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U.S. DEPARTMENT OF ENERGY

BNL Strategy in Biopreparedness: A New Direction within DOE-Office of Science

Martin A. Schoonen, Associate Laboratory Director

May 9th, 2024

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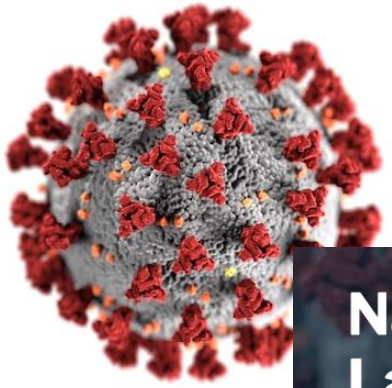
What is Biopreparedness and why DOE?

Utilize Unique Capabilities and Facilities of the National Laboratories to Address Future Biological Crises

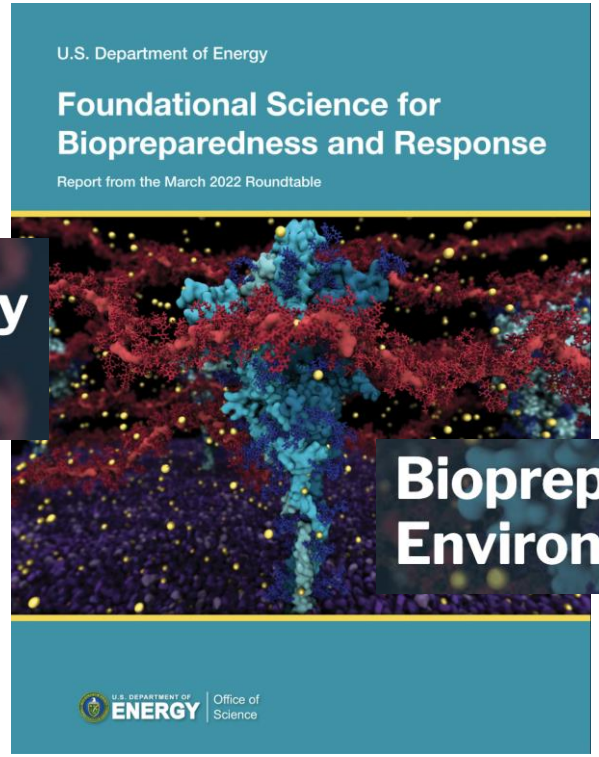
"…revolutionize our understanding of the science underlying a range of potential biological events and transform the nation's ability to prepare for, and respond to, future biological threats,"
Asmeret Asefaw Berhe, Director of the DOE's Office of Science. 9/7/2023

March 2020 → March 2022 → FY22/23-26



National Virtual Biotechnology Laboratory (NVBL)

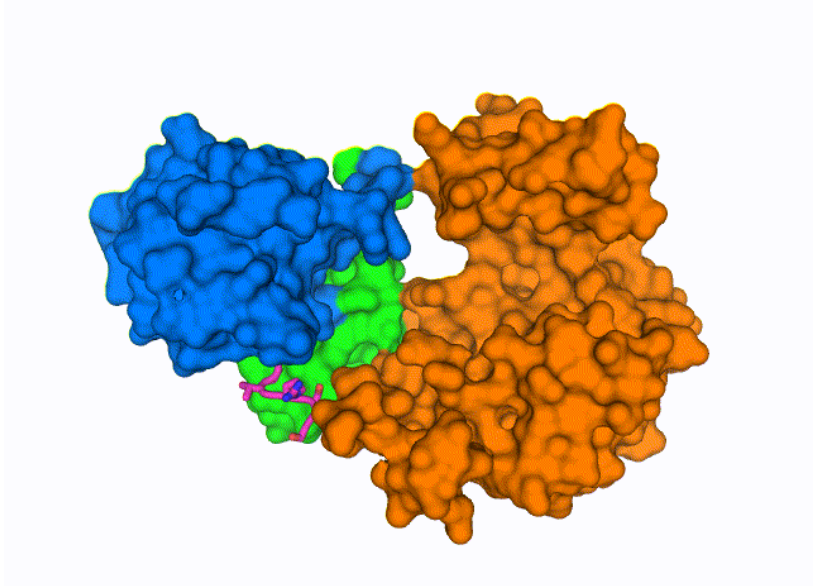
Photo by CDC on Unsplash



Biopreparedness Research Virtual Environment (BRaVE)

BNL's Leadership Position in NVBL

BNL had an important role in NVBL, leveraging expertise in bioscience, materials science, computational science, atmospheric science, and facilities (NSLS-II, CFN)



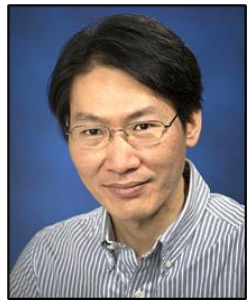
Purple strand virus E-protein, multi color segments are human protein

Chai J, Cai Y, Pang C, Wang L, McSweeney S, Shanklin J, Liu Q. (2021). Nature Communications 12, 3433. https://doi.org/10.1038/s41467-021-23533-x

Significance and Impact

First to resolve how SARS-CoV-2 membrane protein interacts with key human lung protein. This interaction is determining step in disease progression. These insights are needed to develop candidate drugs.

- First published structure from the BNL cryo-EM center
- Collaboration between LBMS, Biology, NSLS-II
- One of the most accessed and impactful papers in 2021 in science (top 5% Altmetric)
- Widely reported on



Qun Liu

JUNE 8, 2021

How COVID-19 wreaks havoc on human lungs

by Brookhaven National Laboratory

PHYS.ORG

SCIENMAG Science Magazine

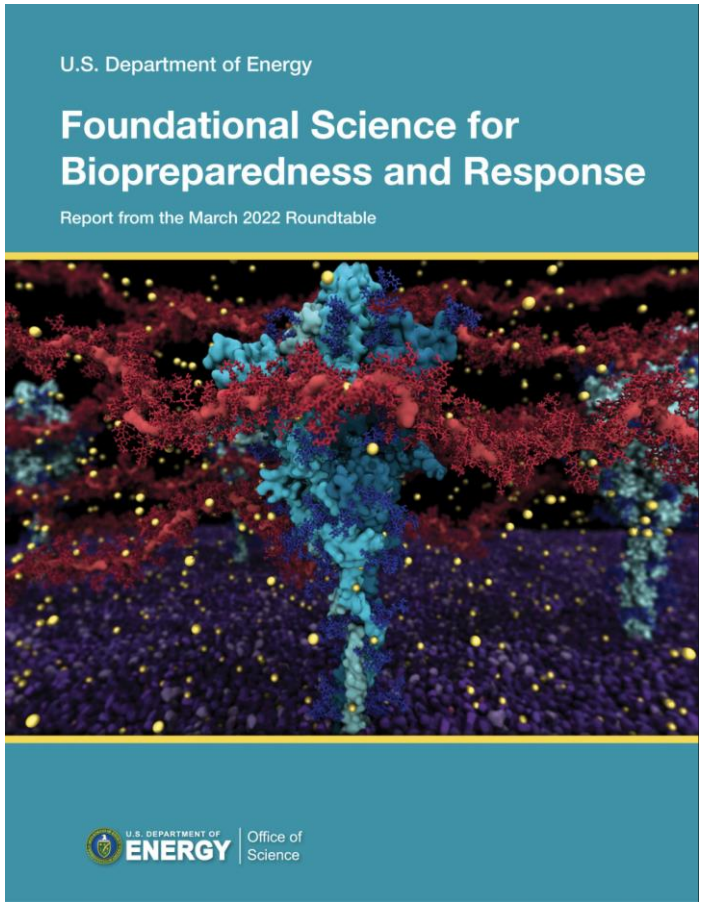
U.S. DEPARTMENT OF ENERGY | Office of Science

Foundational Science for Biopreparedness and Response

DOE-SC Roundtable

Report to BESAC December 7th 2022

John Hill, Deborah Gracio and Pat Fitch



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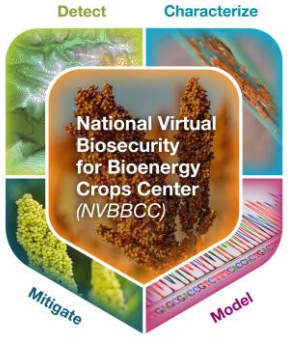
Taken from presentation by John Hill to BESAC, 12/7/22

Conclusion

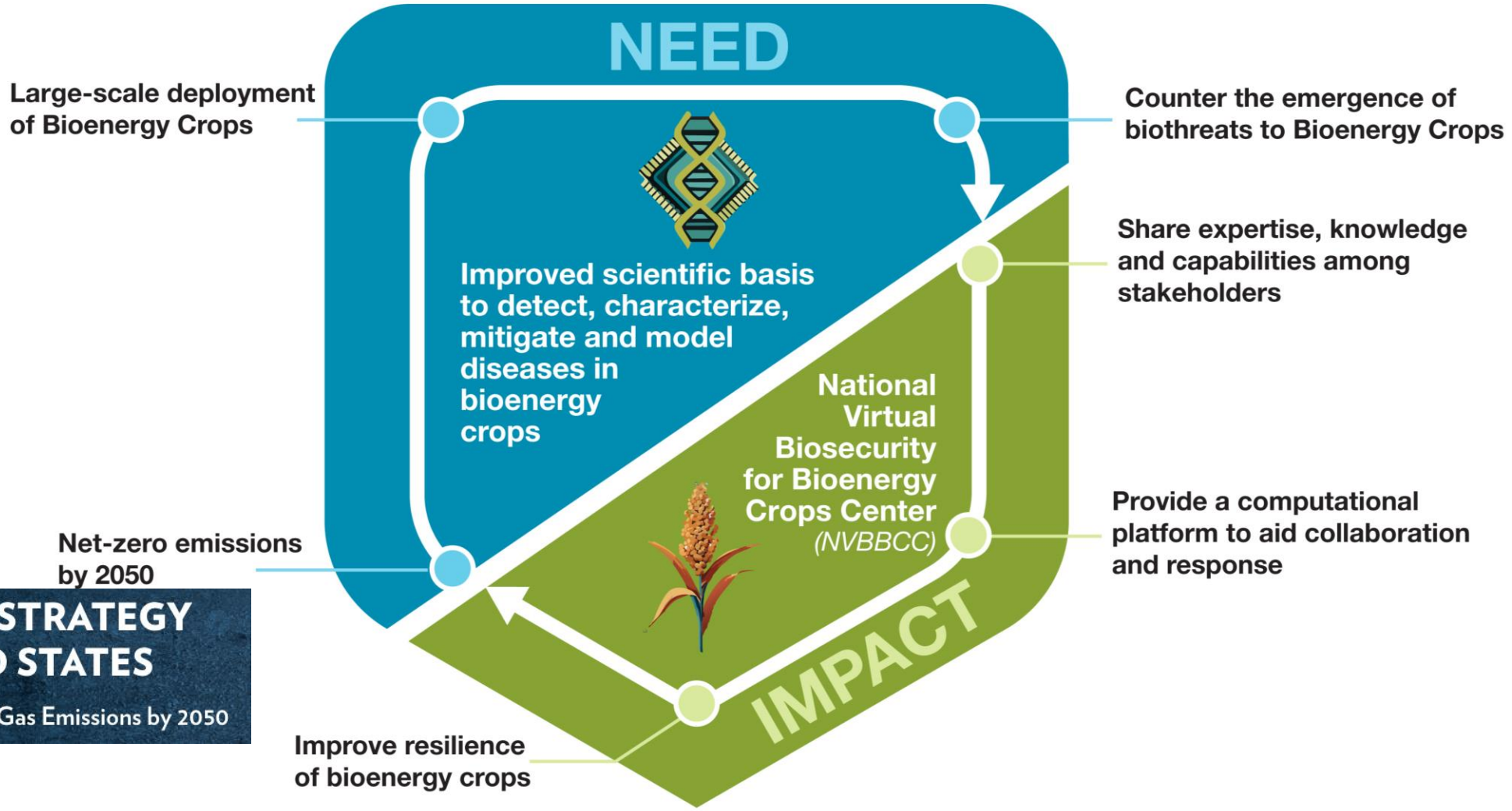
- Basic research, uniquely carried out in DOE-BES, ASCR and BER mission space and supported by the SC user facilities, can address scientific questions with impact on the Nation's biopreparedness.
- Further, capabilities developed for this research will be able to pivot to directly address future bio-crises
- We identified 5 PROs to better position the Nation in this work
- BRaVE act funding in FY23 and beyond will enable some of this work
- DOE-BES, ASCR and BER research can help make the Nation safer in future crises



Rationale

Executive Order 14081 of September 12, 2022

Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy



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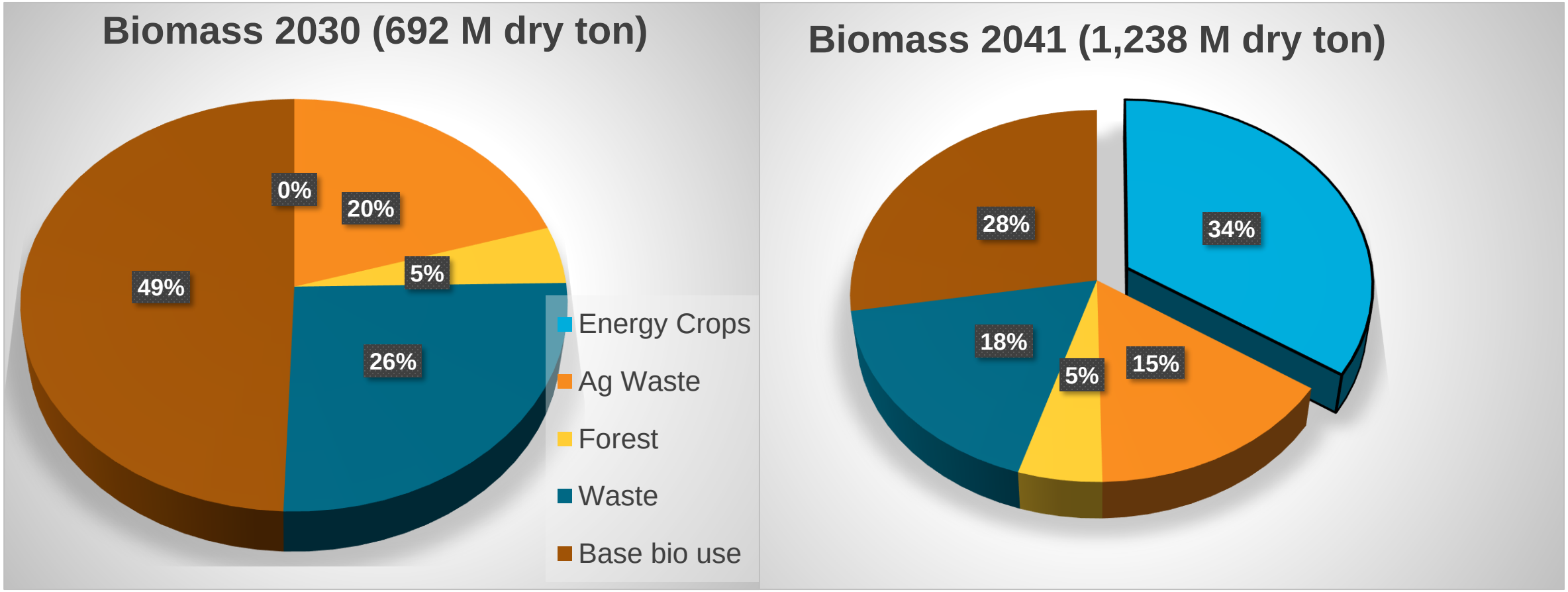
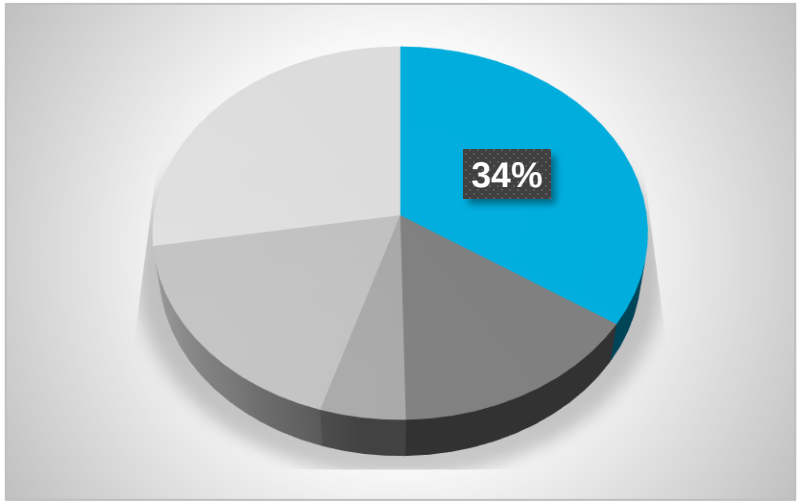
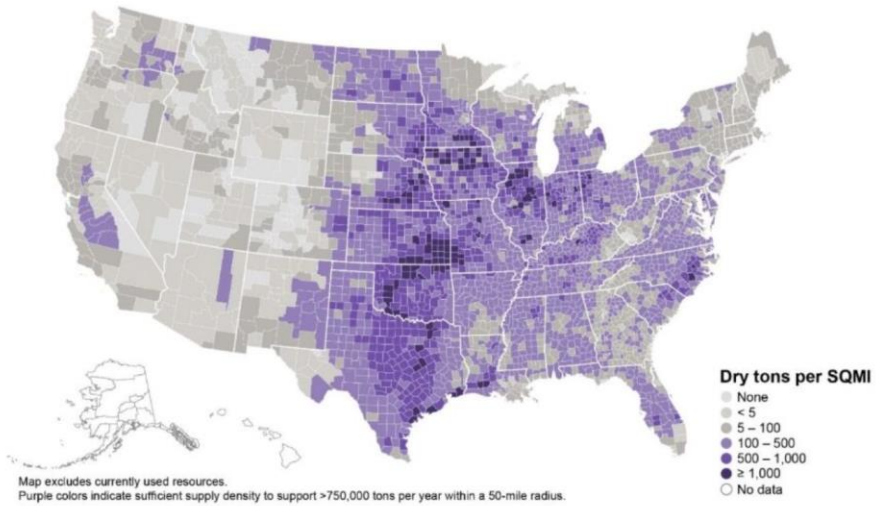
Transition to Large-Scale Bioenergy Crop Deployment

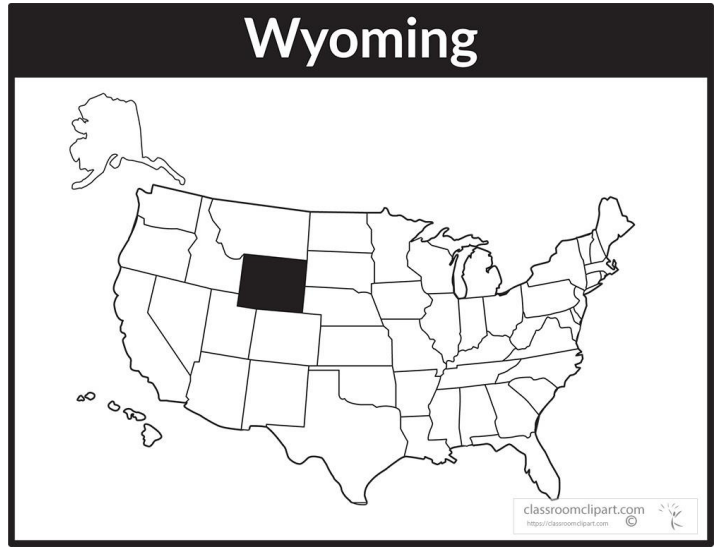


https://www.energy.gov/eere/bioenergy/2023-billion-ton-report-assessment-us-renewable-carbon-resources

Putting Scale into Perspective







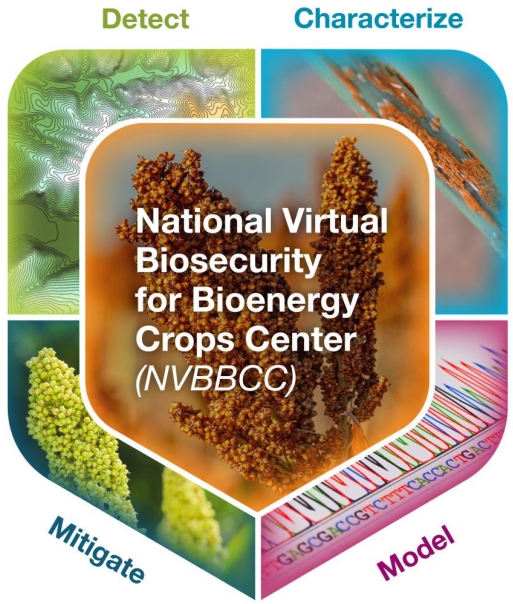
FY22 First Biopreparedness Funding

EBNN-led effort was awarded single investment by Biological and Environmental Research ($5 M).

DOE Funds Pilot Study Focused on Biosecurity for Bioenergy Crops

Research into threats from pathogens and pests would speed short-term response and spark long-term mitigation strategies

October 6, 2022



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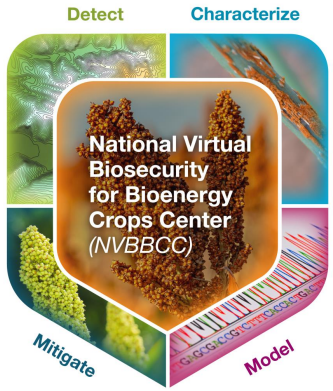


Objectives of FY22 BER Pilot Project

Gather community input and develop Roadmap for new center

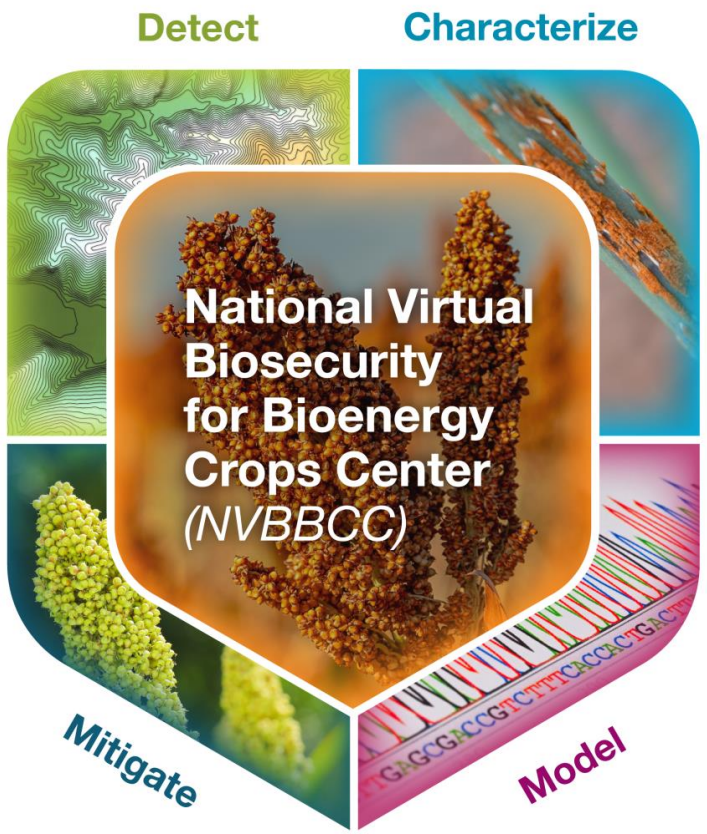
- **Key deliverable Roadmap document**

Conduct an exploratory study on a disease affecting an energy crop to understand what is needed to do this type of work to inform Roadmap (permits, workflow, lab infrastructure needs)

Expand capabilities at existing cryo-EM center so it is possible to study cells in plant tissue. ($1.6 M Cryo-FIB-SEM acquisition)

Build proto-type of computer platform (SciServer) to support a data-intensive, distributed, virtual center (led by Computational Science Initiative)

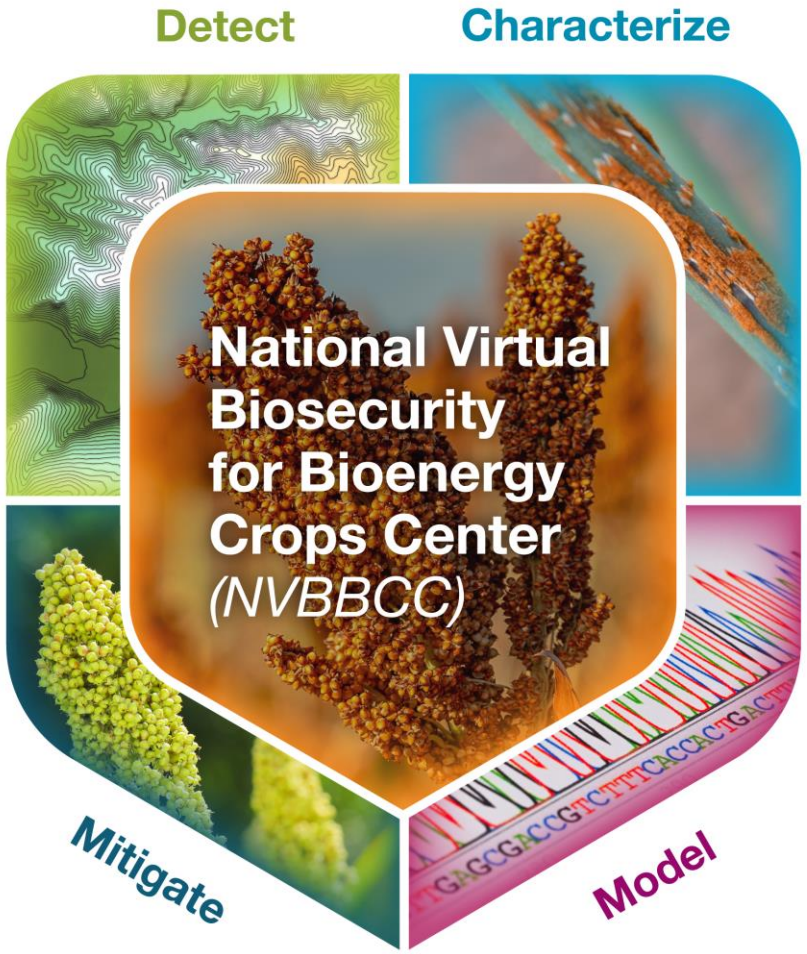
Roadmap development—Community Input



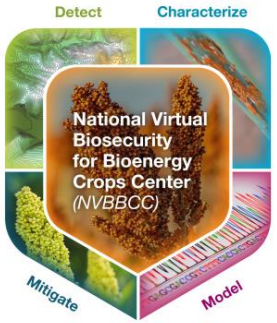
Six consecutive virtual workshops with ~150 participants in total

Agency participation: DOE, USDA, DHS, NIH, NASA
DOE Complex: ANL, BNL, LBL, ORNL, LLNL, PNNL, SNL
Academia: UC-Davis, Cornell, UNC, Duke, UIUC, Stanford, Univ of Chicago, Texas A&M, Cold Spring Harbor, Univ. Utah, Yale, UC-Irvine, UCSF, UCSD, UC-Berkeley, Virginia Tech, Univ. Vermont, Kansas State, Univ. Missouri
Private Sector: Microsoft, Nano Engineering Corp, Globus, Aerosol Devices

Community Vision: Cutting-edge Science to Address Biothreats to Bioenergy crops



- Support a research program focused on bioenergy crop/pathogen/vector systems
- Establish and maintain a capability to address emerging biothreats to bioenergy crops
- Leverage DOE's research and computational facilities across the complex
- Collaborate and coordinate with USDA, DHS, and other stakeholders
- Develop and retain a multidisciplinary and distributed workforce



Research Priorities

- Focus on bioenergy crops that will be deployed at scale to support the US Bioeconomy
- Improve predictability of disease spread in a changing climate across spatial scales
- Provide scientific basis for earlier remote detection of disease
- Advance understanding of bioenergy crop/pathogen/vector systems and their dynamics
- Understand how bioengineering of bioenergy crops may affect susceptibility to pathogen and progression of disease
- Develop a foundational understanding of the combined effects of biotic and abiotic stresses on bioenergy crops.
- Develop and demonstrate novel mitigation strategies to improve disease resistance

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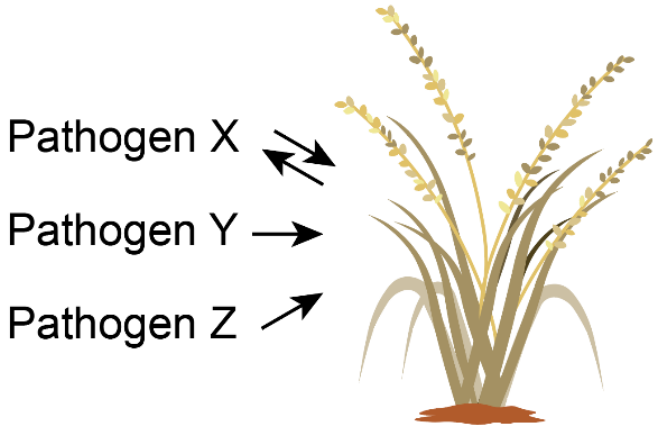
Example Research Priority: Pathogen-inducible, broad-spectrum resistance

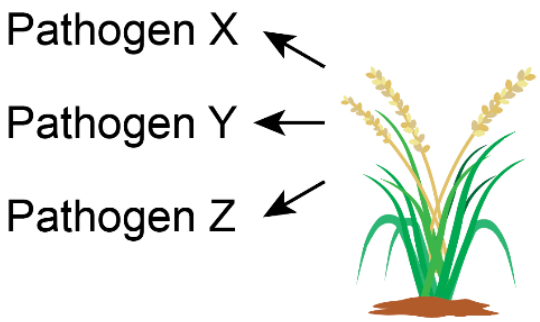
Near-Term

Gene-for-gene disease resistance



Introducing one pathogen-specific resistance gene at a time.
Shortcoming: May not be effective against fast evolving pathogens.

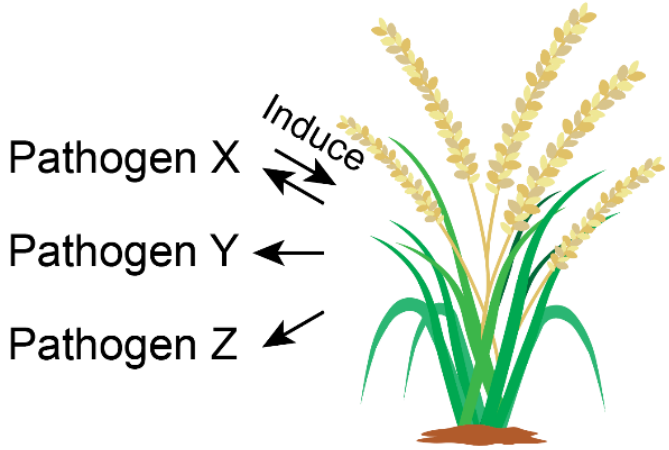
Broad-spectrum disease resistance



Overexpressing broad-spectrum disease resistance.
Shortcoming: Often has yield penalties.

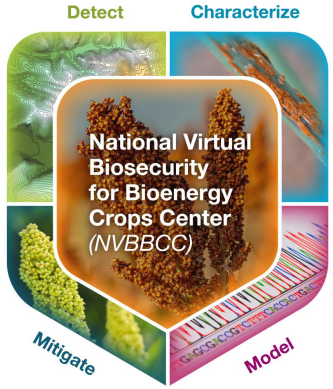
Long-Term

Transient broad-spectrum disease resistance



Transcriptional & translational control of broad-spectrum resistance avoids yield penalties.

Concept: pathogen inducible expression of defense regulators under precise transcriptional & translational control



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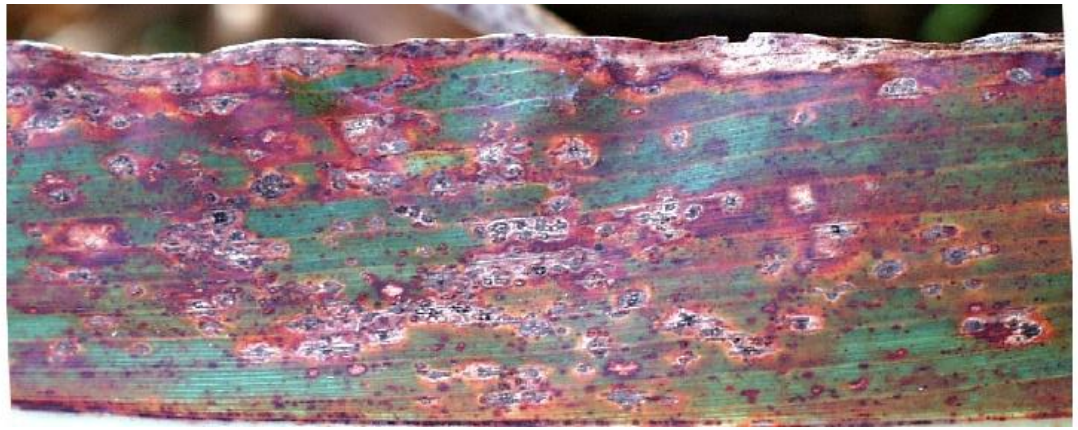
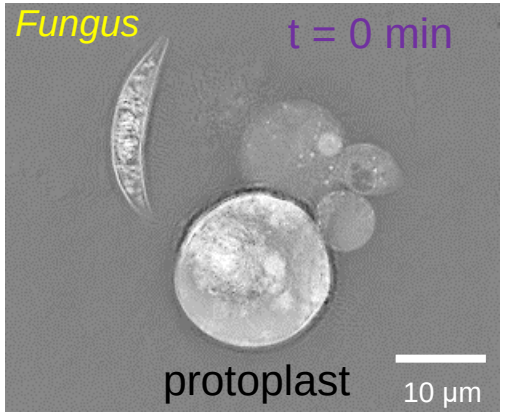
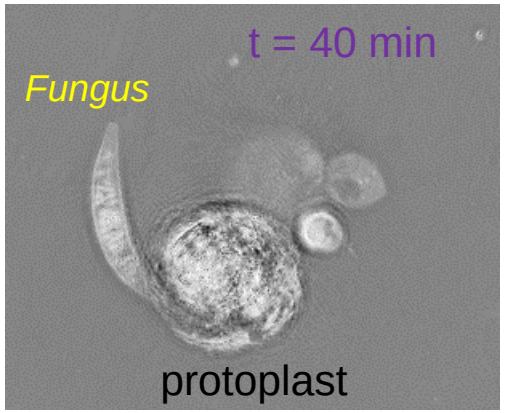
Exploratory Study: Sorghum-pathogen interactions



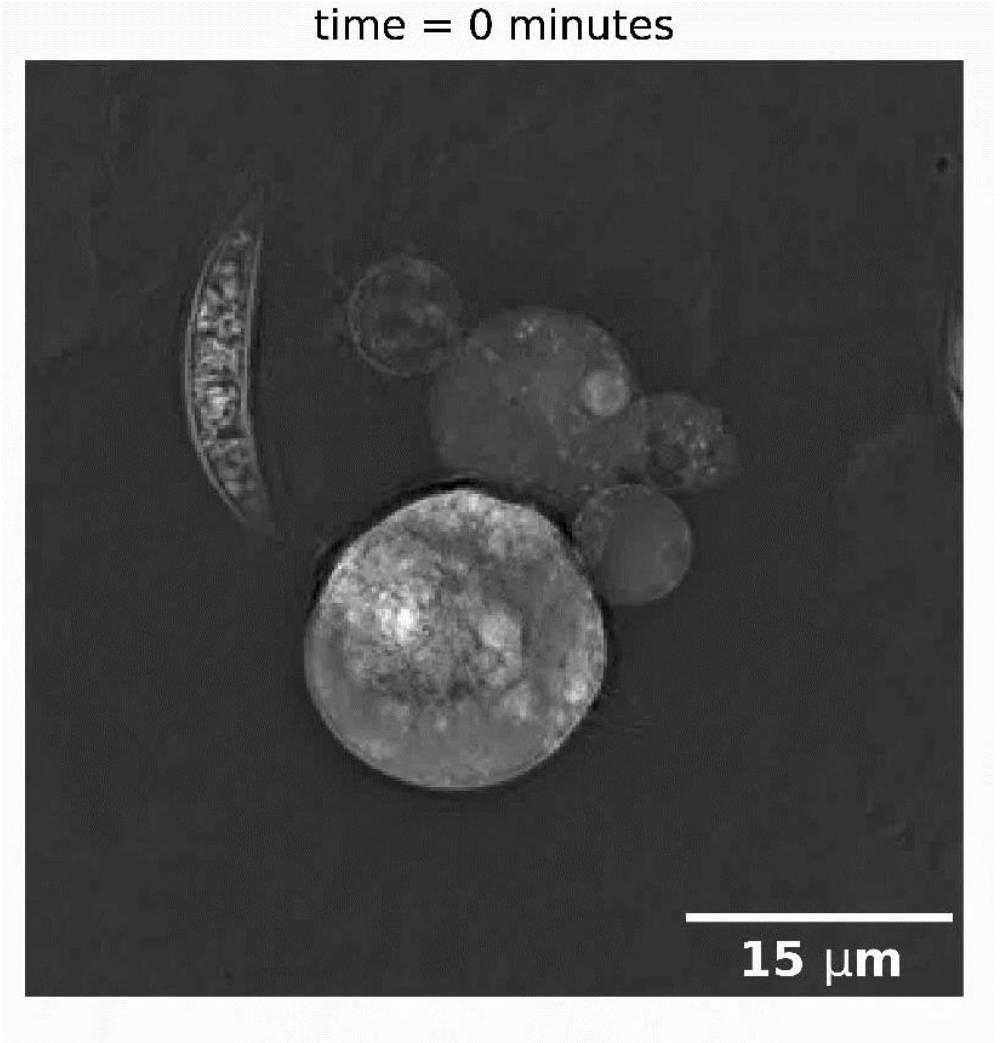
Infected sorghum leave



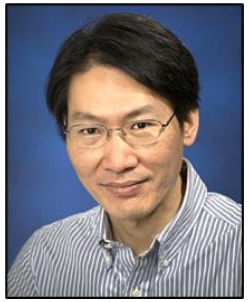
Uninfected



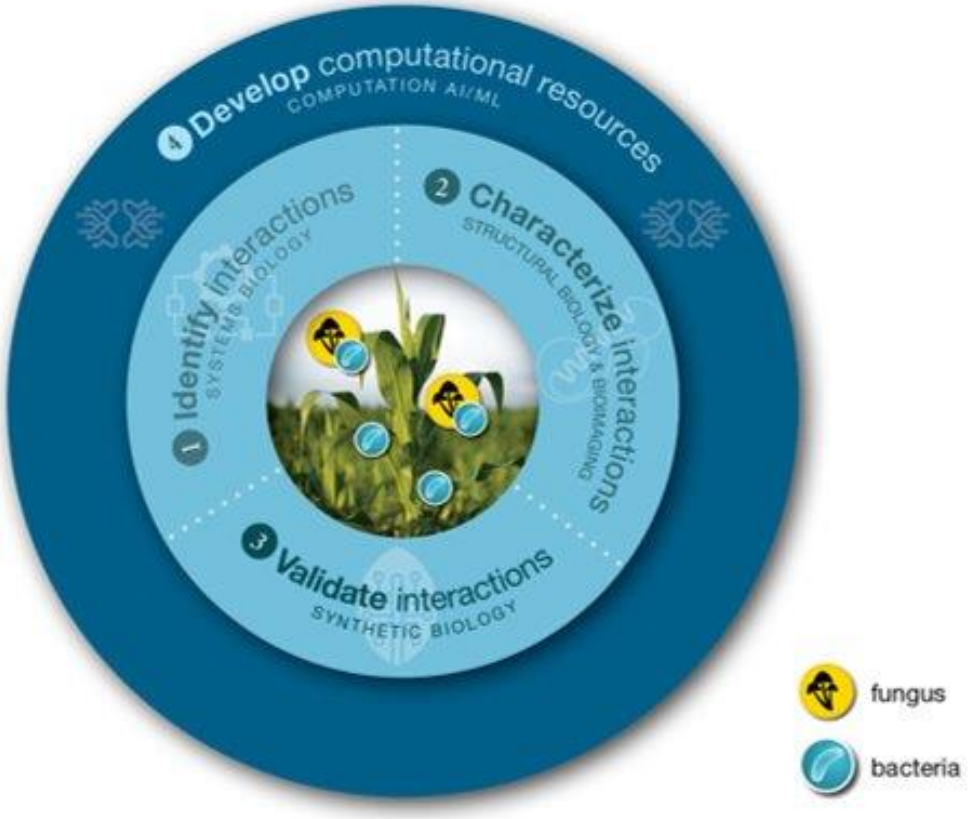
Infected



FY23: Exploratory Study Converted into BNL-led Project



Qun Liu



BREAD (Bioenergy Resilience and Evolution Dynamics)- Unlocking the Molecular Basis of Plant-pathogen Interactions to Create Resilient Bioenergy Crops

$9.8 M, three-year project, expanding exploratory study, involving partners.

Pacific Northwest NATIONAL LABORATORY

BERKELEY LAB

Argonne NATIONAL LABORATORY

UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN

UNIVERSITY OF NORTH CAROLINA CHAPEL HILL

TEXAS A&M UNIVERSITY 1876

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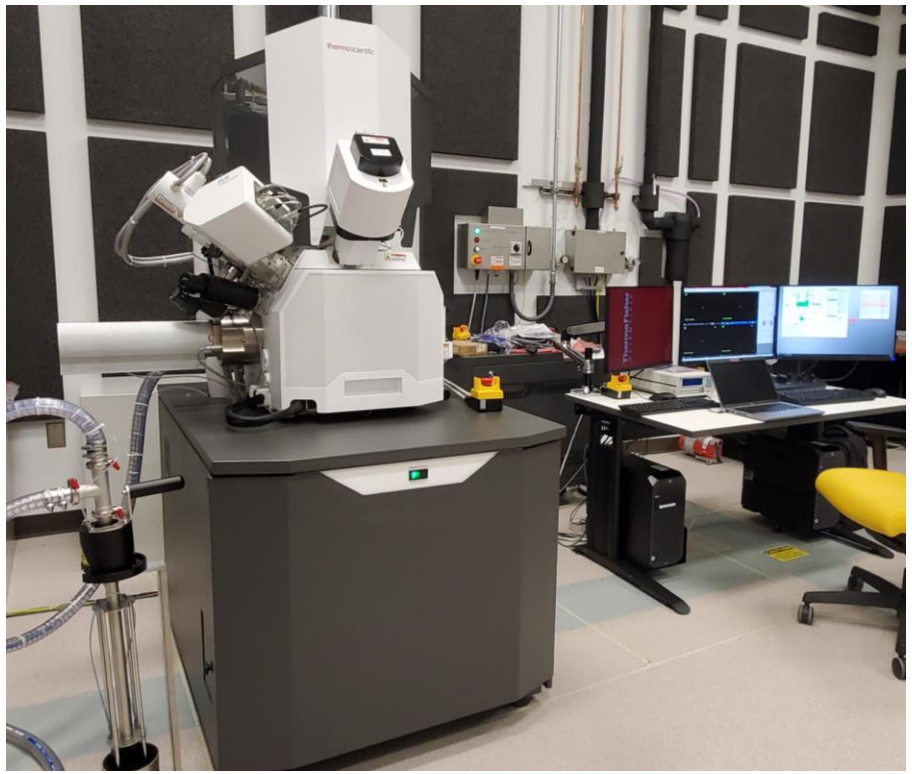
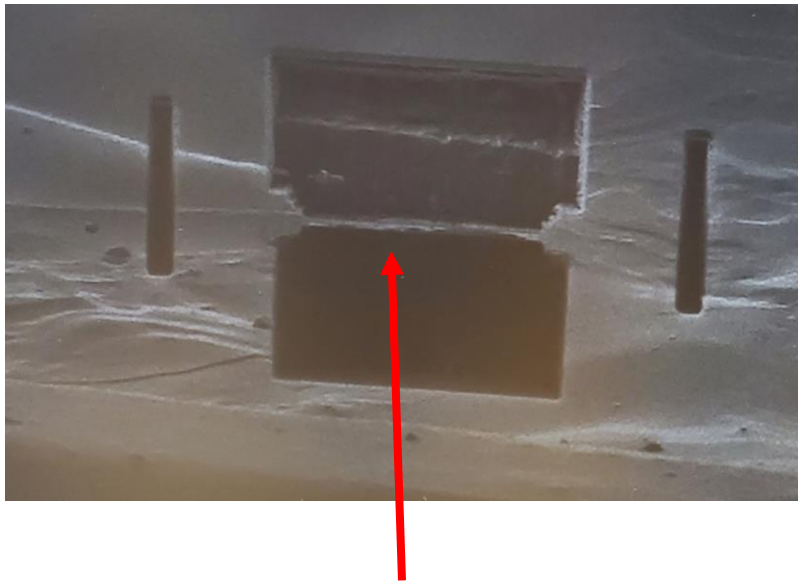
New Cryo-FIB-SEM to study cells in context of tissue installed. Science commissioning in progress



Aquilos 2 cryo-focused-ion-beam SEM

First SEM image of *C. sublineola* *Fungus*



~200 nm sorghum lamella (first). This thin lamella is ready for imaging using Cryo-EM.

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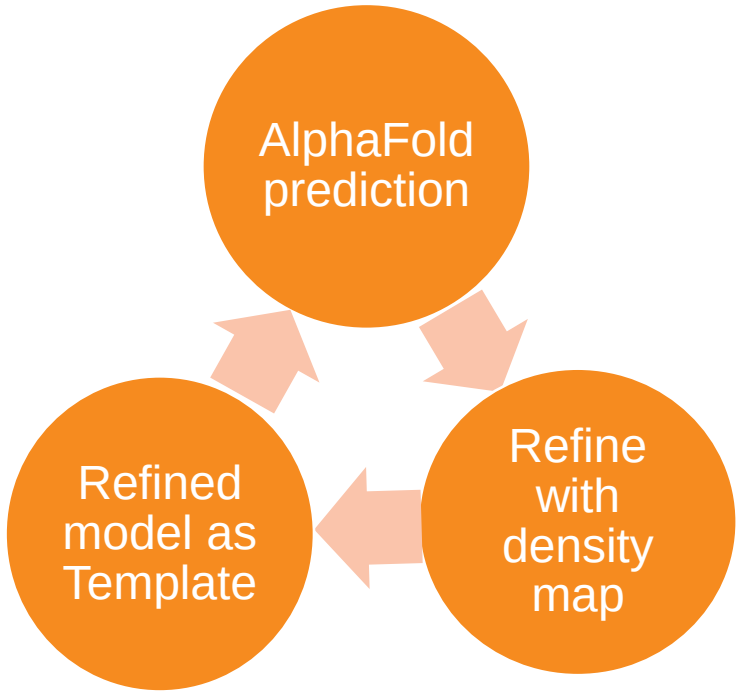
SciServer: Flexible and Scalable Computing Platform Enabling Users to Collaborate Efficiently

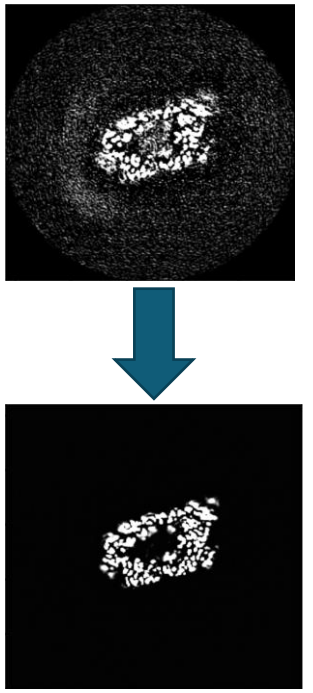
Example: Cryo-EM Feature EnhanceMent (CryoFEM)

AlphaFold is a powerful protein structure prediction tool on its own. By combining it with cryo-EM data and deep learning approaches we can accelerate and improve the interpretation of cryo-EM maps.

The impact is that this novel integration of these three components advances our ability to extract protein structures from cryo-EM maps.

This capability is now available to users on SciServer as a seamlessly integrated package. Ultimate goal is to automate the entire process.



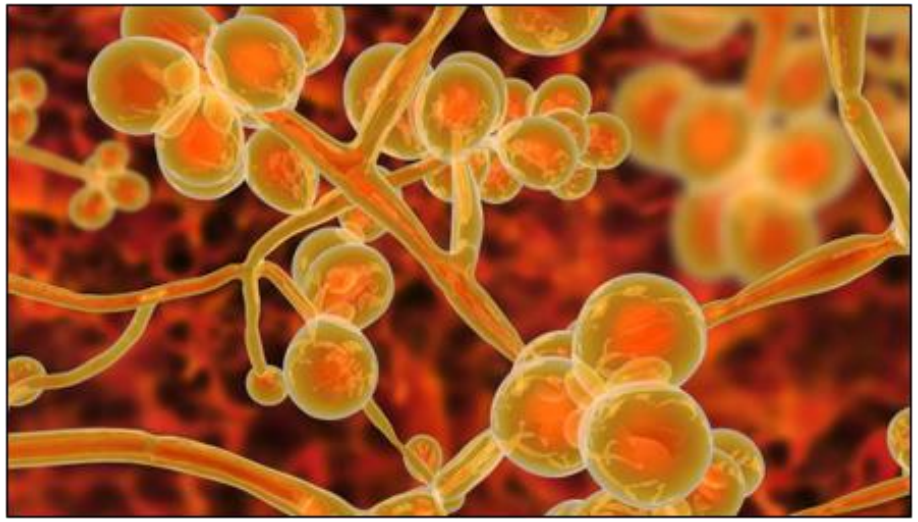


Map enhancement

Dai, X., Wu, L., Yoo, S. & Liu, Q. Integrating AlphaFold and deep learning for atomistic interpretation of cryo-EM maps. *Briefings In Bioinformatics* 2023. DOI: 10.1093/bib/bbad405

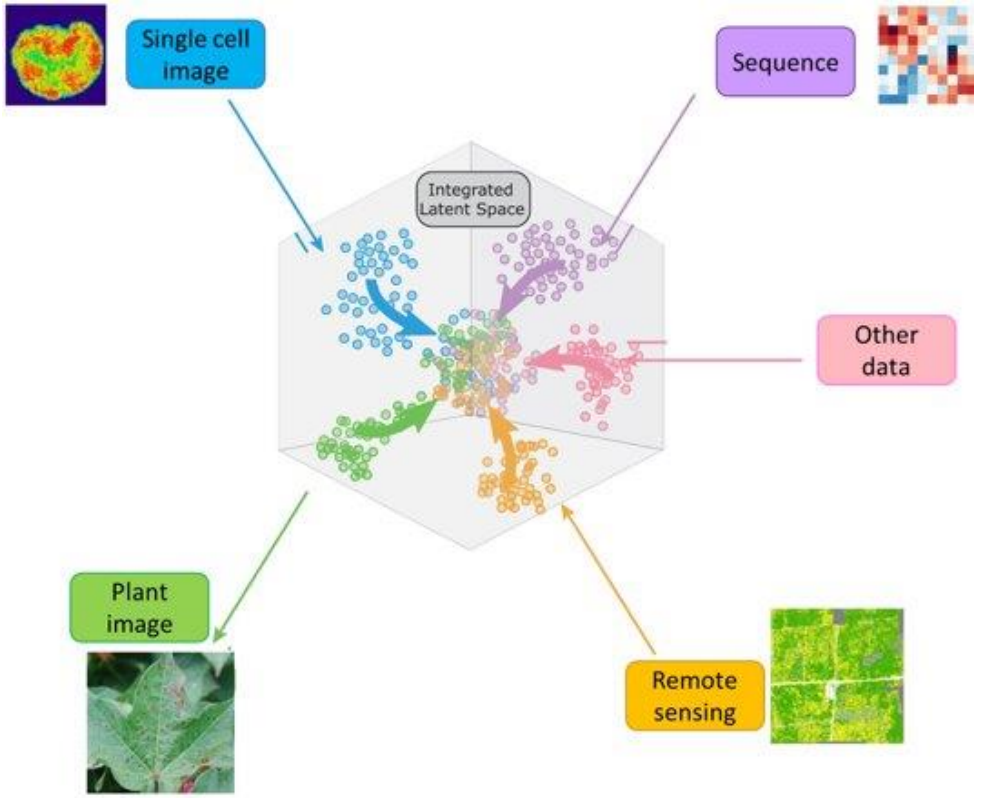
Relevant Internal Investments

FY24 LDRD: Biosecurity Research Environment for Invasive Fungal Diseases, Qun Liu (BNL) & (SBU collaborators)



Identification of critical early stages of infection common to fungal pathogens of animals and plants

FY24 LDRD: New computational platform for plant disease detection, surveillance, and prediction Xu and Lin (CSI)



Two new hires with expertise in plant pathology/genomics from different world-leading labs led by HHMI-supported NAS members

Nak Hyun Kim, Ph.D.
PD with Prof. Jeff Dangl Lab.,
University of North Carolina

Research Interests: Activation mechanism of plant nucleotide-binding and leucine-rich repeat (NLR, resistance) proteins.

Raul Zavaliev, Ph.D.
PD with Prof. Xinnian Dong Lab.
Duke University

Research Interests: Salicylic acid and NPR1-mediated plant immune responses to a broad-spectrum of pathogens.

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Both have complementary research interests, Dr. Kim in mechanisms of specific immunity and Dr. Zavaliev in mechanisms of broad immunity to diverse pathogens.

Longer-term Outlook

Establish Biopreparedness as a new enduring multi-disciplinary portfolio at BNL, leveraging expertise, facilities, and partners

Build out footprint into other areas where we have strengths (e.g. materials research)

Build the capability to conduct research in plant disease and Biosafety Level-2 research at LBMS, NSLS-II, and in Biology in support of broader Biopreparedness research community

Renovate Biology building to support growing program with specific needs

bioenergy
biopreparedness
research
science
cryo-em
roadmap
disease
bnl
new
program
facilities
first
biological
cryo-fib-sem
fy22
exploratory
capabilities
learning
acquisition
prediction
study
usda
project
develop
support
community
sciserver
cells
maps
input
understanding
investments
capability
models
doe
univ
infrastructure
protein
center
plant
crops
led
platform
distributed
partners
biology
fungus
decision-making
needed
collaborate
impact
understand
lab
across
robust
computational
optimal
director
objectives
tissue
alphafold
leveraging
bioassurance
direction
basis