (2) leverage ASCR user facilities to create an exascale computational and explainable artificial intelligence (i.e., XAI) workflow that integrates this data and data from the user community to enable interactive, comparative 4D (i.e., 3D + time) genome and epigenome exploration and predictive dynamic modeling; and (3) integrate 3D genomic structural maps, epigenetic modifications, and ultra-resolution physical images using cryo-electron microscopy to validate genome structure–function relationships. This platform is agnostic by design and can be adapted for any pathogen (e.g., bacteria, fungi, and viruses). This platform will first be applied to examine viral infection in mammalian and plant systems to determine, for the first time, realistic 3D spatial architecture and dynamic reconfigurations of key host genomes induced by viral pathogens. Broad knowledge of epigenetic regulation of host–pathogen interactions will greatly advance the ability to predict pathogens with high potential to cause the next global-scale catastrophe or pandemic and will directly advance genomics capabilities in biopreparedness to transform the nation's ability to prepare for and respond to future biological threats.

Enhancing Biopreparedness Through a Model System to Understand the Molecular Mechanisms that Lead to Pathogenesis and Disease Transmission

Principal Investigator: Margaret S. Cheung (Pacific Northwest National Laboratory and the Environmental Molecular Sciences Laboratory)

Co-Principal Investigator: David Pollock (Pacific Northwest National Laboratory and University of Colorado, Anschutz)

Co-Investigators: James Evans (Pacific Northwest National Laboratory and the Environmental Molecular Sciences Laboratory); Weijun Qian (Pacific Northwest National Laboratory); Olga Kuchar (Oak Ridge National Laboratory); Arvind Ramanathan (Argonne National Laboratory); Omonike Olaleye (Texas Southern University); Greg Morrison (University of Houston); Zaida A. Luthey-Schulten (University of Illinois, Urbana-Champaign); Shannon Matzinger (Colorado Department of Public Health and Environment)

The science of biopreparedness to counter biological threats hinges on understanding the fundamental principles and molecular mechanisms that lead to pathogenesis and disease transmission. The vision to address this challenge is to create a powerful and user-friendly platform to elucidate

the fundamental principles of how molecular interactions drive pathogen–host relationships and host shifts. Investigators will enable groundbreaking discoveries by integrating a wide range of structural, genomics, proteomics, and other advanced omics measurements along with evolutionary and artificial intelligence predictions. To ensure the system is applicable to real-world problems, it will be developed in the context of a tractable model system (i.e., the small, abundant, and accessible photosynthetic cyanobacteria) and its constantly co-adapting cyanophage viral pathogens. This model will maintain the system's applicability to real-world problems and techniques, but the overall focus will be on elucidating general principles of detecting, assessing, and surveilling molecular interaction, adaptation, and coevolution that are system-agnostic and therefore extensible to any other viral–host interaction.

The objectives are to (1) identify the molecular complexes that comprise the cyanobacteria redox macromolecular subsystem and determine how they dynamically change with bacteriophage infection *in situ* using cryo-electron tomography; (2) profile regulatory changes during infection using proteomics, multiomics, and experimental validation and integrate the data with *in situ* structures; (3) use genomics and metagenomics to determine environmental and population factors across time scales that impact the interactions between marine cyanobacteria and their cyanophage parasites, predicting the evolutionary origins of *in situ* structural and functional interactions, convergence, and coevolution; and (4) develop a data integration and transformation platform that facilitates the integration of *in situ*, proteomic, and evolutionary measurements of molecular interactions to surveil diverse hosts and parasites in various environmental contexts.

A powerful and user-friendly platform will enhance connections between the often-siloed fields of structure, molecular phenotype, and evolutionary genomics that are key to biopreparedness but in need of integration. Investigators will do this by building a navigation tool to facilitate the effective use of globally distributed experimental data for integrated analysis and predictive modeling. The impact of the project will be to develop, implement, and test a platform to assess host–pathogen molecular interactions, adaptation to hosts and host shifts, and coevolution between hosts and pathogens. A successful project outcome will transform researchers' ability to study any host–pathogen interaction, encourage diverse community contributions, and gain fundamental insights into how proteins adapt to new contexts. This ability will be critical for designing early interventions to address future threats. Surveillance training capability will be built, aiming for a fair and equitable response to future pandemics and biothreats.

Phage Foundry: A High-Throughput Platform for Rapid Design and Development of Countermeasures to Combat Emerging Drug-Resistant Pathogens

Principal Investigator: Vivek Mutalik (Lawrence Berkeley National Laboratory)

Co-Investigators: Simon Roux, Adam Arkin, Adam Deutschbauer, Hans Carlson, Jamie L. Inman, and Harshini Mukundan (Lawrence Berkeley National Laboratory); Britt Koskella and Brady Cress (University of California, Berkeley); Archana Anand (San Francisco State University); Mark Mimee (University of Chicago); Catherine Mageeney (Sandia National Laboratories); Petr Leiman (University of Texas Medical Branch)

At its current rate, the rise of antimicrobial-resistant (AMR) infections is predicted to paralyze industries and healthcare facilities while becoming the leading global cause of loss of human life. With limited new antibiotics on the horizon, humanity is ill-equipped to respond to an inevitable AMR pandemic. As noted in the American Pandemic Preparedness Plan and DOE's Biopreparedness report, to be prepared for any natural or human-made infectious disease outbreak, the nation urgently needs to invest in foundational knowledge necessary to develop alternative therapies that can be scaled rapidly as new infections emerge. Bacteriophages (phages)—viruses which target bacteria—offer a powerful alternative approach to combat AMR bacterial infections. Despite recent advances in using phages to treat recalcitrant AMR infections, the field lacks broad-scale mechanistic understanding of phage–host interactions in clinically and agriculturally relevant bacteria. The ability to rationally design therapeutic phage formulations to overcome AMR pathogens quickly and with seamless adaptability to new pathogens can revolutionize approaches to combat AMR. With this goal, the research team has brought together multidisciplinary and multi-institutional expertise to develop a foundational Phage Foundry platform that integrates in-depth multiscale characterization of phage–host molecular interactions with high-throughput isolation, phage–host coevolution, machine learning, and engineering design principles to enable rapid development of targeted phage-based therapeutics against AMR pathogens. The team envisions this Phage Foundry platform to serve as an open and integrative knowledgebase available to researchers, clinicians, and industries in a fair and equitable manner. The platform has the potential to power a biobased economy by developing other phage-based biotechnologies, including diagnostics and vaccination strategies to treat emerging viral threats in future.

Unlocking the Molecular Basis of Plant–Pathogen Interactions to Create Resilient Bioenergy Crops

Principal Investigator: Qun Liu (Brookhaven National Laboratory)

Co-Investigators: Sean McSweeney and Shinjae Yoo (Brookhaven National Laboratory); Ljiljana Paša-Tolić and James Fulcher (Pacific Northwest National Laboratory and the Environmental Molecular Sciences Laboratory); Yasuo Yoshikuni (Lawrence Berkeley National Laboratory and the DOE Joint Genome Institute); Christopher S. Henry (Argonne National Laboratory); Huimin Zhao (University of Illinois, Urbana-Champaign); Clint W. Magill (Texas A&M University); Jeffery Dangl (University of North Carolina, Chapel Hill)

The development of resilient and sustainable bioenergy crops, such as sorghum, poplar, and switchgrass, is a BER focal point. Bioenergy crops, like all crops, are susceptible to diseases that can vastly impact yield and quality. With the large-scale deployment of bioenergy crops, pathogen outbreaks will inevitably occur. With climate change and growth in marginal conditions without competition with food crops, bioenergy crops are facing biothreats and diseases. Plant pathogens (i.e., fungi, bacteria, and viruses) produce a stunning array of virulence effector proteins and other molecules that interact and hijack plant defense systems, resulting in infection and disease. Conversely, all plants encode intracellular innate immune receptors called nucleotide-binding leucine-rich repeat proteins (NLRs) that recognize effectors to elicit successful immune responses. The coevolution of plants and pathogens drives cycles of infection and immunity. The investigators propose to integrate systems biology, biomolecular characterization, and synthetic biology with computation and artificial intelligence/machine learning to provide foundational insights into dynamic plant–pathogen interactions. The output of this project will contribute to the development of a resilient bioeconomy, which includes the bioengineering and breeding of broad pathogen-resistant bioenergy crops and biocontrol of disease through mutualistic plant–bacteria interactions. The technologies and resources developed may be rapidly deployable for combating emerging biothreats.

Sorghum is a drought-tolerant biofuel feedstock that can grow on marginal lands without competing with food crops. However, a devastating anthracnose disease, caused by a fungal pathogen *Colletotrichum sublineola* (Cs), can lead to sorghum yield losses of up to 67%. The co-evolution and genetic diversity of both sorghum and Cs make this a highly relevant model system to study plant–pathogen interactions. The primary objective of this project is to advance a fundamental understanding of plant–pathosystem interactions by investigating the molecular interactions between sorghum, its anthracnose-disease causative fungal pathogen Cs, and antifungal biocontrol bacteria to create disease-resilient bioenergy crops. The project is organized into four linked aims: Aim 1, Identify molecular interactions underlying the pathogenicity of Cs and its inhibition by bacteria; Aim 2, Characterize the molecular basis of key interactions determining Cs pathogenicity, anthracnose resistance, and its susceptibility to biocontrol; Aim 3, Create synthetic pathogen infections to study pathogenicity, resilience, and disease biocontrol; and Aim 4, Develop innovative computational resources to study plant–pathogen interactions across biological scales.