# Biomanufacturing and the Circular Bioeconomy: NSF Investments and Opportunities


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# Bold Goals for U.S. Biotechnology and Biomanufacturing (OSTP report)

( https://www.energy.gov/eere/bioenergy/articles/white-house-unveils-new-goals-advance-biotechnology-biomanufacturing)

*Biotechnology and Biomanufacturing R&D to Further Cross-Cutting Advances*

Six themes:

- Leverage Biodiversity Across the Tree of Life to Power the Bioeconomy
- Enhance Predictive Modeling and Engineering Design of Biological Systems
- Expand Capabilities to Build and Measure Performance and Quality of Biological Systems
- Advance Scale-Up and Control of Biological Systems
- Innovate Biomanufacturing Approaches
- Enable Ethical, Safe, and Equitable Co-Generation and Translation of Biotechnology Products

# Theme 1: Leverage Biodiversity Across the Tree of Life to Power the Bioeconomy

Enhance discovery of novel function from diverse organisms across the tree of life:

- Develop a national strategy for selecting organisms to sequence so that comparative analyses are likely to reveal functional variation that can be used for biological design
- Accelerate development of computational and experimental tools to enhance comparative discovery of sequence and functional elements (e.g., regulatory networks, metabolic pathways, and traits) that define genotype-to-phenotype relationships

Put biodiversity to use in new biotechnology applications:

- Use outcomes of functional discovery to expand the number of organisms that can be used as hosts (chassis) in engineered biological systems.
- Combine innovations from chemistry and materials science with outcomes of sequencing and functional analyses to expand the repository of “parts” for so-called “plug-and-play” design-build capabilities that incorporate biotic-abiotic interfaces as control elements.
- Create innovation laboratories to leverage learnings from biodiversity studies for bioinspired design of new materials, devices, and products for the bioeconomy.

# Theme 2. Enhance Predictive Modeling and Engineering Design of Biological Systems

Advance prediction at biomolecular, cellular, organismal, and ecosystem levels:

- Expand the ability to predict the often weak or transient biomolecular interactions that control important functions of small biomolecules and enzymes
- Leverage advances in signal processing and information theory to predict modes of communication among cells, organisms, and communities
- Combine mathematical and computational modeling with knowledge of key steps in development to inform design of artificial tissues and organs
- Explore the limits of biological design via both top-down (i.e., breaking down a complex system into component parts) and bottom-up (i.e., piecing together simple parts to make a more complex system) approaches to build cell-free systems, synthetic cells, minimal cell, or organism systems.

# Theme 3. Expand Capabilities to Build and Measure Performance and Quality of Biological Systems

- Expand biomaterial design by developing and deploying multi-faceted capabilities, including non-natural biopolymers and their building blocks
- Develop novel modalities for precise assembly of cells into organs, organisms, or ecosystems
- Develop platforms and tools for rapid, multimodal measurement of complex signals from cellular and multicellular systems
- Build a national network of biofoundries to enable democratized access to facilities, both virtual and physical, for modern biotechnology associated with design-build-test-learn cycles in cell-free, cellular, organoid, and whole-organism systems.

# Theme 4. Advance Scale-Up and Control of Biological Systems

- Develop the ability to predict performance and behavior (including evolution) of cells, organisms, systems of organisms, and the molecules they use and produce in complex production and processing environments.
- Advance theory-driven and AI-enabled multiscale modeling using data from biofoundries to couple models of biological system performance with models of bioprocess performance.
- Improve bioproduct supply chain resiliency by advancing process design methods to transition from (semi)-batch to continuous and intensified processes, including through the use of modular, geographically distributed, and potentially reconfigurable processes or facilities.
- Leverage existing Manufacturing USA institutes and other public and private infrastructure to support model validation via prototypes and scaled-up or scaled-down systems.
- Advance the capacity to develop process control strategies that include control at the cellular level (e.g., embedded sensors/actuators within cells, and at the whole-system level.

# Theme 5. Innovate Biomanufacturing Approaches

- Advance capabilities in nanomanufacturing that leverage biobased nanomachines and designs.
- Develop engineered biological and biomanufacturing systems to produce biopolymers and process them *in situ* and at scale
- Advance capabilities for bioprinting cell scaffolds, bone or cartilage replacements, and multi-material structures to mimic or replace living tissues.

# Theme 6: Enable Ethical, Safe, and Equitable Co-Generation and Translation of Biotechnology Products

- Develop new research opportunities within the social sciences with a focus on biotechnology and biomanufacturing.
- Invest in programs and efforts that incorporate social scientists within research teams working in fields related to biotechnology and biomanufacturing.
- Conduct research on ethical issues related to biotechnology and biomanufacturing to develop new understanding of how ethical concerns can inform public policies around biotechnology and biomanufacturing.
- Develop the capability to assess the health and environmental risks of products and processes of the bioeconomy.
- Expand investments in research to enable science-based regulation of products and processes.
- Develop educational and training pathways to broaden participation of underrepresented groups to ensure diverse perspectives are included in future biotechnology and biomanufacturing R&D.
- Expand investments in accessibility to enable all individuals to participate in the bioeconomy and benefit from biotechnology and the bioeconomy regardless of disability

# NSF Investments in BioManufacturing

### Foundational Research

- Computational and ML approaches to design, delivery
- Novel and improved processes for cell-based and cell-free biomanufacturing
- Emerging technologies, approaches, and monitoring methods manufacturing

### Translation to Practice

- Engineering Research Centers
- Industry-University Cooperative Research Centers
- Lab-to-Market Platform
- Industry and government partnerships

### Future Workforce

- Diversity, inclusion, equity and access
- K-12, community college, undergraduate, and graduate education
- Experiential learning and professional development

# NSF supports R&D activities in Biomanufacturing using several mechanisms

## Core Programs

### Division of Chemical, Bioengineering, Environmental and Transport Systems (CBET)

- Cellular and Biochemical Engineering (CBE)
- Engineering of Biomedical Systems (EBMS)
- Biosensing
- Particulate and Multiphase Processes (PMP)

### Division of Civil, Mechanical, and Manufacturing Innovation (CMMI)

- Advanced Manufacturing (AM)
- Biomechanics and Mechanobiology (BMMB)

### Division of Electrical, Communications, and Cyber Systems (ECCS)

- Communications, Circuits, and Sensing-Systems (CCSS)

### Division of Engineering Education and Centers (EEC)

- Industry-University Cooperative Research Centers (IUCRCs)
- Engineering Research Centers (ERCs)

### Division of Molecular and Cellular Biosciences

- Systems and Synthetic Biology

### Directorate for Technology, Innovation, and Partnerships

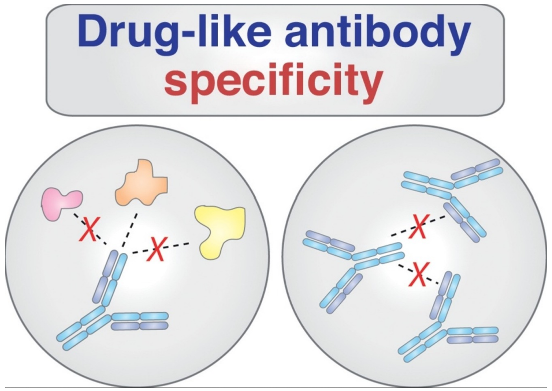
- Partnerships for Innovation

# NSF supports R&D activities in Biomanufacturing using several mechanisms

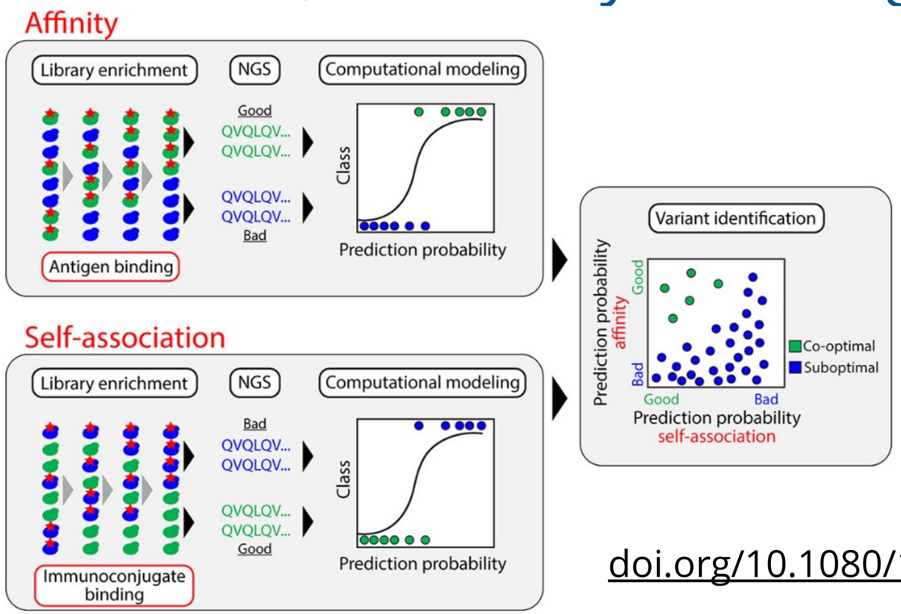
Solicitations and Dear Colleague Letters

- GOALI: Grant Opportunities for Academic Liaison with Industry
- Future Manufacturing (FM)
- Agile BioFoundry (NSF-DOE/ABF collaboration)
- Bioinspired Design (DCL and Convergence Accelerator)
- Computational and Data-Enabled Science and Engineering (CDS&E)
- Regional Innovation Engines (RIE)

# CBET 1813963: *GOALI: Methods for designing antibodies specific for intrinsically disordered proteins*; Peter Tessier, University of Michigan - Ann Arbor




doi.org/10.1016/j.copbio.2019.01.008




Using yeast-display and machine learning to rapidly identify antibody candidates with high affinity and low self-association

doi.org/10.1080/19420862.2022.2146629

- Conjugated quantum dots to IgGs that strongly self-associate ( lenzilumab and bococizumab)
- Enrich yeast-displayed bococizumab sub-libraries for variants with low levels of immunoconjugate binding
- Identified rare variants with co-optimized levels of low self-association and high affinity.
- Most high-affinity variants possess positively charged variable domains and most low self-association variants possess negatively charged variable domains.
- Moreover, negatively charged mutations in the heavy chain CDR2 of bococizumab, adjacent to its paratope, were effective at reducing self-association without reducing affinity.

GOALI: https://www.nsf.gov/eng/eec/goali.jsp

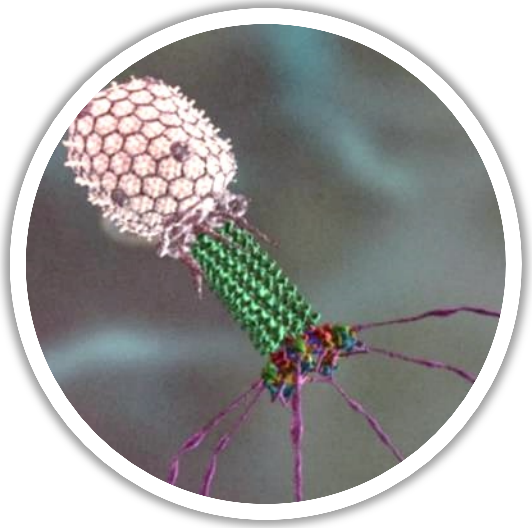
*Proposals may include the participation of a "third partner" such as a National Laboratory or a non-profit organization.*

# Future Manufacturing: Research Grants

https://www.nsf.gov/pubs/2023/nsf23550/nsf23550.htm

*$100 million NSF investment over 3 years*

**Genetically-targeted chemical assembly (GTCA) of functional structures in living cells, tissues, and animals**, led by Stanford University



**Enabling cell-free engineering and biomanufacturing of bacteriophages as a universal platform for tailorable bioactive materials**, led by University of Minnesota

**Distributed methane conversion into value chemicals via synthetic microbial consortia**, led by University of Arizona

*Center image credit: Purdue University and Seyet LLC.*

# EEC 2100800: *IUCRC Phase II+: Johns Hopkins University: Advanced Mammalian Biomanufacturing Innovation Center (AMBIC)*; Michael Betenbaugh, JHU

| | | | | |
|---|---|---|---|---|
| Johns Hopkins University | UMass Lowell University of Massachusetts Lowell | Clemson University | University of Delaware | University of Maryland 1856 |

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The mission of AMBIC is to develop enabling technologies, knowledge, design tools and methods that apply and integrate high-throughput and genome-based technologies to fast-track advanced biomanufacturing processes. AMBIC is dedicated to mammalian cell culture upstream development focusing on Chinese hamster ovary (CHO) cells.

AMBIC brings together leading academic and industrial biotechnologists focused on mammalian cell culture manufacturing at a pre-competitive research level to address the complex problems in biopharmaceutical manufacturing

https://www.ambic.org

IUCRC: https://iucrc.nsf.gov

NSF

# EEC 1648035: *NSF Engineering Research Center for Cell Manufacturing Technologies (CMaT)*; Krishnendu Roy, Georgia Tech

## Vision

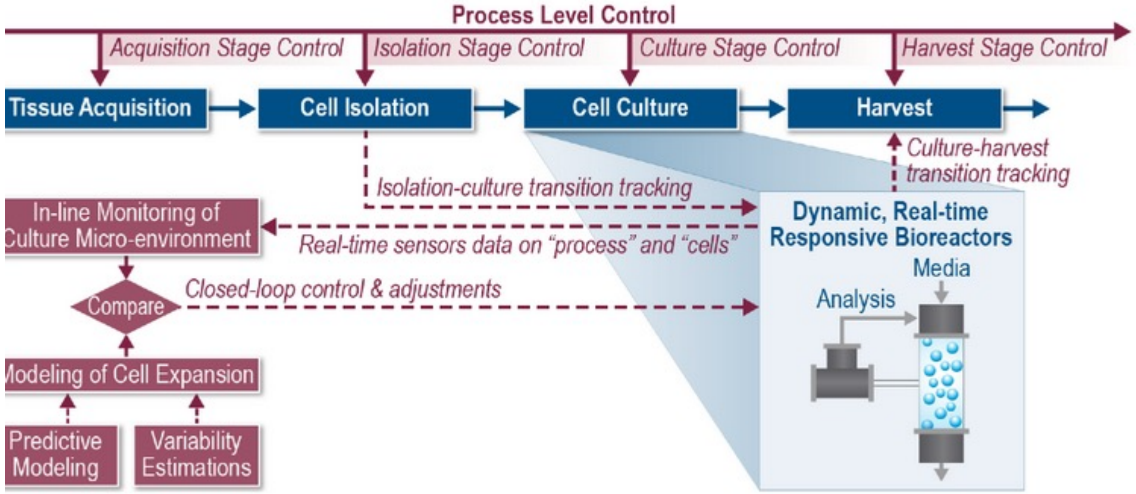
- Transform the manufacture of cell-based therapeutics into a large-scale, lower-cost, reproducible, and high-quality engineered process

## Strategy

- Comprehensive cell and process characterization, big data analytics, & predictive computational modeling
- Technology development for monitoring and assessing potency and safety during manufacturing
- Systems optimization and process improvement
- Integrate real-time monitoring into scalable, quality-controlled manufacturing processes

## Systems Optimization for Scalable Manufacturing

- developing systems that utilize data from real-time sensors to improve potency and reduce variability
- generating robust supply chain and process modeling algorithms to ensure product reproducibility and cost-effectiveness.




CMaT: https://cellmanufacturingusa.org/
ERC: https://www.nsf.gov/pubs/2022/nsf22580/nsf22580.htm

# Accelerating Innovations in Biomanufacturing Approaches through Collaboration Between NSF and the DOE BETO funded Agile BioFoundry (NSF-DOE/ABF Collaboration)

**PROGRAM SOLICITATION**
**NSF 22-549**

**National Science Foundation**

Directorate for Biological Sciences
Division of Molecular and Cellular Biosciences

Directorate for Engineering
Division of Chemical, Bioengineering, Environmental and Transport Systems

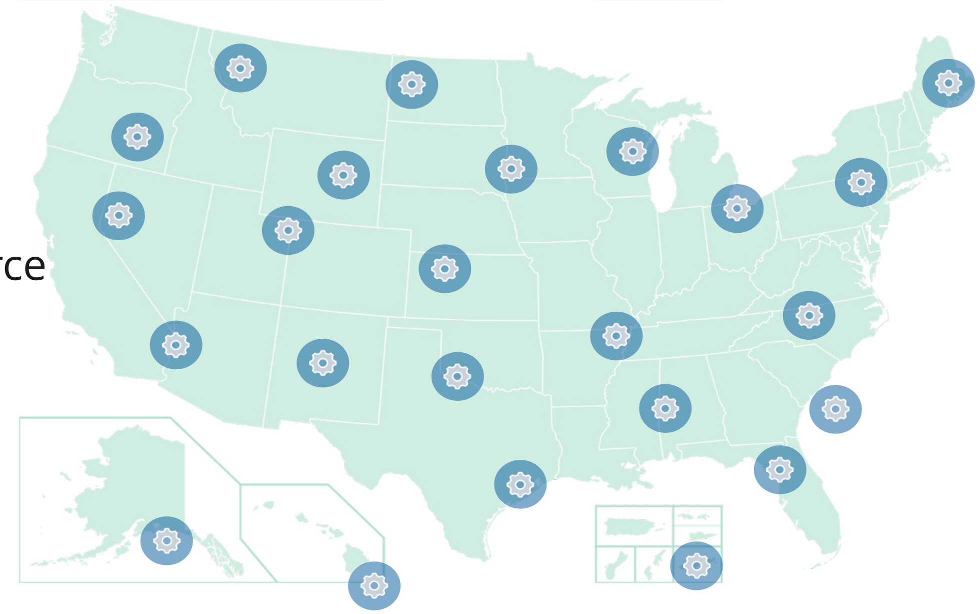
U.S. Dept. of Energy

Argonne National Laboratory
Berkeley Lab — Bringing Science Solutions to the World
Los Alamos National Laboratory — Est. 1943
NREL — National Renewable Energy Laboratory
Oak Ridge National Laboratory
Pacific Northwest National Laboratory
Sandia National Laboratories

- Proposals must
  - leverage the unique DBTL capabilities available at the ABF
  - translate the latest advances in synthetic biology and engineering biology basic research into testable prototype processes and products
  - submit evidence of a positive outcome of the **required feasibility review** by ABF
- NSF support is for all activity at the institution of higher education or non-profit organization that readies the project for translation to practice.
- DOE BETO supports the costs for implementation of projects at ABF through the Agile BioFoundry Cooperative Research and Development Agreement (CRADA).
- NSF will coordinate and manage the review of proposals jointly with DOE BETO through a joint panel review process.

# NSF Regional Innovation Engines

The Regional Innovation Engines, or NSF Engines, program supports the development of diverse, regional coalitions to engage in use-inspired research, drive research results to the market and society, promote workforce development, and ultimately stimulate the economy and create new jobs.



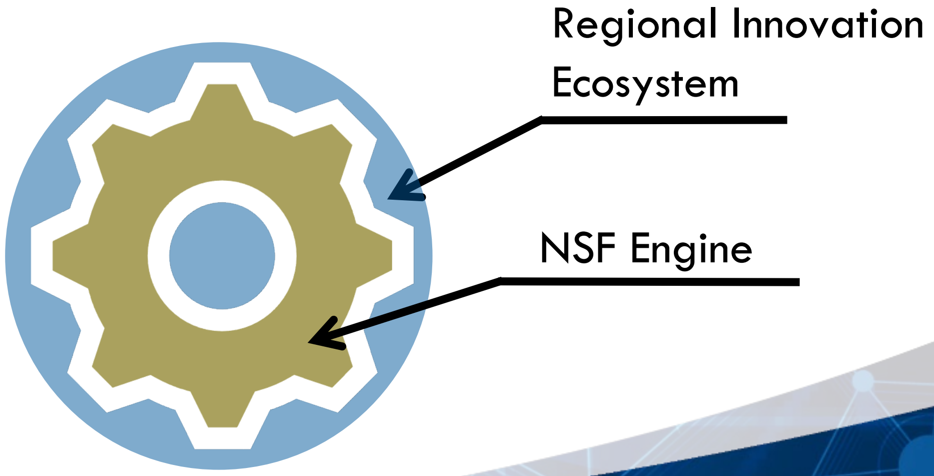
NSF Engines are funded up to $160M for up to 10 years

Teams not ready to launch an NSF Engine, can apply for up to $1M for up to 2 years to plan for an Engine

## What is an NSF Engine?

A multi-sector coalition of regional partners working together to catalyze a regional innovation ecosystem in a topic area of regional relevance and national and societal significance.

Engines are led by CEOs and includes partners from industry, institutions of higher education, government, and non-profit and community organizations.



# Pathways to Enable Open-Source Ecosystems (POSE)

Harnesses the power of open-source development for the creation of new technology solutions to challenges of national, societal, and economic importance

Outcomes:

- Ensure more secure open-source products
- Increased coordination of developer contributions
- A more focused route to impactful technologies

**Phase I** – 1 year

Enables scoping activities to inform the development of the open-source ecosystems and lead to a well-developed and sustainable plan.

Up to $300,000

**Phase II** – 2 years

Supports transition of an open-source research product into a sustainable open-source ecosystems.

Up to **$1.5M**

# More Details on TIP Programs

| Program | Link | Description |
|---|---|---|
| I-Corps | https://beta.nsf.gov/funding/initiatives/i-corps | Immersive, entrepreneurial training program that facilitates the transformation of invention to impact and prepares scientists and engineers to extend their focus beyond the university laboratory. |
| PFI | https://beta.nsf.gov/funding/initiatives/pfi | Assists researchers and innovators from academia, nonprofit and public organizations in accelerating the development of breakthrough technologies and speeding solutions forward. |
| SBIR/STTR | https://seedfund.nsf.gov/ | Seed funding for small business with highly innovative technologies with the potential for significant commercial and societal impact. |
| POSE* | https://beta.nsf.gov/funding/opportunities/pathways-enable-open-source-ecosystems-pose | Aims to harness the power of open-source development for the creation of new technology solutions to problems of national and societal importance. |
| RIE (NSF Engines)* | https://beta.nsf.gov/funding/initiatives/regional-innovation-engines | Catalyzes and fosters innovation ecosystems across the U.S. to advance critical technologies, address national and societal challenges, foster partnerships across industry, academia, government, nonprofits, civil society, and communities of practice, promote and stimulate economic growth and job creation, and spur regional innovation and talent |

* New program