Discussion with VCAT on CETs: Biotechnology and Biomanufacturing

Dr. Christopher Szakal
Acting Director
NIST Program Coordination Office

Dr. Sheng Lin-Gibson
Chief
NIST Biosystems and Biomaterials Division

Dr. Michael Tarlov
Chief
NIST Biomolecular Measurement Division

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
U.S. DEPARTMENT OF COMMERCE

June 10, 2025

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
U.S. DEPARTMENT OF COMMERCE

Biotechnology and Biomanufacturing Update and Alignment with Administration Priorities

Recent External Drivers to Promoting/Protecting Bioeconomy

Recognition that **biotechnology** and **biomanufacturing** provide solutions to pressing needs in manufacturing and technology development across multiple sectors while converging with AI and other fields

Biotechnology*: technology that applies to and/or is enabled by life sciences innovation or product development

Biomanufacturing*: the use of biological systems to produce goods and services at commercial scale

*https://www.nist.gov/bioscience/nist-bioeconomy-lexicon

NSCEB Final Report Release

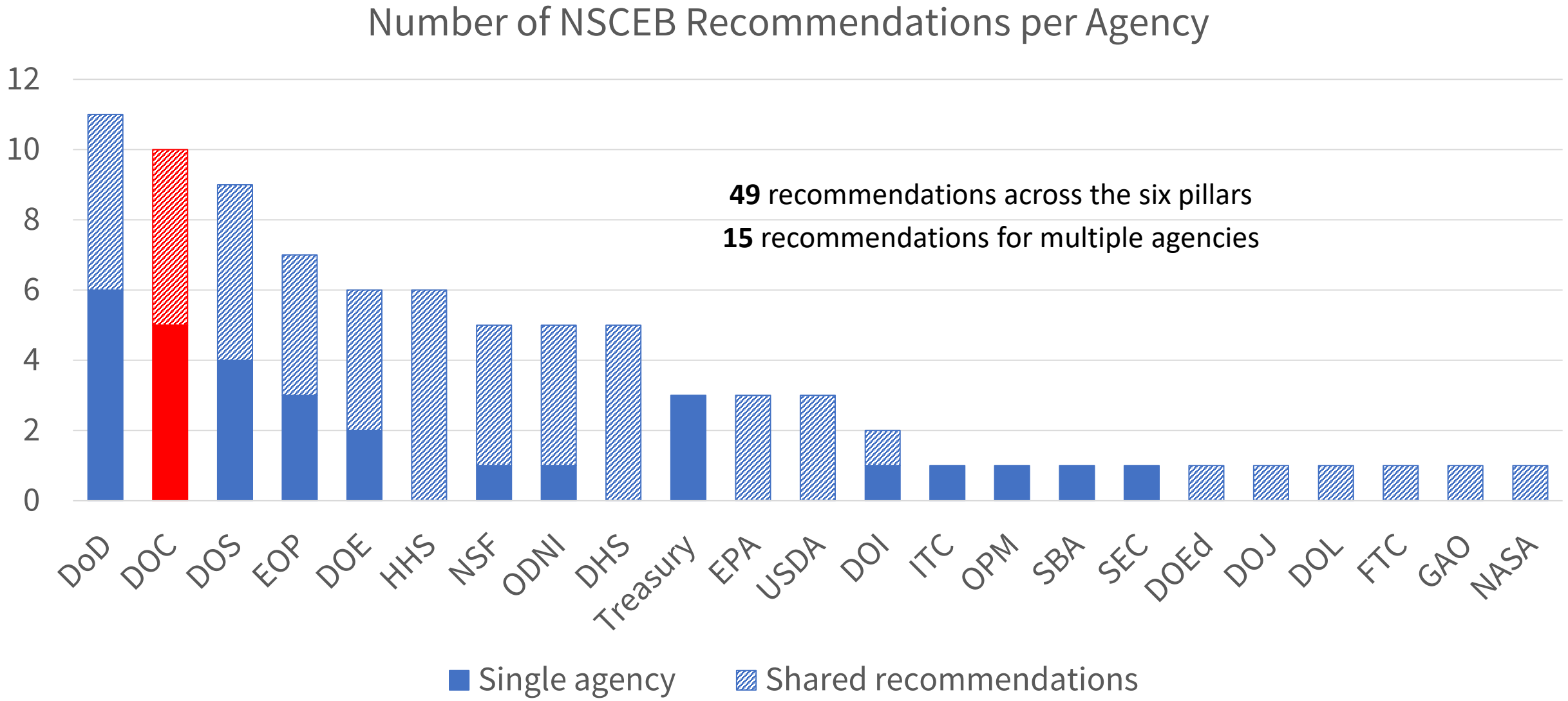
In April 2025, the Commission submitted its comprehensive report to Congress, including policy recommendations responding to the Commission's mandate.

The recommendations fall under six pillars:

1. Prioritize Biotechnology at the National Level
2. Mobilize the Private Sector to Get U.S. Products to Scale
3. Maximize the Benefits of Biotechnology for Defense
4. Out-Innovate Our Strategic Competitors
5. Build the Biotechnology Workforce of the Future
6. Mobilize the Collective Strengths of Our Allies and Partners

https://www.biotech.senate.gov/

NSCEB Recommendations

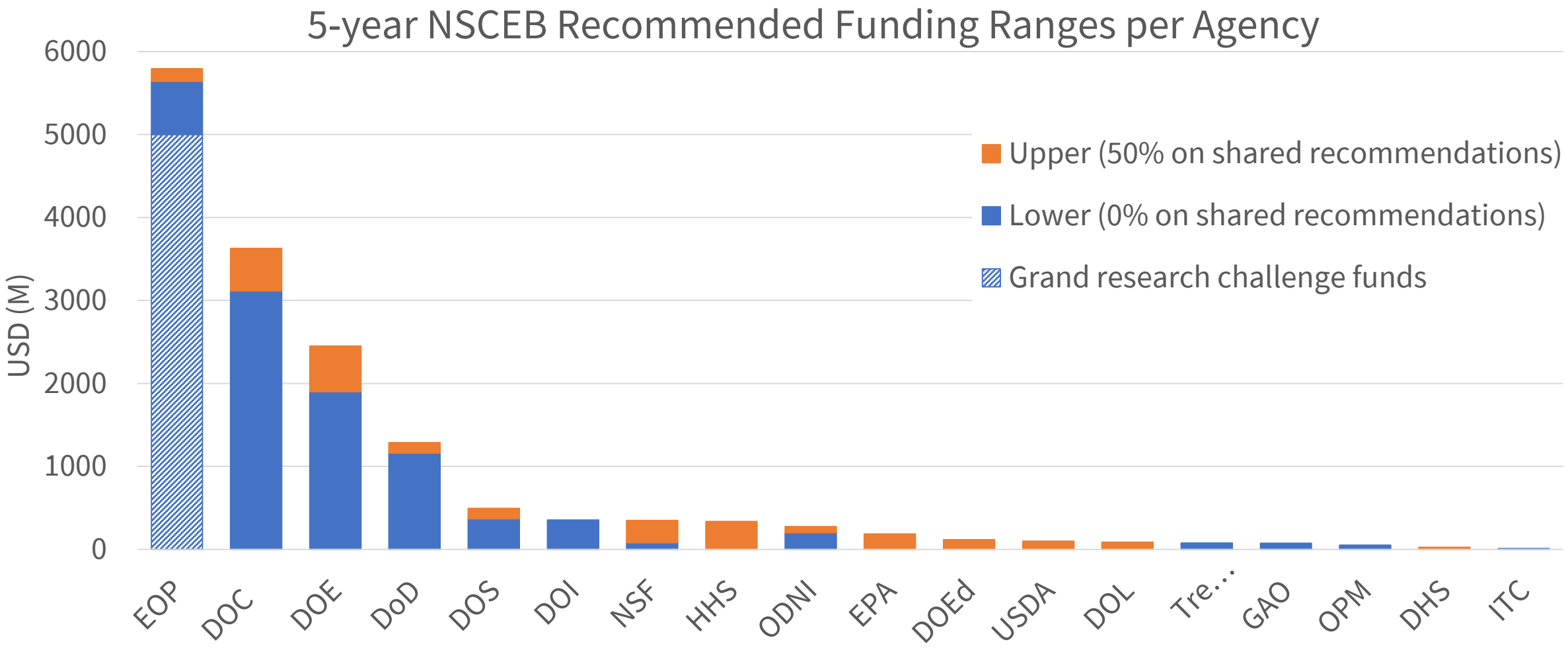


Recommendations for DOC

Chapter	Pillar	Recommendation Agency
1	Prioritize Biotechnology at the National Level	All
1.2a*	Congress should direct each relevant agency to designate a senior official to lead biotechnology policy	EOP, USDA, DOC, DoD, DOE, HHS, DHS, DOI, DOS, EPA, NASA, NSF, ODNI
2	Mobilize the Private Sector to Get U.S. Products to Scale	
2.2a	Congress must establish and fund an Independence Investment Fund, led by a non-governmental manager, that would invest in technology startups that strengthen U.S. national and economic security	DOC
2.3a	Congress must authorize and fund DOE and DOC to develop a network of manufacturing facilities across the country for precommercial bioindustrial product scale-up	DOE, DOC
2.3b	Congress should direct DOC to create a public-private biopharmaceutical manufacturing center of excellence focused on developing and scaling new ways to make medicines	DOC
3	Maximize the Benefits of Biotechnology for Defense	
3.3b*	Congress should direct the DOC to consider country-wide export controls blocking the sale of specific, highly sophisticated U.S. biotechnology items to China that would pose a substantial risk to national security if used for military end-uses	DOC
4	Out-Innovate Our Strategic Competitors	
4.1b	**Congress should authorize NIST to create standards that researchers must meet to ensure that U.S. biological data is ready for use in AI models**	DOC
4.4a	Congress must direct the Executive Branch to advance safe, secure, and responsible biotechnology research and innovation	DOC
5	Build the Biotechnology Workforce of the Future	
5.2a	Congress must maximize the impact of biomanufacturing workforce training programs	EOP, DOC, DOL
6	Mobilize the Collective Strengths of Our Allies and Partners	
6.2a	**Congress should direct DOS, along with NIST, to support the development of international norms and standards, including defining shared values and interests in biotechnology**	DOS, DOC
6.2b*	Congress should require DOS to create a strategy for harmonizing multilateral export controls	DOS, DOC

*No associated recommended funding

NSCEB Funding Recommendations



Total recommended USG 5-year funding: ~$**15B**

DOC-recommended funding: ~$**3.1B to ~$3.6B** (depending on distribution of shared recommendations)

NSCEB Recommendations for NIST Funding

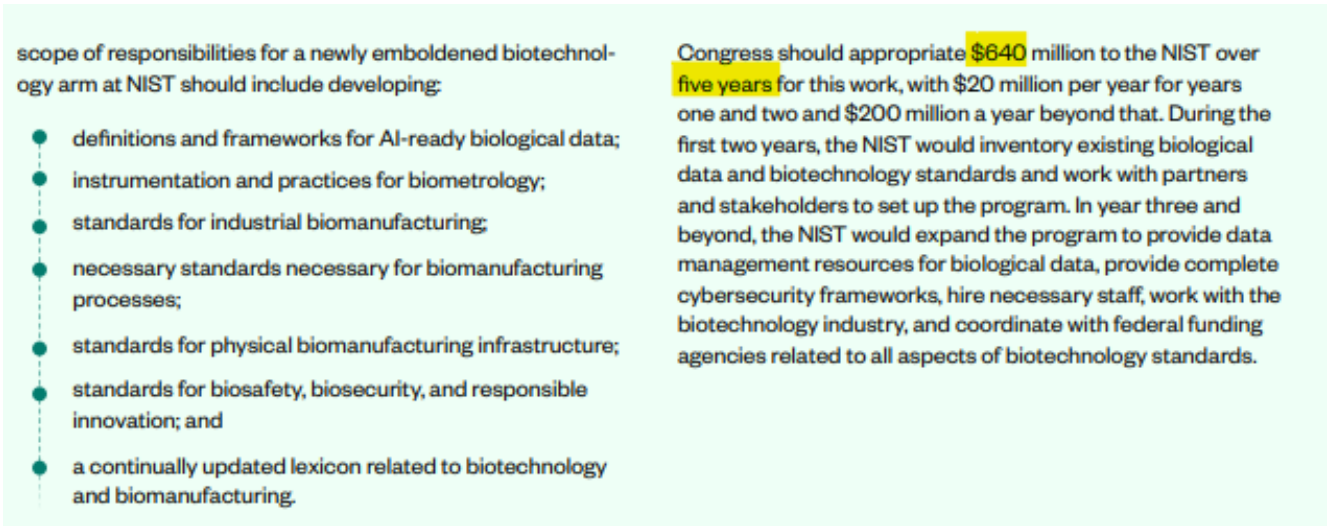
Congress should authorize the National Institute of Standards and Technology (NIST) to create standards that researchers must meet to ensure that U.S. biological data is ready for use in AI models.

Authorize a Hub for Biotechnology, Biometrology, and Biological Data Standards

Congress should authorize the National Institute of Standards and Technology (NIST) as a hub for biotechnology, biometrology, and biological data standards.

Every aspect of biotechnology, from data to biomanufacturing processes to safety and security, needs standards that are agreed upon by stakeholders from the private sector and academia. Establishing a suite of standards and frameworks for biotechnology development will establish one common 'language' for the biotechnology industry. Standards would improve research, manufacturing, product adoption, and collaboration along the product development pipeline. The development of such standards will give industry the opportunity to work closely with government to ensure the needs of different companies are heard and incorporated in the development of standards.

To accomplish this, and ensure a stable path forward for biotechnology, Congress should authorize the NIST to serve as a hub for biotechnology and biological data standards. The



scope of responsibilities for a newly emboldened biotechnology arm at NIST should include developing:

- definitions and frameworks for AI-ready biological data;
- instrumentation and practices for biometrology;
- standards for industrial biomanufacturing;
- necessary standards necessary for biomanufacturing processes;
- standards for physical biomanufacturing infrastructure;
- standards for biosafety, biosecurity, and responsible innovation; and
- a continually updated lexicon related to biotechnology and biomanufacturing.

Congress should appropriate $640 million to the NIST over five years for this work, with $20 million per year for years one and two and $200 million a year beyond that. During the first two years, the NIST would inventory existing biological data and biotechnology standards and work with partners and stakeholders to set up the program. In year three and beyond, the NIST would expand the program to provide data management resources for biological data, provide complete cybersecurity frameworks, hire necessary staff, work with the biotechnology industry, and coordinate with federal funding agencies related to all aspects of biotechnology standards.

Recommendation 4.1b

Detailed in Appendix C

Recommended NIST funding **$640M**

Years 1 and 2:	$20M per year
Years 3 through 5:	$200M per year

https://www.biotech.senate.gov/

Alignment with Administration Priorities

*"How can the United States secure its position as the unrivaled world leader in **critical and emerging technologies** — such as artificial intelligence, quantum information science, and nuclear technology — maintaining our advantage over potential adversaries? We need to accelerate research and development, dismantle regulatory barriers, strengthen domestic supply chains and manufacturing, spur robust private sector investment, and advance American companies in global markets."*

*"In a moment of strategic significance, we must be more creative in our use of public research and development money, and shape a funding environment that makes clear what our national priorities are. Whether in AI, quantum, **biotech**, or next-generation semiconductors, in partnership with the private sector and academia, it is the duty of government to enable scientists to create new theories and empower engineers to put them into practice."*

NIST Emerging Biotechnology and Biomanufacturing

Emerging Biotechnology and Biomanufacturing

Sequencing

aka DNA read

Human Genome Project
1990-2003; $5B in 2021, sequenced 92% of 3B reads

NIST GIAB Consortium critical in providing accuracy and enabling the first complete human genome in 2022

Genome Synthesis

aka DNA write

Digital-to-physical conversion

Point of control for biosecurity via **NIST-led Sequence Screening**

Genome Editing

aka DNA edit

2020 Nobel Prize

NIST Genome Editing Consortium supports the translation of technology

AI Biodesign Tools

DNA to function prediction

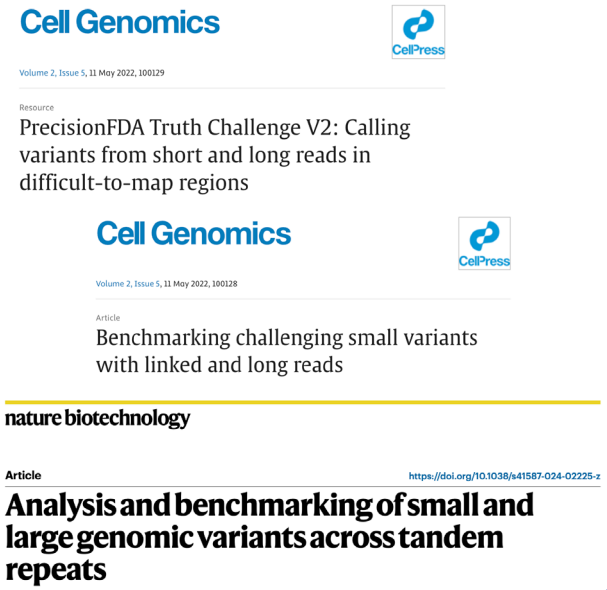
2024 Nobel Prize

NIST provides tools, capabilities, & standards to accelerate the development of AI tools; test the performance of emerging AI tools

Genome in a Bottle Supports Technology Development and AI-based Genomic Methods

Extensive data and benchmarks for normal cell lines

- NIST Reference Materials and data used in challenges with blinded "truth" to benchmark AI-based analysis methods
- Updated to characterize difficult genomic regions for method development



Cell Genomics

Volume 2, Issue 5, 11 May 2022, 100129

Resource

PrecisionFDA Truth Challenge V2: Calling variants from short and long reads in difficult-to-map regions

Cell Genomics

Volume 2, Issue 5, 11 May 2022, 100128

Article

Benchmarking challenging small variants with linked and long reads

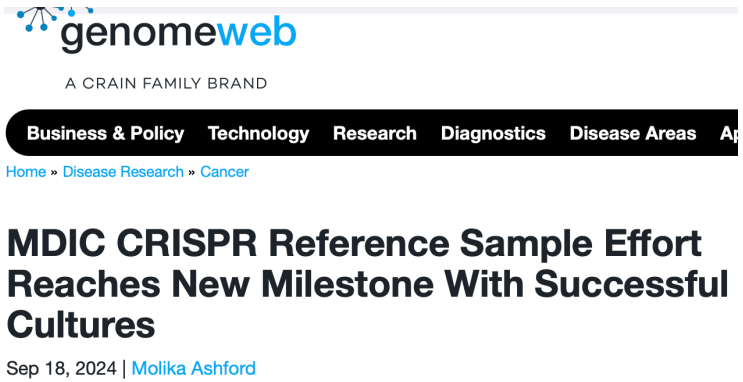
nature biotechnology

Article

https://doi.org/10.1038/s41587-024-02225-z

Analysis and benchmarking of small and large genomic variants across tandem repeats

CRADA to engineer GIAB cell lines for cancer reference samples that give confidence to clinical testing



genomeweb

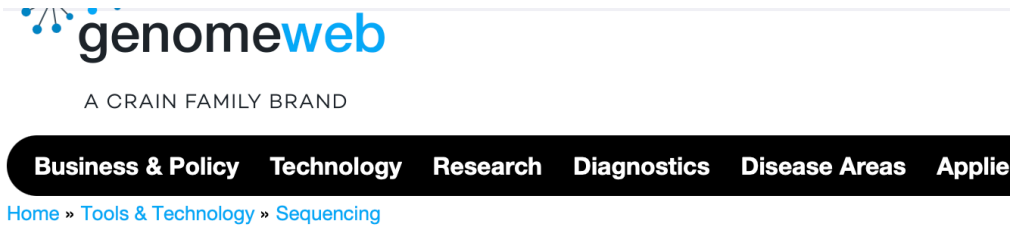
A CRAIN FAMILY BRAND

Business & Policy Technology Research Diagnostics Disease Areas Ap

Home » Disease Research » Cancer

MDIC CRISPR Reference Sample Effort Reaches New Milestone With Successful Cultures

Sep 18, 2024 | Molika Ashford



genomeweb

A CRAIN FAMILY BRAND

Business & Policy Technology Research Diagnostics Disease Areas Applie

Home » Tools & Technology » Sequencing

Genome In a Bottle Consortium Developing Tumor-Normal Reference Materials

Oct 22, 2024 | Huanjia Zhang

- NIST collaborated with Massachusetts General Hospital to develop the **first tumor cell line consented for public genomic data**
- NIST collaboratively published extensive genomic data from many technologies
  - **"the most well-characterized cancer cell line in the world"**
- **Now developing benchmarks for technology development and validation of clinical tests**

NIST *Genome Editing Program* and CRISPR Genome Editing Therapies

December 2023

FDA NEWS RELEASE

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

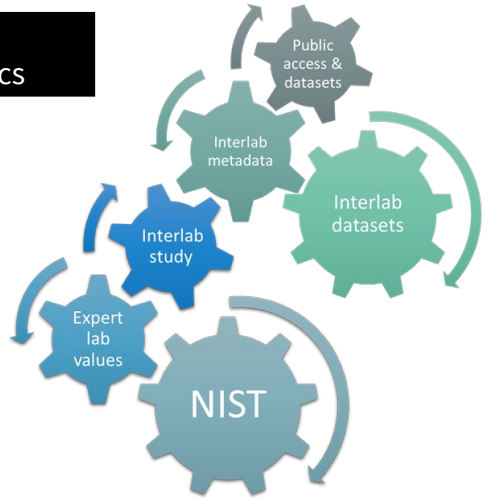
Dec 8, 2023

Vertex and CRISPR Therapeutics Announce US FDA Approval of CASGEVY™ (exagamglogene autotemcel) for the Treatment of Sickle Cell Disease

– First-ever approval of a CRISPR-based gene-editing therapy in the U.S. –

NIST qualified control samples and benchmark values provided via the Consortium interlaboratory study supported CRISPR Therapeutics to have greater confidence in safety assays for detecting on- and off-target editing

CRISPR Therapeutics



NIST

Genome Editing Program & Genome Editing Consortium (~60 member organizations)

EVALUATE measurement challenges

DEVELOP controls, data, community norms, and standards

QUALIFY analytical methods

nature biotechnology

Article | Published: 15 June 2020

CHANGE-seq reveals genetic and epigenetic effects on CRISPR–Cas9 genome-wide activity

Cicera R. Lazzarotto, Nikolay L. Malinin, Yichao Li, Ruochi Zhang, Yang Yang, GaHyun Lee, Eleanor Cowley, Yanghua He, Xin Lan, Kasey Jividen, Varun Katta, Natalia G. Kolmakova, Christopher T. Petersen, Qian Qi, Evgheni Strelcov, Samantha Maragh, Giedre Krenciute, Jian Ma, Yong Cheng & Shengdar Q. Tsai

Nature Biotechnology **38**, 1317–1327 (2020) | Cite this article

May 2025

The New York Times

Baby Is Healed With World's First Personalized Gene-Editing Treatment

KJ Muldoon after a follow up dose of an experimental gene editing treatment at the hospital in April 2025.

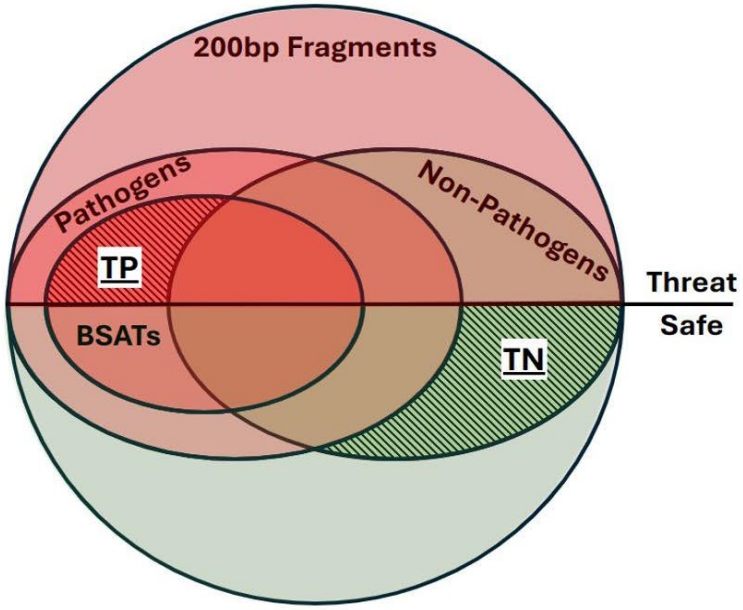
Credit: C. Dawson /Children's Hospital of Philadelphia via AP

NIST collaborated with academia, government agencies, and industry to add confidence to assays and approaches later used to assess safety of the therapy for detecting on- and off-target editing

Collaborators:

- St. Jude Children's Research Hospital
- NIH Somatic Cell Genome Editing Consortium
- DARPA Safe Genes Program
- Massachusetts General Hospital / Harvard
- Integrated DNA Technologies (IDT)

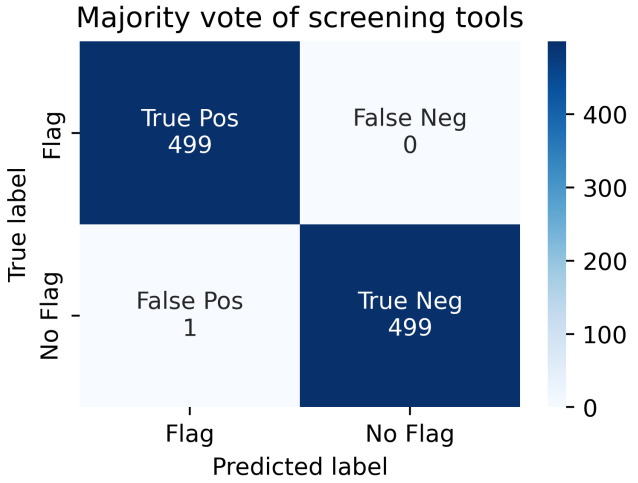
Supporting Global Biosecurity via Nucleic Acid Sequence Screening



Benchmark Dataset

Screening Tool Developers

Aclid
Battelle ThreatSeq/UltraSEQ
IBBIS Common Mechanism
RTX BBD FAST-NA Scanner
SecureDNA



Performance Metrics

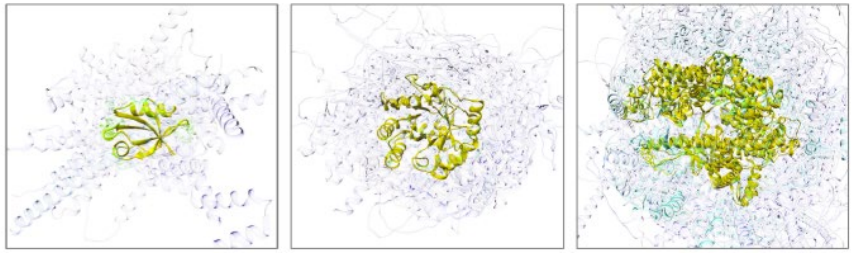
https://www.biorxiv.org/content/10.1101/2025.05.30.655379v1

- An **Attestation Dataset** was generated to include True Positives (TP) and True Negatives (TN)
- **Attestation Dataset** was tested by 6 **Screening Tool Developers**
- **Performance Metrics** showed excellent agreement and demonstrated fit for purpose
- Ongoing: Test data will be offered to **Sequence Providers** for documenting baseline performance

Testing of AI Biodesign Tools

One of the first experimental validations of AI-generated protein sequences (safe protein proxies used)

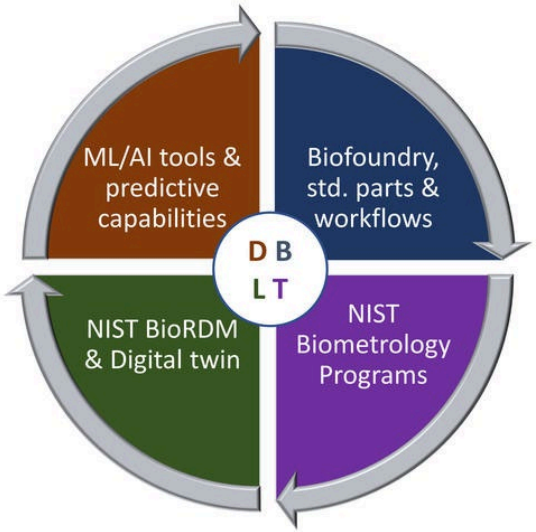
Original proteins: 100% active
AI-modified proteins: ??% active



Basic **Moderate** **Advanced**

Designed basic, moderate, and advanced "difficulty classes" that consider expression, folding, & interaction

Generalized NIST role and contributions to the Design-Build-Test-Learn (DBTL) approach



https://www.biorxiv.org/content/10.1101/2025.05.15.654077v1

Microsoft: used AI tool to design homologs for each protein

Twist: provided synthetic nucleic acids for testing

NIST: applied automation and metrology expertise to test protein function in cells or cell-based systems

Findings:

- Only ~30% of basic "difficulty class" synthetic homologs were active above threshold, 0% of moderate and advanced classes
- AI biodesign tools generate synthetic homologs with predicted structures similar to native template, without necessarily retaining function
- Current AI biodesign tools cannot reliably rewrite protein sequence while maintaining activity and evading screening tool detection

Recent NIST Contributed Publications

Nature Biotechnology Correspondence Published | 28 April 2025 (IF = 33.1)

https://doi.org/10.1038/s41587-025-02650-8

- Proactive, built-in and AI-native safeguards needed within generative AI tools
- Global community effort to research, develop, test and implement measures to ensure responsible deployment of generative AI in biotechnology

Science News Coverage | 28 April 2025

"Built-in safeguards might stop AI from designing bioweapons -- Researchers propose modifying protein-design algorithms to keep bad actors from misusing them"

Workshop Report Released | Jan 2025

- NIST cooperative agreement with EBRC in 2024 to facilitate industry engagement through a series of workshops
  - Six 2-hour virtual workshops and 2-day in person workshop April to September 2024
- Report provided workshop summaries/best practices/recommendations for sequence screening
- NIST **Draft Standard Guide for Providers** Annex to harmonize nucleic acid screening approaches, standardize to enable data interoperability and integration, and support conformity assessment

https://ebrc.org/publications-strengthening-a-safe-and-secure-nucleic-acid-synthesis-ecosystem/#pdf-strengthening-a-safe-and-secure-nucleic-acid-synthesis-ecosystem/6/

Biotechnology + AI + Automation

https://www.nist.gov/programs-projects/nist-living-measurement-systems-foundry

- Nature Biotechnology study: *de novo* sequences to probe ~300 sequences in cells (microbial, yeast) or cell free systems
- NIST Living Measurement Systems Foundry can probe over 7 million quantitative activity measurements per experiment (or 300,000 sequences for 24 conditions simultaneously)

- Emerging biotechnology and biomanufacturing require engineering and measurement of nucleic acids and proteins within cellular context
- Combined engineering biology, biometrology, automation, and AI enable generation of high-quality, AI-ready data for advancing bioeconomy

NIST Biomanufacturing Program

NIST Biomanufacturing Program

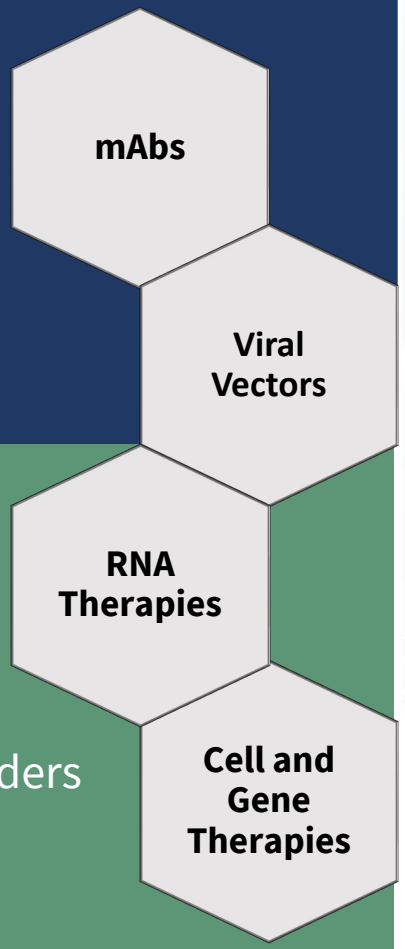
Advancing measurement science, standards, & technology to accelerate development & manufacturing of innovative, high-quality biopharmaceuticals

Mechanism

- Collaborate across ecosystem (biopharma, FDA, suppliers) for current & emerging infrastructural measurement problems
- Draw from a broad array of unique, interdisciplinary expertise, resources, and facilities available at NIST
- Promote cross-industry collaboration & open data sharing

Program Portfolio

- **Basic Research:**
  Foundational measurement science & technology development
- **Applied R&D:**
  Collaborations and consortia with industry and regulatory stakeholders (NIIMBL, AMBIC, CRADAs, MTAs, etc.)
- **Mission Driven Product Delivery:**
  Reference materials, reference data



Biomanufacturing Program Director:

Mike Tarlov
Acting Deputy Director, MML
michael.tarlov@nist.gov

NISTmAb: Paving the Way to Companion Reference Materials

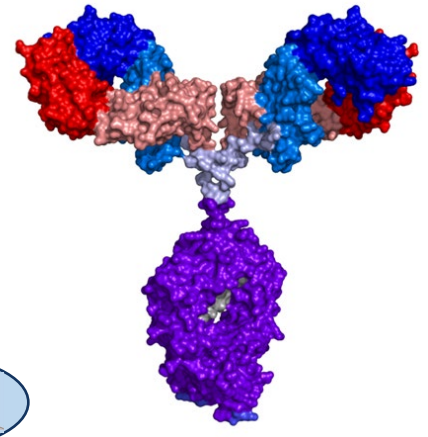
NISTmAb

- Biopharmaceutical grade IgG1 expressed in NS0 (mouse) cell line obtained from Medimmune/ AstraZeneca
- >10,000 units sold, 100s of publications, patents, application notes
- Novel technology development, de-risking, and maturation

NISTCHO

- Clonal Chinese Hamster Ovary (CHO) K1 cell line expressing cNISTmAb with industry-like productivity (>2 g/L)
- Developed collaboratively with MilliporeSigma and NIIMBL
- Enabler for technology benchmarking, research, training & education

cNISTmAb

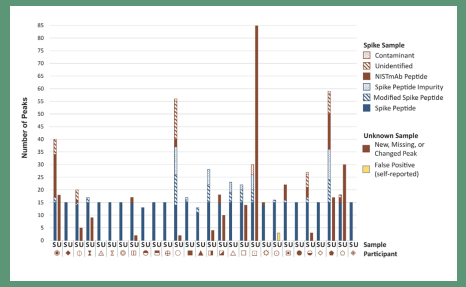


- Non-originator NISTmAb expressed by NISTCHO cell line to be manufactured by MilliporeSigma
- Serve as reference “product” for NISTCHO
- Builds upon NISTmAb and NISTCHO body of knowledge

NIST Reference Materials Driving Adoption of Emerging Analytical Technologies

Multi-Attribute Method (MAM) Consortium

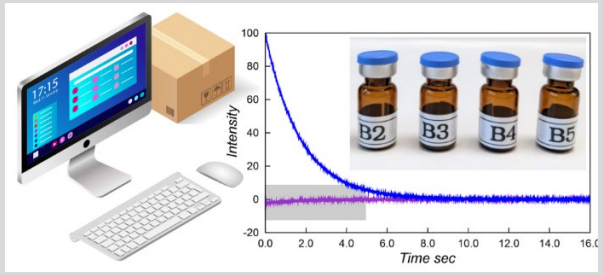
30 industrial participants



Mouchahoir, et. Al. JASMSs. 2021, 32(4):913-928

Multiplatform Benchtop NMR Pilot Study of Pharmaceutical Products

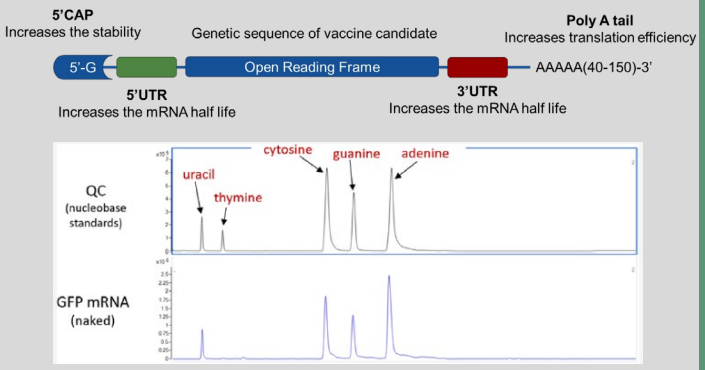
21 participants: 5 Major Vendors



Briggs, KT, et al. (2025), under internal review

LC/MS of Reference Grade Test Material 10202 mRNA Therapeutic Substance

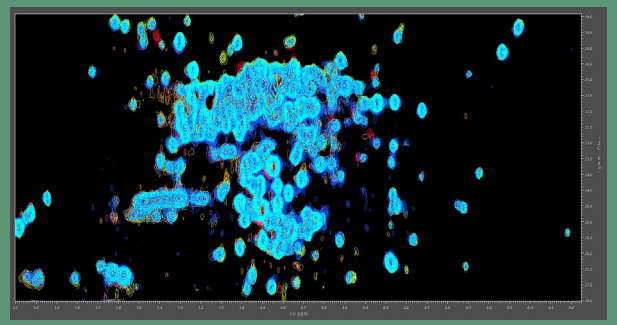
18 industrial participants



Study underway

2D-NMR of NISTmAb Fab

30 participants, ~ 11 industrial



Brinson, et. Al. MAbs. 2019 Jan;11(1):94-105

- Assesses variability between labs and analytical technologies
- Identifies potential technology gaps
- Allows open data sharing (non-IP constrained)
- Fosters collaboration across global biopharma community

Interlaboratory Studies Using the NISTmAb to Advance Biopharmaceutical Structural Analytics

Katharina Yandrofski[1], Trina Mouchahoir[1], M. Lorna De Leoz[2], David Duewer[3], Jeffrey W. Hudgens[1], Kyle W. Anderson[1], Luke Arbogast[1], Frank Delaglio[1], Robert G. Brinson[1], John P. Marino[1], Karen Phinney[3], Michael Tarlov[3] and John E. Schiel[1]*

https://www.frontiersin.org/articles/10.3389/fmolb.2022.876780/full

CBBI* at IBBR*

- Leverages Federal and State investment in biological measurement science and standards to advance biotechnology and biomanufacturing
- Actively engages the local and national biopharma ecosystem to promote innovation and the growth of the MD and National bioeconomy
- Located at IBBR in Rockville, a joint institute with UMD-College Park, UM-Baltimore, and NIST
- Expands expertise and capabilities at IBBR in biological measurements, data science, standards, and state-of-the-art scientific instrumentation

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
U.S. DEPARTMENT OF COMMERCE

*Center for Biomeasurement & Biomanufacturing Innovation (CBBI) @ Institute for Bioscience & Biotechnology Research (IBBR)

CBBI: An Expansion of the NIST Mission @ IBBR

- Developing advanced biomanufacturing testbeds for collaborative research to accelerate next-generation biomanufacturing technologies and biological products
- Consolidating related programmatic activities currently located on the NIST campus to increase the NIST programs at IBBR from 35 to ~75 staff

IBBR GMP-Like Facility

- NIST currently providing $5M/yr to support CBBI; additionally, UMD and NIST providing $5M each, $10M total for facilities alterations
- IBBR strategically recruiting faculty that complement/leverage NIST programs and expand connections to the main campuses

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
U.S. DEPARTMENT OF COMMERCE

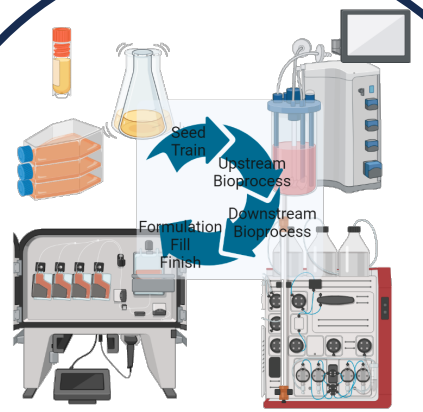
CBBI mAb Testbed

Biomanufacturing Bioprocess Testbeds

- *Reference Production Cell Line for mAbs (Mammalian cell culture)*

  NISTCHO RM 8675
  cNISTmAb RM 8672

- *Industrially-relevant test-beds*
  - *Bioprocess performance*
  - *Fed-batch or perfusion*
  - *Downstream operations*



NISTCHO
cNISTmAb

Biomanufacturing Analytics

- *Process analytical technologies (PAT) in-line/at-line measurements*
- *High-content data spectroscopies (NMR, Raman, Near-IR)*
- *Automation*
- *Real-Time Release*

Data Science, Modeling, & System Integration

- *Curated, high quality data test sets*
- *Digital Twins: product and process replicas*
- *AI-driven, adaptive control of bioprocessing*

Models entire mAb manufacturing process – upstream & downstream

Focus on process analytical technologies & role of measurement precision and uncertainty in predicting process outcomes

Open innovation center to study new bioprocess technologies & generate publicly available data sets

Future testbeds representative of mRNA, viral vector, and cell therapy manufacturing processes

Questions?