Summer 2025

ADVANCED BIOMANUFACTURING FOR MEDICINES

The BRIDGE

LINKING ENGINEERING AND SOCIETY

NATIONAL ACADEMY OF ENGINEERING

The mission of the National Academy of Engineering is to advance the welfare and prosperity of the nation by providing independent advice on matters involving engineering and technology, and by promoting a vibrant engineering profession and public appreciation of engineering.

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Mission Statement of *The Bridge*

The Bridge publishes articles on engineering research, education, and practice; science and technology policy; and the interface between engineering and technology and society. The intent is to stimulate debate and dialogue both among members of the National Academy of Engineering (NAE) and in the broader community of policymakers, educators, business leaders, and other interested individuals. *The Bridge* relies on its editor in chief, NAE members, and staff to identify potential issue topics and guest editors. Invited guest editors, who have expertise in a given issue's theme, are asked to select authors and topics, and independent experts are enlisted to assess articles for publication. The quarterly has a distribution of about 7000, including NAE members, members of Congress, agency officials, engineering deans, department heads, and faculty, and interested individuals all over the country and the world. Issues are freely accessible at *www.nae.edu/TheBridge*.

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NATIONAL ACADEMIES *Sciences Engineering Medicine*

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. John L. Anderson is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the National Academies of Sciences, Engineering, and Medicine at **www.nationalacademies.org**.

President's Perspective

The Importance of Engineering and the NAE

John L. Anderson

Election to the National Academy of Engineering (NAE) is a great honor for any engineer. Yet, the purpose of our organization is not primarily honorific. The NAE exists to serve: to advance the welfare and prosperity of the nation by providing independent advice on matters involving engineering and technology, and to promote a vibrant engineering profession and public appreciation of engineering. Advancing this mission depends on active engagement by our members, and they have answered the call. As shown in figure 1, NAE members can take pride in their consistent and impactful service to the nation.

One of the NAE's unique strengths is its election of members from all three sectors of the technical workforce: industry, academia, and government (see figure 2). This broad base makes the NAE truly representative of the engineering enterprise and enables it to convene practitioners, educators, and researchers who bring diverse knowledge and perspectives to bear in the activities of the National Academies. The achievements of the NAE's members also highlight the importance of our profession and the technical excellence of the United States.

As I conclude my term as president, I reflect on what I've learned in this role. First, engineering is a creative endeavor. My favorite quote comes from Theodore von Kármán, a giant in aeronautics and recipient of the first US National Medal of Science in 1962 (National Science & Technology Medals Foundation). He said, "A scientist studies what is, whereas an engineer creates what never was." The public didn't demand smart phones, remote-controlled appliances, or wearable health monitors. Visionary engineers, however, saw these possibilities and created innovations that have since become essential to our lives. Creativity in engineering isn't only about solving problems—it's also about imagining and building things we didn't know we needed but have made our lives better.

Second, engineering is not a subset of science, as is often assumed. During my 48 years as a teacher, researcher, and academic leader, I did not fully appreciate the methodological differences between science and engineering. As president of the NAE, I have come to better understand and respect both endeavors. Importantly, one need not hold a formal engineering degree to be an engineer. In fact, more than 10% of NAE members do not have such a degree.

A recent National Academies report, *Impacts of National Science Foundation Engineering Support on Society*, defines engineering as:

> *"The act of creating artifacts, processes, or systems that advance technology and address human needs using principles of the sciences, mathematics, computing, and operations. Engineering encompasses not only the design of systems, structures, and devices but also their construction, implementation, deployment, and function"* (NASEM 2024, p. 18).

Engineering is a distinct, action-driven way of thinking that bridges science and technology. It shapes daily life. Unlike applied science, engineering progress can outpace

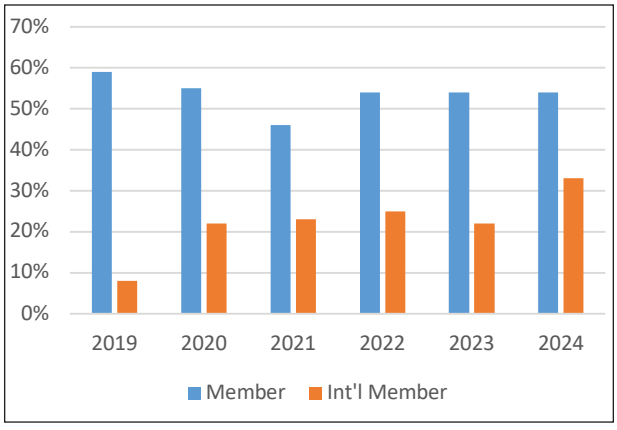

FIGURE 1 NAE member and international member participation in National Academies activities by year.

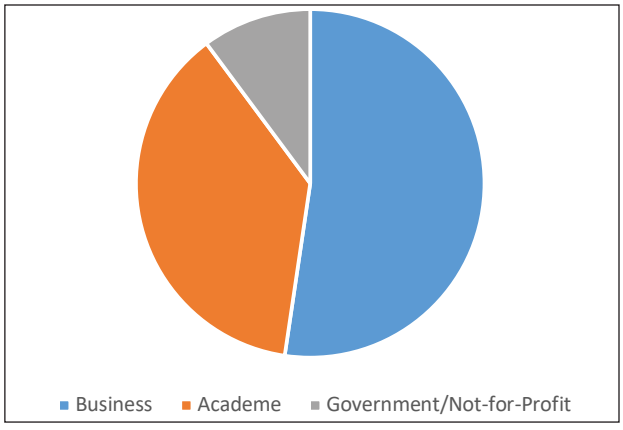

FIGURE 2 Work sector of NAE members (class of 2025).

scientific understanding. Both science and engineering are vital to economic prosperity, public health, and national security, but they are separate and equally important fields (Anderson 2019; Hammack and Anderson 2022).

As we approach the 250th anniversary of the United States, we should recognize the extraordinary contributions of science, engineering, and medicine to our national development. Consider our transportation systems, physical infrastructure, economic growth, healthcare and medicine, and defense technologies—not to mention our understanding and management of the natural and social worlds. The technologies on which we rely are products of these three technical pillars. To continue improving our quality of life, the nation must sustain its investment in research, invention, and technology development.

As I pass the torch to the NAE's next president, engineering dean **Tsu-Jae King Liu** at UC Berkeley, I offer my deepest thanks to the NAE's members and staff for their dedication and support. They are among the most thoughtful and generous individuals I have known. I have learned much from them. I now look forward to returning to the role of volunteer and continuing to work alongside them to strengthen our profession and our country.

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Guest Editors' Introduction

Advanced Biomanufacturing for Medicines

Barry C. Buckland

Kelvin H. Lee

Barry C. Buckland is executive director at NIIMBL. Kelvin H. Lee is institute director at NIIMBL and Gore Professor of Chemical & Biomolecular Engineering at the University of Delaware.

In the fall of 2013, Professors Phillip A. Sharp and **Robert Langer** guest edited an issue of *The Bridge* on the theme of the Convergence of Engineering and the Life Sciences. The collection forecast the breadth in manufacturing approaches, capabilities, and innovation that would define the decade that followed. Since that pivotal issue, the advanced biomanufacturing community has developed practical approaches to manufacture a diverse range of medicines across a range of scales while maintaining high quality—marking a period of remarkable advancement in medicine.

An emerging reality highlighted in the 2013 issue of *The Bridge* that remains true today is the beneficial synergy among academic institutions, small and large biopharmaceutical companies, and government agencies. Partnerships across these sectors have improved market access to safe, efficacious, high-quality, robustly manufactured medicines that lead to positive patient outcomes. Another residual theme is the multidisciplinary contributions from engineers working with biologists and biochemists. For a process engineer or manufacturing expert, biological research presents a constant reminder of the urgency for—and remarkable opportunity in—innovation. For manufacturing, this connection is critical for developing analytical methods to fully characterize and define both intermediates and the final product. Currently, we are at an inflection point with a sudden increase in the different modalities used to treat disease. Advances in biomanufacturing are needed to help individuals benefit from these new medicines. Success will rely not only on having a safe and efficacious medicine, but also on having a way to scale up, or scale out, the consistent manufacturing of that medicine while maintaining the quality of the product.

Innovative biomanufacturing approaches are being developed all the time across a range of applications, including medicine, but many manufacturing technology innovations come from academia or small companies. De-risking those technologies so that they can be adopted to make medicines can be a complicated process, requiring a broad range of stakeholder input and expertise from academia, industry, and government. The Manufacturing USA program was established in 2014 to address this need. Convening diverse stakeholders for precompetitive work and advancing manufacturing technologies, Manufacturing USA aims to increase US advanced manufacturing competitiveness in today's global environment. The 18 Manufacturing USA institutes each have a primary agency sponsor: the Department of Defense, the Department of Energy, or the Department of Commerce. Three have a biotechnology focus: Bioindustrial Manufacturing and Design Ecosystem (BioMADE), National Institute for Innovation in Manufacturing of Biopharmaceuticals (NIIMBL), and BioFabUSA. Several focus on adjacent technology spaces relevant to the biomanufacturing industry,

Manufacturing x Digital, Collaborative Ecosystems for Smart Manufacturing Innovation Institute, and Advanced Robotics for Manufacturing Institute, among others.

We serve in leadership roles at one of these institutes, NIIMBL. We are fortunate to see firsthand, and in real time, the benefits of precompetitive collaboration towards advancing biomanufacturing capabilities for certain kinds of medicines and medical countermeasures. Incredible advances in biology have led to a much better understanding of many diseases. Our community has been challenged to develop, understand, and adopt new manufacturing approaches to convert these advances into new medicines, heralding an era where medicines are invented but also manufactured in the United States, thereby reducing our reliance on competitor nations for access to medicines and increasing our resilience and economic security. Both are important goals recently outlined in the final report issued by the National Security Commission on Emerging Biotechnology.[1] Both were also articulated in a 2020 Consensus Study on Safeguarding the Bioeconomy released by the National Academies of Sciences, Engineering, and Medicine.[2]

Whereas in 2013, when the issue of *The Bridge* guest edited by Sharp and Langer was published, biotechnology was used primarily to manufacture antibiotics, vaccines, and recombinant proteins, today it is used to make everything from materials for the manufacturing process to products including multispecific proteins, gene therapies, antibody drug conjugates, and cell therapies. This issue of *The Bridge* is a timely follow-up to the 2013 issue, this time focusing on the topic of Advanced Biomanufacturing for Medicines, which integrates the theme of biologists working with engineers and echoes that earlier issue through the theme of collaboration across sectors. In celebration of the fact that a remarkably successful community has been built, we chose contributors to this 2025 edition that represent industry, government, and academia.

Chris Love summarizes some of the unique manufacturing challenges of biopharmaceuticals in comparison with other industries. Because biopharmaceuticals generally have smaller production volumes (low metric tons or smaller) and are high-value products, different drivers exist in the industry compared to chemical manufacturing, which is characterized by high-volume production (millions of metric tons per year) for generally lower-value products. Love outlines a range of innovations, emphasizing in many cases the opportunity in using different host organisms. Further development and partnership across academia, start-ups with innovative new technologies, industry, and regulatory agencies can begin to realize a new paradigm to provide broad access to these medicines and the ability to make them. Love emphasizes urgency and cautions that failure to invest with haste in ground-breaking new biomanufacturing technologies so as to establish a distributed, resilient base could bring sobering consequences for the country.

Paul Collins sees hope in the proliferation of approaches for breakthrough new medicines such as peptides, oligonucleotides, and other gene delivery approaches. Carrier molecules such as lipid nanoparticles have been designed for the purpose of delivering these new molecules to their intended target. Concurrent with the proliferation of these new treatment modalities and delivery vehicles is a new creativity in how these might be combined for patient benefit. Future conjugate structures could include various targeting structures with any number of linked payloads. Can the entire array of creative new potential molecular entities be accommodated by existing platforms? What is the value of new versus retrofit? To what extent should new platform development be encouraged in a pre-competitive collaboration?

The central role that analytics and the establishment of standards play in biopharmaceuticals is described by Katharina Yandrofski, Megan Cleveland, Zvi Kelman, Mike Tarlov, and John Marino from the National Institute of Standards and Technology (NIST). In this piece, the NIST team focuses on the manufacture and release of antibodies, currently the largest and most successful biologic platform. By extensively characterizing a reference material and at the same time providing a sample, the NIST team made it possible for many groups to participate in the development of improved analytical methods and better understand the clinical impacts. The resulting program, based on a reference material known as NISTmAb along with a cell line to express the antibody known as cNISTmAb, has had a significant impact on progress in antibody manufacturing and provides a widely available, commonly understood approach to analytical measurements that helps ensure high-quality products are consistently made.

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[1] NSCEB [National Security Commission on Emerging Biotechnology]. 2025. Charting the Future of Biotechnology: An Action Plan for American Security and Prosperity. Online at https://www.biotech.senate.gov/final-report/chapters/.

[2] NASEM [National Academies of Sciences, Engineering, and Medicine]. 2020. Safeguarding the Bioeconomy. Washington, DC: The National Academies Press.

The contribution by Chris Williams, Eric Hacherl, Tim Charlebois, Erik Barton, Stephen Kaminsky, Brenna Kelley-Clarke, Angie Snell Bennett, Marco Thomann, and Anastasia Yemelyanova makes the case for an innovative approach to treating rare diseases. The significant number of rare diseases that affect small patient populations could, in theory, be treated by a single dose of a gene therapy. For small companies and universities, the cost of developing a manufacturing process to make clinical-grade treatments is high, yet for large companies the market for any resulting product is small. This article describes a promising approach to solving this issue in the design of a platform to support a decentralized user base, potentially accommodating hundreds or even thousands of user applications. Platform services will prioritize growth and maturity in digital resources, data aggregation, and critical starting-material availability. The platform is intended to be compatible with existing industrial infrastructure and thus will remain agnostic to competing product lines of non-critical equipment and materials. This approach fosters sustainable and scalable development, reducing the financial and logistical burdens of large capital projects and extensive administrative overhead.

The contribution by Melanie Tomczak and Penny Norquist from the BioMADE Manufacturing USA institute describes three example approaches that rely on bioindustrial manufacturing to make critical products. The BioMADE institute advocates for the use of American-grown crops (e.g., corn, soybeans, and sugar beets) to produce everyday items as well as more specialized products. In this piece, Tomczak and Norquist describe approaches to manufacture SARS-CoV-2 antigens using different cell hosts and to manufacture vaccine adjuvants such as squalene and saponins that can be difficult to source and are now manufactured microbially in large quantities.

The piece by Misti Ushio and **Barry Buckland** is a retrospective study of one of the most important medicines ever developed: penicillin. The original development of penicillin in the 1940s is an excellent example of a successful government, academic, and industry consortium. This gave birth to the widespread and transformative use of antibiotics. Until the late 1970s, leadership and capacity of this manufacturing infrastructure operated in the United States, but since then, this capability has been outsourced or migrated offshore. As a result, little microbial fermentation capacity remains available for manufacturing antibiotics in the United States or Western Europe. At the same time, antibiotics continue to be incredibly effective against many infectious diseases. Over 200 million prescriptions were written in the United States in 2023 alone. This chapter illustrates the need for a national policy for the supply of critical medicines such as antibiotics and, in the promising future, for antibodies. It also illustrates the benefit and urgency for investing in improved methods for manufacture using tools such as synthetic biology and continuous culture.

Synthetic biology has played a central role in the discovery of the current portfolio of biologically made medicines. Mruthula Rammohan, Akash Vaidya, Spencer Grissom, Rachel Silvestri, Christopher Pirner, Kevin Solomon, and Mark Blenner describe the impact of continued progress in synthetic biology as a way to address biopharmaceutical manufacturing challenges. For example, these approaches can help with the manufacture of bispecific antibodies at high purity, messenger ribonucleic acid manufacturing, and with the targeting of recombinant adeno-associated viral vectors toward specific tissue types. The authors describe the use of continuous cultivation to better understand both drivers of phenotypic variation and the synthetic circuits that control culture stability. They suggest the benefits of genome reduction to remove sources of instability. Synthetic biology is no longer restricted to the natural protein building blocks. Recent decades have seen tremendous strides in genetic code expansion, enabling the incorporation of non-canonical amino acids into full-length proteins. This has created new manufacturing challenges as described in the chapter by Collins.

Collectively, these pieces demonstrate the significant impact of advanced biomanufacturing developments and innovations on today's world and our country's health and economy. If the United States is to maintain its competitiveness and resiliency, then creating and nurturing rapid development and adoption of advanced biomanufacturing innovations for life-altering and life-saving medicines is vital. The proof is in the pudding. During the past 30 years, our nation has experienced the remarkable growth of the biotechnology industry, resulting in better health and the creation of significant value through improved medicines for devastating diseases, including cancer, infectious disease, and autoimmune disorders. Given the multitude of developments in progress, we are excited for the future.

Acknowledgments

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Maintaining US leadership in the biomanufacturing sector requires investment in groundbreaking biomanufacturing technologies.

Transforming Manufacturing to Continue Leading the Innovation of Biopharmaceuticals

J. Christopher Love is the Raymond A. (1921) and Helen E. St. Laurent Professor of Chemical Engineering at MIT and director of the MIT Alternative Host Research Consortium. He is a co-founder of Sunflower Therapeutics, PBC.

J. Christopher Love

Biopharmaceuticals have become essential medicines for preventing and treating diseases ranging from cancer and autoimmune disorders to neurological conditions, complementing vaccines and small-molecule pharmaceuticals. Derived from biological sources, they include monoclonal antibodies, mRNA therapies, engineered viruses, and cell-based therapies, among others. The global biologics market exceeds $500 billion and represents approximately half of all approved new medicines (Senior 2024).

Manufacturing these medicines is more challenging than manufacturing traditional small-molecule drugs (e.g., acetaminophen). The processes rely on dynamic living cells to produce complex active biological substances. Over the past 40–50 years, the industry has developed reliable manufacturing practices to deliver these life-saving treatments to patients.

This adolescent industry now faces new challenges to continue its growth. At least three external forces—rapidly diversifying therapeutic pipelines, shifting geopolitical risks and global competition, and demands for long-term sustainability—are converging to require new agile and flexible manufacturing strategies to ensure the timely and efficient delivery of new medicines from concept to patients. Without continued innovations in manufacturing practice itself and strategic infrastructure for a broad biomanufacturing base, the United States in particular risks losing its leadership in this sector.

The State of the Industry and Manufacturing Today

Breakthroughs in recombinant DNA technologies and genome-scale biology gave birth to the modern biopharmaceutical sector. The promise—and increasingly realized potential—of biologic medicines are their precision for targeting disease and their general safety, compared to small molecule drugs. The complexity of these products is significant, however. Biomolecular or cellular materials can vary in many ways and can impact their safety or efficacy. Biopharmaceuticals are typically produced using genetically engineered living cells, such as Chinese hamster ovary cells, yeast, or bacteria. These cells express therapeutic proteins or engineered viruses that in turn are purified from the residual complex mixture of cellular components (DNA, other proteins). The industry has optimized processes to make these products despite their complexity, relying predominantly on highly centralized, bespoke facilities to achieve consistent supply to the market.

Scale and Industry Structure

Compared to other industrial sectors, biopharmaceuticals remain both small in production volumes and highly specialized as products. Chemical manufacturing (including pharmaceuticals) routinely produces millions of metric tons of products annually compared to tens of metric tons per year for all biopharmaceuticals and vaccines. There are also ~5-10 times more registered small molecule pharmaceuticals; the 100th monoclonal antibody (mAb) was just approved in 2021 by the Food & Drug Administration (FDA) (Mullard 2021). This low mix of moderate-volume products, coupled with the operational oversight needed for the complex, highly manual processes to assure consistent high-quality products, has contributed to an industrial structure wherein a handful of large biopharma companies and contract development and manufacturing organizations (CDMOs) control most of the global capacity for manufacturing (Kelley et al. 2021).

This structure contrasts with other mature industries such as the aerospace/defense industry, where large manufacturers rely on a robust network of small and medium enterprises as subcontractors and key suppliers for parts to form a manufacturing base. The structure more closely aligns with that of the semiconductor industry, where historically a small number of manufacturers have produced most chips supplied to the market. Much like the biopharmaceutical sector, the semiconductor industry has evolved to separate innovation and manufacturing. Various innovator companies design new chips manufactured by a small number of other companies (or predominantly one today [Taiwan Semiconductor Manufacturing Company (TMSC)]). This dynamic is similar for small biotechnology companies advancing new assets for acquisition by large biopharmaceutical companies.

Without continued innovations in manufacturing practice itself and strategic infrastructure for a broad biomanufacturing base, the United States in particular risks losing its leadership in this sector.

Long timelines to bring products to market—along with high drug prices in the United States and elsewhere—have reinforced the sector's structure. Venture capital-backed biotechnology companies rely on partnerships or licensing and contract manufacturing to achieve key value inflections and the sale of the company/assets pre-commercially. Large companies in turn recoup their research and development (R&D) investments in the commercialization of the products acquired through sales. Only a limited set of large innovator companies today have the capital resources to absorb these expenses and maintain the comprehensive manufacturing, clinical, and regulatory capabilities necessary for commercial sales. There is an increasing divide between the innovation of biopharmaceuticals and their manufacture.

Regulatory systems have further codified this highly centralized manufacturing model. Historically, limited capabilities to characterize clinically relevant attributes of these complex products have led to guidance for extensive characterizations of the processes themselves as a partial proxy—the so-called "the product is the process" perspective (Geigert 2019). Uncertainties in scaling processes and the high degree of expert knowledge needed can add ~20-40% to the overall cost of manufacturing a drug throughout its commercial lifecycle (Mahal, Branton, and Farid 2021). With a predictable, successful cadence for financing and approval in an era of globalization, there has been little urgency to reform this structure or under-

lying manufacturing practices beyond those that enhance operational efficiency.

Drivers to Continue Innovating Biopharmaceutical Manufacturing Practices

The biopharmaceutical sector is not immune to three accelerating external trends: the rapid expansion of new therapeutic candidates from accelerating biological knowledge, the shifting geopolitical landscape with increased global competition, and the urgent need for more sustainable production practices. Without innovations, current manufacturing paradigms risk becoming bottlenecks to continued growth, limiting the industry's ability to efficiently translate breakthrough discoveries into life-saving medicines for patients worldwide.

Without innovations, current manufacturing paradigms risk becoming bottlenecks to continued growth, limiting the industry's ability to efficiently translate breakthrough discoveries into life-saving medicines for patients worldwide.

The Explosion of Therapeutic Candidates is Outpacing Manufacturing Capabilities

The sheer rate of discovery in biology—and the tools to engineer it—are outpacing the ability to advance biomanufacturing processes to support their commercialization at scale. The landscape for new therapies has changed substantially in the last five years. The number of approved monoclonal antibodies reached 50 in 2015 but then surpassed 100 in 2021. Advances in genomics, immunology, and gene editing are fueling an unprecedented pipeline of potential therapies (Barbosu 2024). Mature protein engineering and nascent artificial intelligence (AI)-driven protein design have rapidly expanded the diversity and complexity of protein-based therapeutics in pipelines (Notin et al. 2024). The COVID-19 pandemic validated nucleic acid-based products like mRNA that require entirely different manufacturing than protein-based biologics. Cell and gene therapies have emerged as an important class of complex biologic products as well for cancers and genetic conditions.

There is, therefore, a growing mismatch between the speed of drug discovery and the capacities for industry to develop and validate manufacturing processes for commercialization and for regulatory agencies to review them. There simply are not enough trained personnel, development resources, or manufacturing infrastructure to support the timely advancement of novel therapeutic candidates emerging from academia and biotech startups around the world.

Geopolitical Shifts and Competition Threaten Global Supply Chains and Markets

The biopharmaceutical industry today relies heavily on globalized supply chains to support its centralized production hubs. Drug substances manufactured in one country are often finished into final drug products in another. Rising geopolitical tensions, supply chain disruptions due to unpredictable global events, and shifting trade policies make this model increasingly fragile, however.

Governments worldwide are prioritizing both national and economic security. They have implemented a range of policies introducing trade barriers and encouraging local, end-to-end manufacturing. Countries such as China, India, Canada, and France have made large public and private investments in both state and private contract development and manufacturing organizations (CDMOs) to secure domestic manufacturing capabilities.

The US-centered advantage in biotechnological innovation is diminishing. Faster timelines for regulatory reviews and lower costs for development in other regions of the world are leading to new follow-on or "me too" products targeting similar pathways or mechanisms as existing innovator drugs, as well as biosimilars. These products are beginning to gain approval in the United States, presenting new competition for US biotechnology innovators. Examples include Biocon's insulin glargine, which has been approved for the US market, and innovative new Chinese-designed biologics (Agten and Wu 2024).

Supply chain resiliency presents another emerging risk. Many critical raw materials, including media additives, plastics, and other specialized reagents, are sourced from global markets, including China. Trade restrictions, tariffs, or export bans by one or more countries will impact US- and European-centered biopharmaceutical

production, increasing costs and potentially delaying drug availability. Considerations for alternative models, including more vertical integration within companies, may be essential to enhance self-sufficiency in reliably delivering products to market.

Sustainability Demands More Resource-Efficient Biomanufacturing

Biomanufacturing today requires disproportionately large amounts of water, energy, and chemicals compared to the volume of the final product, largely due to the low conversion rates of the biological systems used in production and the strict aseptic conditions needed to maintain quality. Process Mass Intensity—a simple ratio of raw materials input to final product output—is 1,000 times greater for biopharmaceuticals than for small-molecule drugs or fine chemicals (Budzinski et al. 2019). More than 90% of the input mass is water (Madabhushi et al. 2018), an inefficiency similar to that found in semiconductor manufacturing. As global efforts to address sustainability intensify, this sector (like all industries) will face pressure from the public to reduce its environmental footprint while also attempting to expand access to therapies worldwide.

There is an emerging transition from fixed stainless-steel bioreactors to single-use technologies (SUTs)—a counterintuitive shift offering substantial benefits for sustainability. Disposable process materials generate plastic waste, but they also eliminate intensive processes using steam and chemicals for sterilization and reduce energy use (Ottinger et al. 2022). Further process intensification—achieving higher product yields in smaller, more efficient facilities—is still needed, however, to make biomanufacturing truly sustainable. Expanding biomanufacturing capacity today without addressing sustainability challenges could impose further strain on global resources and introduce other unintended consequences with the corresponding supply chain expansion.

Together, these extrinsic factors are dynamically and rapidly reshaping the environment in which the biopharmaceutical sector operates. They add increased uncertainty on operational strategy, increased competition for regulatory review and indication areas, and increased scrutiny on pricing and business practices that impact global health and sustainability.

Reassessing Biomanufacturing for a New Stage of Growth

The changing landscape of the sector provides an opportunity to re-evaluate the assumptions underlying biopharmaceutical manufacturing optimized for a globalized economy led by US-centric innovations in biotechnology. It is useful to consider whether the present assumptions are still sufficient to address both the pace of innovation and the needs of the global population (IAVI/Wellcome 2020).

Limitations of Today's Biomanufacturing Model for Tomorrow

The biopharmaceutical industry today has focused primarily on a common manufacturing paradigm for the dominant class of products—mammalian-based expression systems with well-defined steps in purification and recovery for monoclonal antibodies (Kelley 2009). Steady, incremental process improvements, principally aimed at increasing operational efficiency with fed batch-based processes, have yielded remarkable gains in productivity. For instance, monoclonal antibody titers have improved by nearly 100-fold since the early 1990s with process optimizations. A large network of facilities exists today to accommodate approved products with some capacity for new candidates.

Expanding biomanufacturing capacity today without addressing sustainability challenges could impose further strain on global resources and introduce other unintended consequences with the corresponding supply chain expansion.

Establishing new manufacturing capacity remains expensive and time-consuming (figure 1). Building and validating a conventional stainless-steel facility to produce monoclonal antibodies at scales of approximately 1-10 metric tons per year can require investments approaching $2 billion and three to five years to complete (Kelley et al. 2021). Even smaller-scale facilities for clinical-stage production today cost $100-200 million

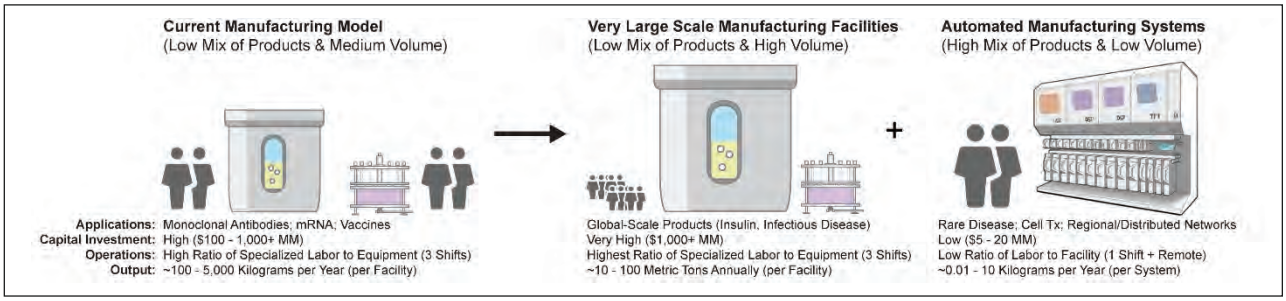

FIGURE 1 Current and future manufacturing models for biopharmaceuticals.

and take three years to complete. This economic barrier hinders creating a more robust manufacturing base for production and forces innovators (without commercial revenues) to wait on contract manufacturing until capacity becomes available. CDMOs for mammalian-cell-based biologics report operating at 65-80% of capacity with some regional variation, but the practical available capacity—particularly for small volume production like IND-enabling lots of proteins other than mAbs—can be much less than the apparent unused capacity due to long lead times, unique process requirements, or geographic/logistical constraints for supply (BioPlan Associates, Inc. 2022). This structural challenge to expansion in turn limits the number of innovative therapies that can be evaluated annually and adds costs to development by delaying initial (and subsequent) clinical trials.

Shifting Scales of Demand

The industry is also experiencing a bifurcation in manufacturing needs. Many new therapeutic candidates are designed for low doses (e.g., bi/trispecifics) or smaller populations, including personalized cell and gene therapies and biologics tailored to well-defined or rare diseases. These present a need for "small-volume, high-mix" manufacturing capabilities that can generally benefit from agile, standardized approaches to scale or adapt predictably without incurring the cost of large, specialized facilities. Examples from other sectors include foundries for semiconductors, where standardized processing tools allow for different chip designs, or the Tesla Gigafactories that can reconfigure to address current demand and products.

Some products will continue to need "high-volume, low-mix" biologics that may exceed tens or even hundreds of metric tons in annual demand for a global population. Examples include insulin products (~40-50 metric tons today estimated from global disease burden [Magliano et al. 2021]), weight management therapies based on semaglutide, and antibodies for infectious or neurodegenerative diseases (Kelley, Renshaw, and Kamarck 2021). Such products will benefit from large-scale facilities optimized for maximum throughput of individual products to realize cost efficiency. The current industrial manufacturing strategy is better positioned to address this scenario than that for agile and flexible production.

The Business Rationale for Advancing Distributed Biomanufacturing

Complementing the currently installed infrastructure for manufacturing, establishing new modular, small-footprint solutions designed for various product classes (proteins, cells, mRNA, virus) could enable agile, standardized biomanufacturing, expanding the manufacturing base and mitigating external risks. For small- and mid-sized biotech, modular platforms would reduce capital and operational complexities. Lower barriers to in-house production help circumvent long timelines and high costs of contract services while improving quality control and retaining intellectual property. Rapid access to manufacturing in early development can foster faster iteration and commercial development (Berger 2013). Distributed modular systems for regionalized production in other industries like automobiles have been used to strengthen the resiliency of supply chains and diversify the risk of disruptions (Shih 2020), though this model does require regional access to suitable raw materials and supplies as well.

Large pharmaceutical companies can also benefit from the agility provided by standardized modular systems across multiple product classes, making the transition from clinical to commercial production more predictable and resource efficient. Retrofitting needs can be minimized, enabling swift responses to changing pipelines or market demand. Modular facilities may also allow selective in-house production of key materials like growth factors

or enzymes, reducing reliance on external suppliers. One key advantage is "scaling out" rather than "scaling up." Instead of committing to a multibillion-dollar facility for uncertain demand, organizations can incrementally expand capacity, lowering risks of overbuilding or underutilization (Pollard et al. 2016; Walther et al. 2015). Novel financing—through public-private partnerships, regional consortia of smaller enterprises, and academic-industry-government-supported non-profits like Landmark Bio—could further expand the manufacturing base and accelerate product development (Asin-Garcia et al. 2024). Rather than replacing large-scale operations, this model would add capabilities for speed, flexibility, and resilience; reduce capital costs; shorten time-to-market; and broaden patient access to cutting-edge therapies.

Enabling Distributed Biopharmaceutical Manufacturing

Advancing a sustainable distributed manufacturing model requires identifying where current practices can be enhanced to overcome the inertia of implementing a new model. A highly optimized facility design and operations to support manufacturing monoclonal antibodies is based on efficient scheduling and use of materials (primarily chromatographic resins) to achieve low costs of goods manufactured (COGsm) (Kelley 2009). Analyses and implementation of continuous bioprocessing have shown the potential to reduce the capital costs and timelines to construct facilities and offer competitive costs for the COGsm (Mahal et al. 2021; Partopour and Pollard 2025; Walther et al. 2015). There is an emerging consensus process for continuous production of recombinant proteins by mammalian cells (Coffman et al. 2021). The configuration uses direct pairings of one bioreactor with one line for recovery using SUTs, sized according to the volume/mass of product/fluids processed.

Analyses on COGsm that compare continuous processes to both traditional stainless steel and single-use, fed batch operations offer key insights into the beneficial features they afford. Continuous operations can offer similar COGsm as traditional stainless-steel batch configurations, even with increased development costs and additional testing for quality arising from smaller batches (Mahal et al. 2021). This approach also can reduce CO_2 equivalents by over 50% due to the smaller facility (and energy use for ventilation and air handling) and equipment (Partopour and Pollard 2025).

The convergence of continuous processing and SUTs provides a basis for how to enhance agility, speed, and flexibility. Contributions to COGsm include the fixed capital investment (the facility and associated costs) and its operations (labor, materials, quality assurance), as well as those associated with process development. Reducing complexity or time required for each can directly reduce both the upfront capital investment and ongoing costs of manufacturing (recurring cost per gram). Three general areas for continued innovation are process intensification, standardization, and process consolidation.

Process Intensification

Increasing space-time yields while minimizing volumetric footprints of facilities (mass per unit volume fluid processed per time for a given cubic volume of space) is a critical goal to realize capabilities for distributed production (Crowell et al. 2024). The basic tenets are simple: Improve yields for process steps, reduce the total number of process steps, and reduce the total space required to operate the process steps while managing the input and output materials. The current platform for producing monoclonal antibodies has very effectively improved the yields on both the bioreactor process and downstream recovery to where further gains now require improved capacities of the chromatographic resins and reduced volumes/costs of media (Partopour and Pollard 2025). This current state for monoclonal antibodies, however, is neither representative of the state for all other recombinant proteins (e.g., insulin, vaccine subunits) nor the limit for process intensification. Further gains would enable even smaller facilities (lower capital investments in facility and equipment and lower operating costs with fewer input materials).

Removing low-value, or non-value-add steps, like hold tanks and buffer tanks in a process, can reduce material, labor, and space requirements. In-line dilution systems and other mixing systems are one solution to removing buffer preparation equipment and space (Ram et al. 2023). Straight-through chromatography, where there are no additional holds or adjustments between serial chromatographic steps, can also reduce the number of buffers required and can potentially eliminate entire columns in a sequence (Crowell, Rodriguez et al. 2021; Vecchiarello et al. 2019).

Further reductions in process operations can be achieved by changing the host biology used to catalyze the conversion of raw materials into drug substance. Options for hosts were historically constrained without tools to characterize the product extensively or to engineer the cells. Today, these constraints have been removed with

deep analytical capabilities like mass spectrometry and genome editing/sequencing technologies. Cells have been engineered to produce human-like glycoproteins with commercially relevant titers (Ye et al. 2011). Aglycosylated antibodies, cytokines, growth factors, nanobodies, and AI-designed proteins are all well suited for alternative hosts. Conservative modifications to molecular sequences can also render them more host-agnostic (Yang et al. 2025). Advancing capabilities for alternative host cells would allow removal of viral filtration/inactivation steps and Protein A chromatographic steps (Coleman 2020), reduce the numbers of chromatographic steps (for non-mAbs) (Crowell et al. 2018), and reduce the facility infrastructure, material costs, and development time spent on those operations. Faster growth rates also reduce the cycle times in iterating on process development or clonal development (Brady and Love 2021). Leveraging the same advances in biotechnology accelerating drug development can benefit the manufacturing development as well (Dalvie, Brady et al. 2021). The benefits of the host extend well beyond the bioreactor, and they offer the single greatest (and most underdeveloped) "knob" to transform process intensity.

These combined features make it feasible to establish so-called "platform" processes for a multiplicity of non-mAb proteins like cytokines, nanobodies, Fc fusion proteins, vaccine subunits, and others. The reduced complexity of the overall process in turn makes predictive capabilities for process development possible, including relating protein sequences to process conditions (Crowell, Goodwine et al. 2021). More predictive and deterministic process development could reduce costs and time to the clinic. As an example, at the outset of the COVID-19 pandemic, we developed a new end-to-end process and generated phase-appropriate proteins for a subunit vaccine in 29 days from sequence to protein using the modular process development tools we had demonstrated in other examples (Dalvie, Rodriguez-Aponte et al. 2021). The technology transfer, however, was hindered by the global lockdown, highlighting one case where regional manufacturing could have facilitated fast response times (Brady and Love 2021).

Standardization

For agile manufacturing of a high mix of products, standardizing the manufacturing process is important. The same facility and equipment should accommodate different products with minimum reconfiguration. The consensus process for monoclonal antibodies relies on a standardized process, but not the facility and equipment. These elements are still adapted to the specific manufacturing company's needs or preferences. Today's biomanufacturing equipment is modular for individual operations but requires plant-level integration for control of a "mix-and-match" system. This arrangement allows a certain degree of flexibility in the configuration but adds costs for configuration, interoperability, and maintenance.

In contrast, foundries for semiconductor manufacturing use standardized equipment and processes with little or no customization to accommodate different designs or architectures. Given the variations in biological products (cells, proteins, mRNA, viruses), one can envision standardized "all-in-one" platforms designed "fit for purpose" to produce products within a class. For example, one biomanufacturing system for proteins could produce many different types of proteins from cytokines and hormones to vaccine components, nanobodies, and antibodies with only changes in the chromatographic resins employed (Crowell et al. 2018; Dalvie, Brady et al. 2021; Dalvie, Rodriguez-Aponte et al. 2021). There are now several emerging examples of such technologies for good manufacturing practices (GMP) use (table 1).

Fully integrated solutions designed for end-to-end production and closed bioprocessing would allow highly flexible facilities capable of multiple modalities. Such solutions also provide the opportunity to achieve true "walk-away" automation and remote monitoring or even control, reducing labor and overhead in operations. Technology transfer from one system to the next is also seamless when the system itself is standardized, much like biomedical devices or computers. Extending guidance for the FDA's Platform Technology Designation or Drug Master Files to include manufacturing systems designed and validated for a class of products could streamline the review of new applications and accelerate the use of innovative new manufacturing systems.

One perspective on standardization is to unify features like connectors or communication standards (Erickson et al. 2021). This effort is analogous to standards like USB for computers. There is relatively little financial incentive for large suppliers to freely adopt this approach, and it could harm innovation from start-up companies and innovators. To support a broad manufacturing base, establishing user requirement specifications for capabilities instead would allow for continued innovation of the form of the equipment itself and promote competition on other features (user experience, software).

TABLE 1 Summary of Emerging Manufacturing Systems for Different Classes of Biologic Products

Product Class	Entity	Stage of Development
mRNA	Quantoom Biosciences	Commercial-Stage Production Equipment for GMP
	Nutcracker Therapeutics	GMP Manufacturing Facility
Protein	Just / Evotec	GMP Facilities in US & Europe
	Sunflower Therapeutics	Commercial-Stage Bioreactors for GMP / Early-Stage Integrated Production System
	Stämm Bio	Early-Stage Bioreactor
Viral Vectors	Univercells Technologies / Donaldson	Commercial-Stage Bioreactors for GMP / Early-Stage Integrated Production System
Cell Therapies	Cellares	Commercial Services with Cell Therapy System
	Cellino	Clinical-Stage Systems
	Oribiotech Ltd	Early Access Systems

Examples could include types of host biology, equipment features (flow rates, sensor tolerances) and materials (USP Class VI), or order of operations. This type of competition exists in other sectors, including desktop printing and additive manufacturing, to help drive innovation for features and capabilities that improve the breadth and quality of products. Broadening the range of manufacturing systems while maintaining certain requirements for specifications would also help address concerns for single-source supply of a given solution.

Process Consolidation

A third area to enable more sustainable and intensified biomanufacturing solutions would take advantage of the intrinsic benefits of biological systems—namely their ability to create complex outputs from common inputs. Much of today's biomanufacturing practice has focused on controlling the complexity of biology to achieve a well-defined output (e.g., a monoclonal antibody). Cells, however, can produce multiple complex products at the same time, and naturally do so. For certain classes of products, simultaneous production of multiple components of the drug could reduce the number of campaigns or testing required.

One example is the contemporaneous expression and purification of a multivalent subunit vaccine using one host cell (Dalvie, Brady, et al. 2021). For a trivalent vaccine, this consolidation reduces the total number of campaigns required by threefold. For certain immunotherapy combinations in oncology or raw material generation for defined media for cell therapies, this type of approach could offer advantages over preparing each component individually. There is no regulation that prevents such an approach, and many less defined products are licensed (immunoglobulins from sera; attenuated vaccines). Advances in engineering biology offer the potential to add conditional controls to the cell lines to maintain relative expression levels.

Conclusions

The biopharmaceutical industry has achieved remarkable success both in terms of market growth and impact for patients. These successes have resulted from significant investments in time and thought by the people who have advanced the current manufacturing practices. The state of the world and the industry are changing rapidly, though. There is an increasingly urgent need to reconsider how to strengthen the biomanufacturing capabilities in the United States and abroad (NSCEB 2025).

Maintaining US leadership in this sector will now require true "leapfrog" innovations in manufacturing. In 1928, penicillin was discovered in the United Kingdom—a leader in science and technology innovation at that time. Manufacturing that critical medicine was outsourced to the United States with its significant capacity and knowledge on deep-tank fermentation and at-scale processing. The United States has held the economic benefits of biotechnology since then. Nearly four out of five US biotechnology companies now rely on manufacturing capacity overseas. The time and financial resources needed to reshore that capacity are significant and growing.

The technologies exist to develop a more robust biomanufacturing base that does not depend on centralized production with narrow supply chains to deliver new

medicines to patients. There are indeed challenges to realizing modular and distributed manufacturing with lower capital barriers for entry that are similar but different from those faced at the beginnings of this sector. Further development and partnership across academia, start-ups with innovative new technologies, industry, and regulatory agencies can begin to realize a new paradigm that provides broad access to these medicines and the ability to make them. A decision to not invest with haste in groundbreaking new biomanufacturing technologies and establish a distributed, resilient base is one the industry and country should soberly consider.

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The new era of creativity and diversity of treatment modality in the biopharmaceutical industry has accelerated the need to adopt new platforms.

Biopharmaceutical Manufacturing Platforms: Breaking Away from Our Past

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"Platform" is a term that is often used in the biopharmaceutical manufacturing industry, but with different connotations and intentions depending on whether the originator is from a regulatory authority or a biopharmaceutical company. The United States Food and Drug Administration (FDA) has had a long-stated goal of modernizing biopharmaceutical manufacturing and raising the level of technology to be more in line with that of other manufacturing sectors (Arden et al. 2021; Rantanen and Khinast 2015). The notable starting point for this modernization effort was the Quality by Design (QbD) initiative in the early 2000s (Woodcock 2004). QbD sought to achieve a different approach to pharmaceutical process development and manufacturing with a mutual goal for industry, society, and regulators being "*a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight*" (Yu and Woodcock 2015). QbD, as initially proposed, offered an aspirational opportunity whereby the traditional procedural approach to assuring compliance might be improved by demonstrating greater scientific understanding and incorporating more advanced approaches. However, achieving the QbD goal was left open to the interpretation of individual companies. As such, the biopharmaceutical industry never came to a common understanding of an end goal, and the opportunities associated with QbD were incompletely realized.

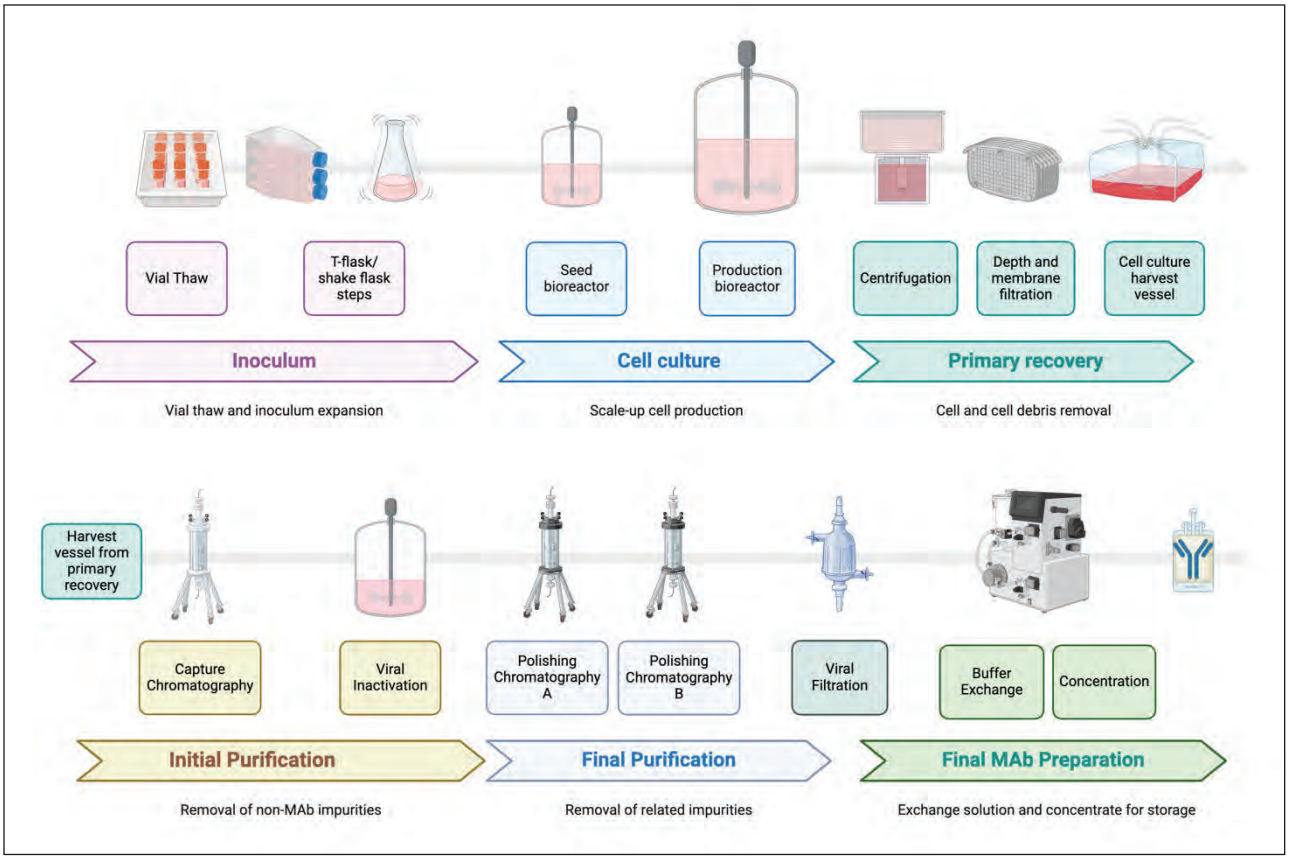

FIGURE 1 Standard manufacturing platform for generating MAbs. The arrow blocks represent major processing steps and their intended purpose. The icons depict standard pieces of equipment typically used in this platform. The process begins with inoculum and follows the arrow direction.

Since that time, the FDA has continued to issue new guidances associated with approaches to biopharmaceutical manufacturing modernization (Collins 2018). Guidances dealing with the term "platform" were very recently issued, with a guidance on advanced manufacturing technologies (AMTs) (FDA 2024a) and the platform technology designation program (FDA 2024b). In the latter guidance, the FDA describes a platform technology within the specific manufacturing context as a "well understood and reproducible technology" that "facilitates the manufacture or development of more than one drug through a standardized production or manufacturing process or processes." The term "designated platform technology" is used by the FDA when a newer AMT (or other existing technology not in the AMT program) has been deemed to meet the "well understood and reproducible" requirements associated with their designated platform program. Platforms, therefore, from a regulatory perspective, are typically associated with efforts to improve pharmaceutical manufacturing efficiency and robustness, and they should reduce the need for regulatory oversight—in keeping with the goals for QbD.

From an industry perspective, platforms may often be conceived as unit operations defined by pieces of equipment along with the instrumentation and computer automation necessary to control them. An excellent example of a well understood existing platform is the one by which most monoclonal antibodies (MAbs) are made. Figure 1 is a simplified representation of a standard MAb manufacturing platform. While some companies may use slight derivations of the operations shown here, the major purposes of this platform are ubiquitous in the biopharmaceutical industry:

- Thawing of frozen mammalian cells and inoculum development
- Production bioreactor and MAb expression
- Primary recovery and cell removal
- Capture chromatography for initial impurity removal
- Polishing chromatography for final purification

- Viral filtration
- Buffer exchange and concentration to render the active ingredient

Over 100 MAbs now have been approved and matriculated into the marketplace (Mullard 2021), with the overwhelming majority utilizing the above-described platform or a reasonably close facsimile (Pluschkell et al. 2025).

Platforms are also useful to businesses for ensuring quality: Familiarity with equipment and similarity of process across products increases experience in manufacturing operations. Looking back at figure 1, a MAb process making an oncology product looks a lot like a MAb process making a diabetes product—the difference is the DNA *inside* the cell, with a few process condition changes to account for the specific generated molecule. The equipment associated with the cell culture platform through to the final active ingredient remains largely the same. Training across products is largely the same, allowing for excellent reproducibility in manufacturing execution.

Having a clear and common vision of future success for biopharmaceutical manufacturing platforms is key.

Platforms are therefore best viewed as *business constructs* for biopharmaceutical manufacturers—an approach to maximizing capital investment by utilizing the same equipment over and over to minimize cost while maintaining flexibility with suppliers and partners similarly invested in the platform. However, the investment made in these industrial platforms over years of use de-incentivizes new platforms, as new platforms require large capital investments. New processing platforms likely require a greater degree of technical explanation in regulatory filings to ensure authorities are comfortable that product control strategies will be reliable (Algorri et al. 2022; NASEM 2022). Increased effort, complexity, and risk in regulatory filings and manufacturing site inspections tend to be viewed negatively. Displacing existing platforms for ones that are newer and more technologically advanced is thus bad for business. And if existing platforms can be massaged to produce new products, why should they be changed?

Inflection Point: The Challenge of New Treatment Modalities

The aspirational QbD initiative was conceived in a time when MAbs and small molecules dominated the pharmaceutical landscape, and, as such, established manufacturing platforms were available to service these two broad classes of modalities. While displacing these platforms with improved technology may have been an FDA goal, timing was poor in that the incumbent platforms had demonstrated their utility. In the 20+ years since, the promises associated with decoding the human genome are being seen in biopharmaceutical R&D portfolios. Peptides, oligonucleotides, and other genetic medicines have proliferated (Davies 2013; Matsuyama et al. 2023). Carrier molecules such as lipid nanoparticles have been designed for the purpose of delivering these new molecules to their intended target if the molecule alone cannot (Hammond et al. 2021). Concurrent with the proliferation of these new treatment modalities and delivery vehicles is a new creativity in how these might be combined for patient benefit. These combination molecules pose interesting platform challenges and choices as they combine features seen in both chemical synthesis and biotechnology, such as the carrier-linker-drug options shown in figure 2.

One example of these conjugates is the antibody-drug conjugate (ADC) in the figure 2 inset, which is the combination of an antibody, a synthetic linker, and a cytotoxic payload—a molecule that targets a cancer cell with the antibody portion and releases the cytotoxic payload into that cell. In considering how to make an ADC, it can be broken down into its parts—MAb, linker, and synthetic payload—and the individual components made through existing platform approaches. Combining the three elements of the ADC creates some platform challenges, such as ensuring that appropriate chemical conjugation conditions can be maintained in a biologics facility. With some minor modifications to existing equipment and added processing inefficiency, it is likely that a molecule such as an ADC can be made in existing platforms. However, when the multitude of potential combinations illustrated in figure 2 are considered, it should be expected that future conjugate structures could include a MAb, peptide, or alternative targeting structure with any number of linked payloads such as oligonucleotides, radionucleotides, or carriers containing payloads (Grairi and Le Borgne 2024; Lindberg et al. 2021; Wathoni et al. 2022). Can the entire array of creative new potential molecular entities be accommodated by existing platforms? What is the value of new versus retrofit?

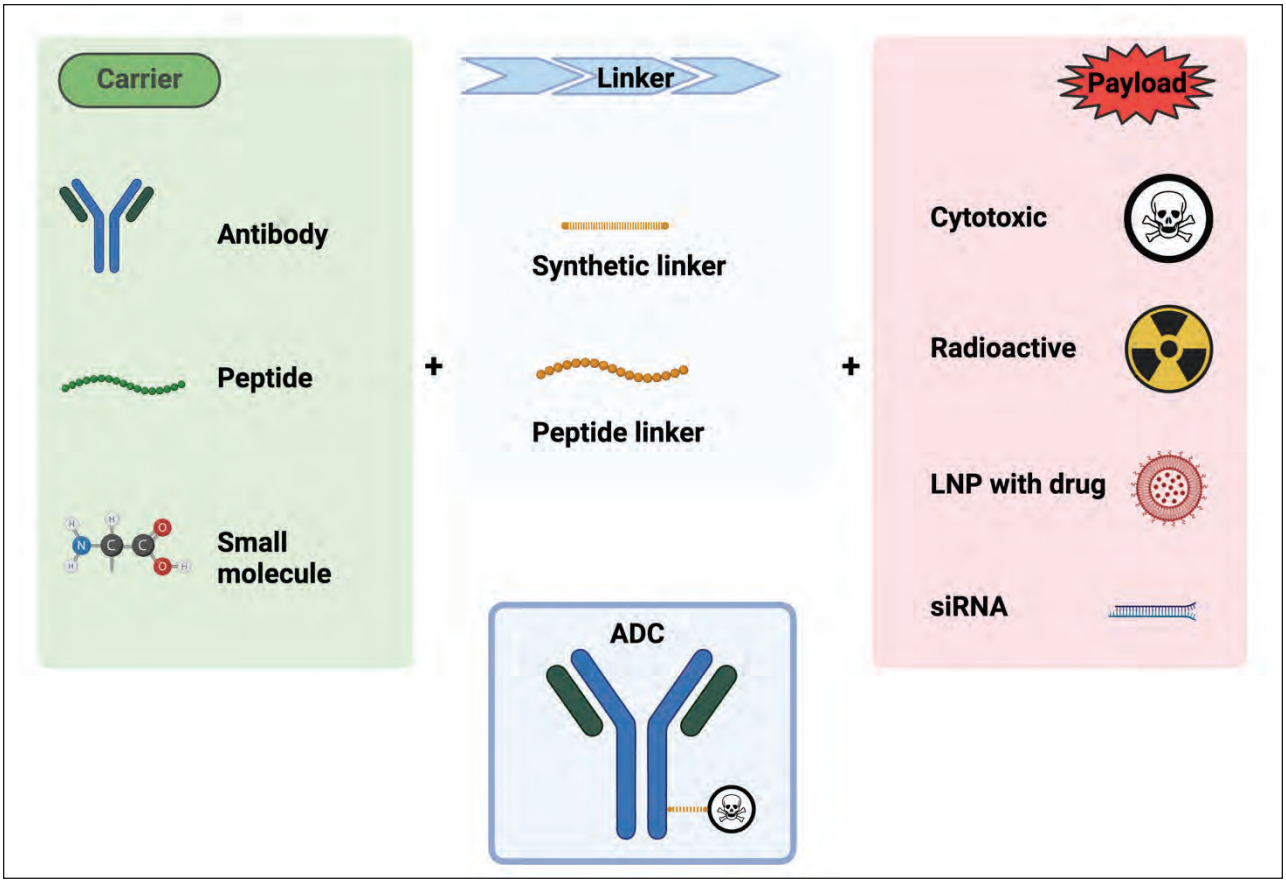

FIGURE 2 A simplified look at potential biopharmaceutical molecules that can be created with a variety of carriers, linkers, and payloads. The inset picture (ADC) is the combination of an antibody, synthetic linker, and cytotoxic payload.

Peptide synthesis provides an interesting angle from which to view the importance of the platform decision. Peptides are an important molecular approach to treating disease, with insulin perhaps being the best-known example. But outside of insulin and the tremendous effort to synthesize and purify it over 100 years ago, the synthesis of peptides has only become a major biopharmaceutical manufacturing need in the last 10 years (Thayer 2011). The breakthrough approach for peptide synthesis was discovered in the 1960s (Stawikowski and Fields 2002). Solid-phase peptide synthesis (SPPS) was the term given to the synthetic approach, and this approach provided the ability to generate any peptide given knowledge of its amino acid sequence. SPPS is effective and powerful as a technique but unfortunately not efficient from an environmental/sustainability perspective (Andrews et al. 2021). For many years, producing even one kilogram would have been incredibly unusual for SPPS, and it was likely never an approach intended for multi-metric tonnage needs (Thayer 2011). Nevertheless, the SPPS platform has become established and increasingly available in the contract manufacturing marketplace (Brooks 2024; CDMO News 2024; Vecchione 2023).

Scaling SPPS to fulfill the high-volume needs associated with the incretin peptides now utilized for diabetes and related metabolic disorders has led to the inadvertent establishment of a technically inefficient manufacturing platform that lacks agility and environmental sustainability. This occurred because the industry was caught without a better large-scale alternative at a time when world peptide needs exploded. Other approaches to generating peptides do indeed exist. Biological methods can be utilized to manufacture peptides, and they offer opportunities with regard to reduction of solvent usage and beneficial economics, particularly at larger scales (Du et al. 2022; Enninful et al. 2024). As such, biological systems could, and should, represent an excellent manufacturing platform. Yet, cell expression systems require engineering to facilitate the production of peptides containing unnatural amino acids, and subsequent engineer-

ing would be needed for new unnatural amino acids. This is theoretically possible to accomplish but would require an industry-level focus on this potential platform to enable it to compete with the incumbent SPPS platform. Replacing SPPS with potentially more desirable platforms will be difficult to achieve, regardless of the benefits associated with doing so.

The reality is that the perception of risk must be lowered to encourage the creation and implementation of new platforms.

The speed with which non-optimal, yet existing, approaches such as SPPS have been scaled and adopted, combined with the industry aversion to implementing newer platforms, speaks to the lack of patience in the industry for manufacturing groups to adapt to the changes in molecular structure or to invest in more technically efficient approaches to generating material. The pressure placed upon biopharmaceutical companies' CM&C units to keep pace with molecular creativity will result in the propagation of existing platforms that are not technically, environmentally, or economically efficient. Having a clear and common vision of future success for biopharmaceutical manufacturing platforms is key. If we do not achieve this common vision, it is likely that, just as in the case of QbD, success will be defined in multiple, individual ways—none of which truly advance the goals of efficiency, agility, or flexibility, and most of which will not enable reduced regulatory oversight.

Recommended Path Forward

"Perception is reality" is an aphorism that holds particularly true in the regulated pharmaceutical manufacturing industry. Despite regulatory agency encouragements over 25 years to innovate new manufacturing platforms, the perception remains that great risk is associated with doing so (Collins 2016; Pluschkell et al. 2025). The reality, therefore, in the pharmaceutical manufacturing industry, is that the perception of risk must be lowered to encourage the creation and implementation of new platforms. Public-private partnerships and consortia, such as the National Science Foundation Engineering Research Centers (NSF 2025) and the National Institute of Standards and Technology Manufacturing Institutes (NIST 2025), have long been utilized in the United States as an attempt to strengthen competitiveness in the global marketplace. Yet, it is difficult to point to broad implementation of biopharmaceutical manufacturing platforms identified from such efforts.

The reason for this is likely rooted in the typical consortia structure itself. Most consortia models tend to receive their inputs from member entities. As such, they receive a large number of different inputs based on the interests/ideas/preferences of individual partners. Consolidating sets of differing member tactics into a mutually agreeable strategy is always difficult, and output from these efforts tends toward very incremental improvement. A different approach is needed to make step-change advances, and the question becomes how best to foster this. Companies may well discover that in the realm of new modalities, they are independently creating similar new technologies and taking similar approaches. As their commonalities are discovered, these similar approaches could be generalized into a consensus platform for the industry. This approach would be effective, but it does require a desire to collaborate and share without a formal interaction structure. It is also an approach that is likely to have a similar trajectory to that of the QbD initiative, yielding more incremental progress due to its more serendipitous nature.

Proactively bringing together stakeholders to embrace a desired future is more likely to transform the industry in a shorter period. The role of public-private partnerships currently utilized to generate excellent *ideas* for the industry simply needs to be modified to reach a more tangible endpoint. Manufacturing USA and the national institutes underneath that banner are comprised of member companies from industry and academic research groups, and they have intimate connections to government agencies. Such a collaboration is structurally well-suited for a heavily regulated manufacturing industry needing improved technology and provides a way to defray the perceived regulatory filing risk associated with change.

The National Institute for Innovation in Manufacturing of Biopharmaceuticals (NIIMBL) has developed a good understanding of current trends, future needs, and challenges associated with biopharmaceutical manufacturing (Pluschkell et al. 2025). The next logical step is to play a proactive role in helping industrial partners implement platform change. The US FDA has offered an intriguing opportunity in the establishment of their guidelines

around manufacturing platforms. More important, however, would be the purposeful connection of these guidance documents. How might we not only rapidly generate AMTs but intentionally progress them to designated platform status? The role of institutes such as NIIMBL could be key to the success of such an endeavor. Establishing the future vision of biopharmaceutical manufacturing platforms and associated AMTs, and prioritizing which become designated platforms should optimally be done through these institutes for the benefit of the entire sector.

A critical part of the vision needed to benefit all manufacturers is the concept of open-source technology. While open-source is an understood concept in the software industry, it is not in pharmaceuticals. Particularly within the branded-manufacturer space, intellectual property and patenting are incredibly important. Of the multiple types of patents available, the composition patent, which describes the components of the medication, is the primary patent in terms of value to the innovator biopharmaceutical company (Gurgula 2020). Patents associated with how medications are manufactured are secondary patents and are often referred to as "methods" patents. Methods patents have lesser value than primary composition patents and are also much more difficult to establish (Price and Rai 2019; Rai and Price 2021). If the biopharmaceutical industry can agree that such method patents are not worth pursuing, then perhaps the time has arrived where we can agree that our primary area of competition is on the molecule alone. If this sort of understanding could be gained, a new type of pre-competitive collaboration might be achieved, one that would enable the acceleration of new technology platform integration. Ideas for this type of collaboration might be found in examining these two quoted sections from the platform designation guidance:

- "A different sponsor may also be able to leverage platform technology data if they receive a full right of reference to the leveraged data under a business arrangement with the originator of the platform technology."
- "Leveraging data from a prior product that used the designated platform technology, such as leveraging batch and stability data from a related product as prior knowledge that can supplement product development studies."

Could NIIMBL or an equivalent institute perform the role of receiving the full right of reference on behalf of all their member companies? Could NIIMBL or an equivalent institute own member company data in a way that allows prior knowledge to be shared across member companies? This type of collaboration is possible, given some appropriate guardrails are in place, if manufacturers can agree that they really don't derive financial benefit through owning new manufacturing platform technologies. Having a central entity steer the usage of platform-derived data across companies and gaining the buy-in of regulatory agencies would defray the real and perceived risk of doing something new. Some biopharmaceutical companies, particularly those filing newer modality molecules, will struggle with the perception that they might be giving up valuable IP and therefore not participate in the effort. However, there will be those that do participate, and the "coalition of the willing" will generate change for others to ultimately follow. Without an approach such as this, incumbent manufacturing platforms in the biopharmaceutical industry will be difficult to displace, and the level of technical and economic efficiency associated with them will continue to degrade as the complexity of new molecules increases.

A new era of treatment modality creativity and diversity is upon our industry, and the need to adopt new platforms has been accelerated.

Conclusion

Incorporating new and superior technologies into biopharmaceutical manufacturing platforms has been a goal of the US FDA for nearly 25 years. While this goal is not new, a new era of treatment modality creativity and diversity is upon our industry, and the need to adopt new platforms has been accelerated. Advanced manufacturing technologies and the platforms that will derive from them are the right approach to modernizing this sector. Achieving a state where advanced manufacturing technologies can be developed, matured to designated platform status, and implemented broadly within the biopharma sector will require a shift in how the process of change is implemented. A clear vision of success is needed in the very near future, and collaborative, centralized groups that represent industry, academia, and government must cement that vision and then outline a clear roadmap to implementation.

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The NIST Biomanufacturing Program has made significant progress in antibody manufacturing and provides an approach to analytical measurements that can expedite the time to market of life-saving products and enable broader access to them.

NIST Biomanufacturing Reference Materials: Development, Applications, and Impact

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Monoclonal antibody (mAb) therapeutics, currently the largest and most successful biologic platform, harness the naturally evolved specificity of adaptive immunity to treat a variety of conditions such as cancer, autoimmune disorders, and infectious diseases (Kelley 2024). MAbs are complex, multidomain proteins with post-translational modifications (PTMs), including N-glycosylation, at a single site that can play a particularly important role in determining drug safety and efficacy (Schiel et al. 2014). These therapeutics are manufactured

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using highly controlled bioprocesses that typically employ mammalian cells such as Chinese hamster ovary (CHO) or non-secreting murine myeloma as the production host (Kelley 2009; Li et al. 2010). During drug development, manufacture, formulation, and product release, a wide variety of analytical technologies are used to characterize mAb therapeutics and the processes used in their manufacture (Schiel et al. 2014; Schiel et al. 2015a; Schiel et al. 2015b). These methods are used to measure the critical quality attributes of a drug product related to its identity, purity, stability, potency, and safety and the critical process parameters in the manufacturing process. Due to their large size and the nature of cell-based production, mAbs, like other protein-based therapeutics, are inherently complex, heterogenous products—defined by determined acceptable ranges of variance in measured critical quality attributes and critical process parameters (as described in guidelines developed by working committees of the International Conference on Harmonization, e.g., ICH5, ICH6, and ICH8) that correlate to performance of the therapeutic in clinical application (Schiel et al. 2014).

Around 2010, with the approaching patent expirations of the first innovator biologic medicines, it was recognized that reference materials (RMs) to support advances in the state-of-the-art in analytical and biophysical methods would benefit both innovator companies developing new medicines and emerging companies developing biosimilars, which are highly similar but not generic versions of biologic innovator drugs (Kozlowski 2009). At this time, it was also recognized that the National Institute of Standards and Technology (NIST), working with industry and regulatory authorities, could assist in establishing a measurements and standards infrastructure to support a science-based regulatory path for bringing follow-on biosimilar therapeutics to the market.

In response, the NIST Biomanufacturing Program (https://www.nist.gov/biomanufacturing) was initiated in 2012 to address infrastructural measurement science problems and biopharmaceutical standard needs to support the development and manufacture of biologic medicines, with a focus on advancing state-of-the-art measurement science RMs, and standard reference materials (SRMs) that could support the development and manufacture of mAb therapeutics. NIST, a non-regulatory US government agency, cannot compel adoption of methods or technologies arising from its measurement science program nor the use of its RMs, so it relies on extensive stakeholder engagement and feedback to gain community consensus. Through such outreach, NIST identified broad infrastructural measurement challenges faced by the biopharmaceutical industry in mAb development and manufacture. NIST has worked to address these measurement challenges and foster innovation by leveraging pre-competitive collaborations and data sharing across academic, government, and industry stakeholder groups that are enabled by the availability of open access, publicly available RMs (figure 1). An example of the unique niche that NIST fills in supporting the biopharmaceutical ecosystem of the bioeconomy will

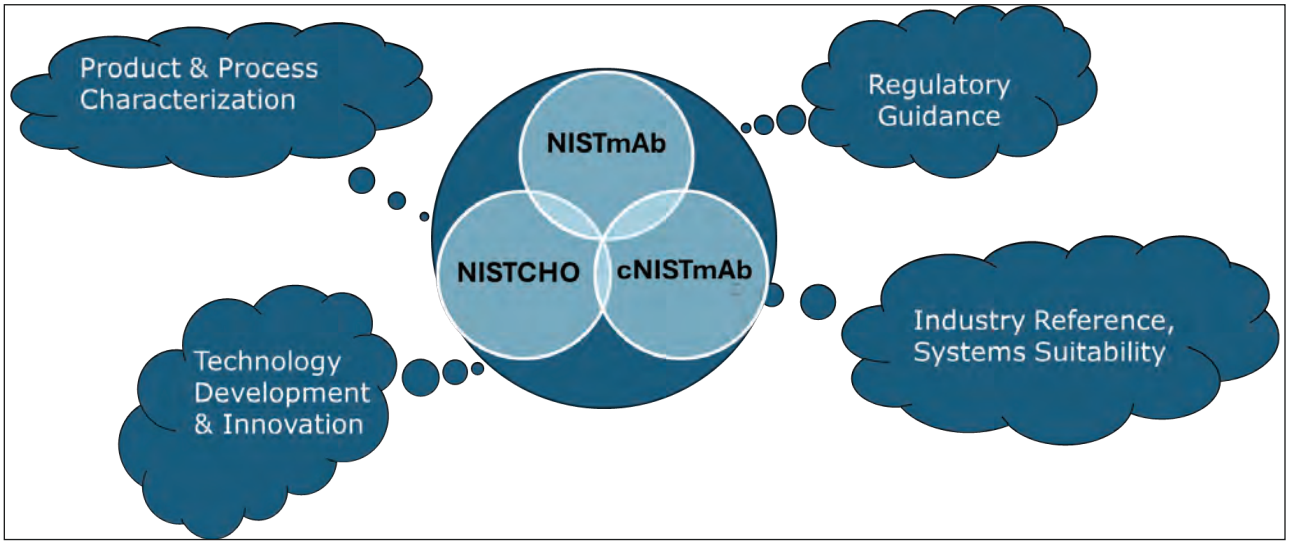

FIGURE 1 Examples of stakeholder value that can be provided by well characterized, widely available, accepted biomanufacturing reference materials in supporting commerce and innovation.

be described in terms of three novel biopharmaceutical RMs (RM 8671 NISTmAb, RM 8675 NISTCHO, and RM 8672 cNISTmAb) and related measurement science and technology innovation that has been enabled by the availability of these standards (Cleveland et al. 2025; Dahodwala et al. 2025; Mouchahoir and Schiel 2018; Schiel and Turner 2018; Schiel et al. 2018; Turner et al. 2018; Turner and Schiel 2018; Yandrofski et al. 2022; Yandrofski et al. 2023).

NIST Biomanufacturing Reference Materials

Biopharmaceutical companies typically rely on in-house reference standards, derived from well-characterized lots of drug products, to establish product-specific specifications when developing new drugs. These in-house standards, together with challenge materials typically derived from controlled physical or chemical degradation of drug products, are used for analytical method qualification and validation. While these materials serve an essential role in product-specific mAb drug development and lifecycle management within a pharmaceutical company, in-house standards are often limited in broader use in the evaluation of analytical methods and for collaborative studies due to intellectual property limitations. Additionally, while commercial mAbs can, in principle, be used as standards since they are stable and well characterized, the industry does not normally make data used to characterize these therapeutics publicly accessible. A publicly available, well-characterized mAb RM addresses these limitations and provides the biopharmaceutical stakeholder community with a unique resource.

The proprietary nature of commercial mammalian cell-based manufacture of mAb therapeutics also severely limits sharing of industrial cell lines and a company's internal process knowledge and data. As described for the drug product standards, it was recognized that a publicly available, well-characterized reference production host cell line, representative of a CHO host cell used by the industry for mAb manufacturing, would greatly benefit the biopharmaceutical stakeholder community. This tool allows evaluation of all aspects of the processes, methods, and instruments used in controlled commercial biomanufacturing. This living cell RM can also be used in collaborative, pre-competitive studies and benchmarking of new bioprocess technologies, including new continuous and process-intensive manufacturing methods, cell culture media, process analytical technologies, and other technologies used in upstream and downstream processes employed in the manufacture of mAbs.

NIST's Approach to Biomanufacturing Reference Material Development

Under the NIST Biomanufacturing Program, NIST has focused on the development of RMs that can be used for ensuring that analytical methods for mAbs provide consistent results across methods and labs. NIST also anticipates that its RMs may be used to benchmark emerging analytical technologies, thus accelerating the development and adoption of new and advanced analytical and biophysical methods needed to address the unique challenges of characterizing these complex and heterogeneous protein-based drugs.

To identify and establish broad consensus around the development of mAb and CHO RMs, NIST extensively engaged stakeholders (industry, regulatory and other government agencies, and academic institutions) through workshops, roundtables, and other forums. Once a decision was made to pursue these RMs, NIST faced an immediate challenge of sourcing an appropriate, stable material in the amount required for developability into a NIST RM that would be available for wide distribution over many years to the stakeholder community.

A publicly available, well-characterized mAb reference material addresses these limitations and provides the biopharmaceutical stakeholder community with a unique resource.

In this respect, NIST has benefited from partnerships with industry stakeholders who have provided typical industry materials through material transfer agreements. In the case of NISTmAb, NIST received a pharmaceutical-grade mAb drug substance through a material transfer agreement with MedImmune (now AstraZeneca) for the expressed purpose of its development into RM 8671 NISTmAb. For NISTCHO, MilliporeSigma and the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) partnered with NIST to develop an industry-relevant,

open-access CHO cell line with limited constraints that expresses a mAb with the same primary sequence as the NISTmAb, referred to as cNISTmAb. The NISTCHO cell line produced by MilliporeSigma was transferred to NIST through a material transfer agreement for development into RM 8675 NISTCHO. For cNISTmAb, NIST has a contractual agreement with MilliporeSigma to manufacture cNISTmAb (expressed from NISTCHO) for transfer to NIST for development into RM 8672, cNISTmAb, a complementary monoclonal antibody RM to RM 8671 NISTmAb. Through its ability to distribute candidate RMs, unencumbered by intellectual property restrictions, with stakeholder communities, NIST is able to use crowdsourcing as an approach for characterization of these materials through pre-competitive, collaborative interlaboratory studies.

These studies generate deep characterization data on each material, including information on stability and homogeneity, and establish fit-for-purpose uses for the RM. For NISTmAb, the initial crowdsourcing approach yielded extensive characterization data on primary structure, PTMs, higher-order structure, and biophysical properties that were described in a series of articles that were compiled into a three-volume American Chemical Society book series (Schiel el al. 2014). NISTmAb, NISTCHO, and cNISTmAb, like all NIST RMs, are designed to be fit for an intended use and determined to be sufficiently homogeneous and stable by assigning non-certified measurement values and uncertainties (Beauchamp et al. 2020). A RM information sheet (NIST 2023) includes these values and is distributed with each unit of the RM, which is sold on a cost recovery basis through the NIST Office of Reference Materials or through certified third-party distributors.

NISTmAb (RM 8671): An IgG1κ Antibody Standard

In 2016, NIST took its first step in introducing biopharmaceutical standards to the public when it released the first of its kind IgG1κ monoclonal antibody RM, RM 8671 NISTmAb. NISTmAb was an ideal candidate for development into a RM to fill the need for an industry-wide test material for analytical method control and evaluation of the performance of emerging technologies used to characterize critical quality attributes of mAbs. Among classes of mAb biotherapeutics, the IgG1κ subclass and allotype is the most prevalent in both clinical use and development. In addition to meeting the requirements for establishing a NIST RM, a biopharmaceutical industry-like approach to characterization and life-cycle management was used in the development of the RM 8671 NISTmAb material (Turner and Schiel 2018). The initial characterization of the material (Schiel et al. 2014) was performed on a single production lot, NISTmAb Primary Sample 8670, which is now held in reserve as the NIST in-house primary standard. Additional lots of the material were pooled, homogenized, and vialed at 10 mg/mL as RM 8671 NISTmAb (Schiel and Turner 2018). RM 8671 NISTmAb was found to be homogeneous and stable and assigned non-certified values using test methods (e.g., UV, SEC, CE-SDS, CZE, and DLS) qualified by NIST and representative of industry best practices (Schiel et al. 2018; Schiel and Turner 2018; Turner et al. 2018). As with all NIST RMs, a stability verification is performed every five years to evaluate homogeneity and stability by repeating the qualified methods used for initial value assignment to demonstrate that the assigned values still fall within the originally reported limits of uncertainty. The first renewal of RM 8671 NISTmAb was carried out in 2020 (Yandrofski et al. 2023), and the second is currently underway in 2025.

NISTCHO (RM 8675): Clonal CHO-K1 Cell Line Producing cNISTmAb (RM 8672)

Building upon the experience of NISTmAb as an industry-representative standard, two new complementary RMs are currently being developed under the NIST Biomanufacturing Program: (1) NISTCHO, a first-of-its-kind, open-access living RM, a CHO-K1 producer of a non-originator NISTmAb, and (2) cNISTmAb, the non-originator product expressed by NISTCHO. A reference CHO host cell line that could be used as a general reference for product manufacturing was identified by engaging the community through the NSF Industry-University Cooperative Research Center Advanced Mammalian Biomanufacturing Innovation Center as a highly desirable RM for NIST to develop. Furthermore, it was recognized that it would be of value to link the CHO host cell RM to the well-characterized NISTmAb RM. Thus, the NISTCHO RM 8675 was engineered to express the same amino acid sequences as the heavy and light chains of the NISTmAb RM 8671.

To inform the development of RM 8675 NISTCHO, NIST released a research-grade test material (i.e., a candidate RM material) to the public in 2023, which was quickly taken up for use by early adopters who provided feedback to NIST on use cases and its fit-for-purpose. Following industry best practices, NIST contracted the production of a master and working cell banks for the

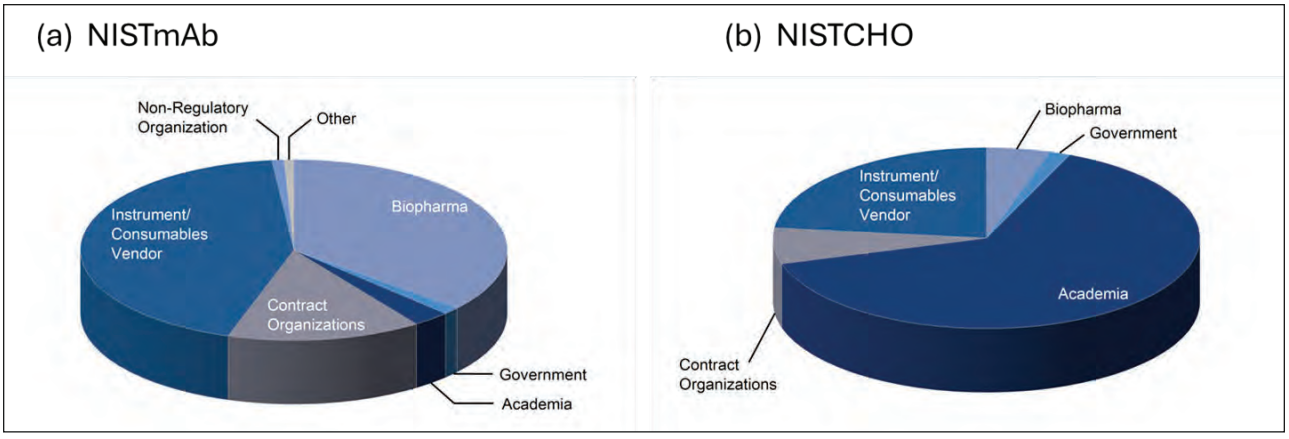

FIGURE 2 Stakeholder update of NIST biomanufacturing reference materials based upon sales and distribution metrics from the NIST Office of Reference Materials: (a) NISTmAb and (b) NISTCHO.

NISTCHO, the latter of which would then be developed by NIST into RM 8675 NISTCHO, to the contract research organization Eurofins Lancaster Laboratories to be produced under good manufacturing practices conditions. The development and initial characterization of the NISTCHO material followed industry practices and norms for clonal selection, genetic stability, and high titer (Dahodwala et al. 2025). The assigned values for NISTCHO will be based on the copy number ratio of the mAb genes (heavy chain, light chain) and integration sites to known CHO genes using digital PCR.

NIST is also developing RM 8672 cNISTmAb based on the IgG1k monoclonal antibody expressed by NISTCHO. This RM is a companion to RM 8671 NISTmAb that will have assigned reference values and be maintained through a life-cycle management system that mimics industry best practices similar to those used for NISTmAb. As the cNISTmAb is produced in CHO cells, it has distinguishing PTMs, such as glycosylation (Luo and Zhang 2024), as compared to the original RM 8671 NISTmAb that was produced in non-secreting murine myeloma cells. Having this RM provides direct coupling of process to product using the predominant industry production host CHO cell, as well as a close comparator molecule with distinguishing PTMs relative to the original NISTmAb RM.

Applications of NISTmAb, NISTCHO, and cNISTmAb

The NISTmAb, NISTCHO, and cNISTmAb RMs are used by stakeholders (figure 2) in a variety of applications, including serving as a system suitability sample, establishing method or instrument performance, bridging analytical test methods, and assisting in method qualification. NISTmAb, which has been available to the public for almost 10 years, has been used extensively to evaluate the best practices and develop innovative analytical technologies. Based on NIST Office of Reference Materials sales over this time, we find that biopharmaceutical companies and analytical instrument vendors make up more than 50% of the stakeholder uptake for NISTmAb. Roughly a third of the distributed material is used by mid-to-major biopharmaceutical companies as a method performance standard to support implementation of analytical assays for characterization of mAb products and to monitor analytical and manufacturing processes to ensure consistent product quality and safety. Moreover, NISTmAb is used by biopharmaceutical companies as a method performance standard to ensure quality and consistent manufacturing of mAb products, including use as a test material for development of physicochemical characterization and methods, a system suitability standard, and an analytical cross-check material when a test method deviation is observed. Approximately 20% of distributed NISTmAb is used by analytical instrument vendors to benchmark the performance of new analytical technologies and methods that have been described in application notes and patent applications. To date, NIST has been featured or used in over 100 application notes by instrument vendors. Instrument vendors and others have also used NISTmAb in over 130 US patent applications to demonstrate the performance of new analytical methods and technologies.

NISTCHO is currently scheduled to be released as RM 8675 by summer 2025. During its release as a research-

grade test material, NISTCHO was used as a test material to demonstrate process analytical methods, downstream purification methods, and emerging bioprocess workflows, such as continuous manufacturing and process intensification strategies. Additionally, NISTCHO has been widely used by community colleges and other educational institutions for use in the development of workforce training programs that will provide students with the unique opportunity to gain laboratory experience with a CHO production host cell line that is representative of current industry standards (Fredericks et al. 2024; Nadour et al. 2024).

As the biopharmaceutical industry trends towards using other platform-based approaches, such as mRNA and cell and gene therapy products, in developing new therapeutics, there will be opportunities for NIST to follow a similar path to provide reference materials to the community for use in advancing these emerging modalities.

As previously mentioned, NIST biomanufacturing RMs also enable collaborative, precompetitive research studies between academic, industry, government, and regulatory agencies. For example, NISTmAb has found wide use in interlaboratory studies (Yandrofski et al. 2022) of current and emerging analytical technologies, including studies of two-dimensional nuclear magnetic resonance (2D-NMR) (Brinson et al. 2018) and hydrogen-deuterium exchange mass spectroscopy (Hudgens et al. 2019) for higher-order structure analysis, the multi-attribute method for detecting PTMs (Mouchahoir et al. 2021), and glycosylation analysis using different analytical methods (De Leoz et al. 2020). Interlaboratory studies are designed to provide important insights into the current state-of-the-art performance and variability of analytical methods between different methods, instruments, operators, or sites. Results from these studies serve to promote harmonization and best practices and reveal potential limitations in analytical instrumentation and methods. Lastly, these community exercises support benchmarking and foster collaboration across the stakeholder community to promote adoption of emerging measurement technologies. With the more recent availability of NISTCHO and cNISTmAb, we anticipate that these RMs will be used similarly to NISTmAb and expand the type and scope of interlaboratory studies that can be carried out to address broad infrastructural measurement challenges faced by industry. Importantly, the use of publicly available, non-intellectual-property-constrained materials like NISTmAb, cNISTmAb, and NISTCHO in these studies allows free exchange of materials and data sharing among participants.

Conclusions

Well-characterized, industry-representative materials like the NISTmAb, NISTCHO, and cNISTmAb form a complementary set of RMs that can benefit the entire biomanufacturing research community and help drive progress across the field of manufacturing of biopharmaceutical products by underpinning quality measurements that support an accelerated time to market and broader access to these life-saving drug products. These RMs can serve broad purposes including support for the evaluation and adoption of new analytical technologies, applications in method development and performance evaluation, and roles in fostering community collaboration through inter-laboratory studies and workforce development. In addition to the mAb and CHO RMs, additional RMs have been developed under the NIST Biomanufacturing Program to meet the specific needs of the industry, such as protein glycosylation and glycan analysis (SRM 3655, Glycans) (Lowenthal et al. 2022) and aggregated proteinaceous particle measurements (RM 8634, Ethylene Tetrafluoroethylene for subvisible particles [Ripple et al. 2019]) and SRM 1989 for visible particles (Telikepalli et al. 2025). The success of the NIST Biomanufacturing Program and RM development stems from the convening power of NIST to unite diverse stakeholders with varied perspectives and expertise to establish community consensus. NIST also benefits from its stakeholder community

through candidate material donations and in-kind donations of time and resources to crowdsourcing exercises for material characterization and other interlaboratory collaborative studies. This public-private partnership and the generous participation of scientists and experts from industry, academia, and other government agencies have been invaluable to NIST's mission to develop RMs and advance measurement science for biopharmaceutical products and manufacturing.

Taken together, NISTmAb, NISTCHO, and cNISTmAb provide a roadmap for how platform RMs are developed and widely disseminated through stakeholder engagement and can find broad application in biopharmaceutical development and manufacturing. As the biopharmaceutical industry trends towards using other platform-based approaches, such as mRNA and cell and gene therapy products, in developing new therapeutics, there will be opportunities for NIST to follow a similar path to provide RMs to the community for use in advancing these emerging modalities.

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A promising model for gene therapy development is outlined that supports a thriving gene therapy community and increases access to therapies, particularly for patients with rare and ultra-rare diseases.

An Open-Access Platform: A NIIMBL Approach to Gene Therapy for Rare Diseases

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Developing gene therapies for rare diseases faces significant challenges, including high costs, lengthy timelines, and the specialized expertise required for technical drug development and manufacturing. Small biotech companies, academic institutions, and philanthropic groups often lack the resources to bridge the gaps

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between diagnosis and therapy development. At the same time, market potential may be questioned by the for-profit pharmaceutical industry. These barriers disproportionately affect the rare disease community, limiting the development pipeline for life-changing therapies.

To attempt to address some of these challenges, the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) has launched an initiative to develop an open-access adeno-associated viral vector manufacturing and analytical platform. This program brings together academic and industry partners to develop scalable solutions derived from their experience developing gene therapies. The platform is designed to be modular and pre-competitive, allowing for adaptation for novel gene therapies while remaining accessible to non-profit and academic research organizations with limited budgets.

Gene therapy represents a groundbreaking approach that has the potential to overcome the limitations of conventional treatments by providing targeted, sustained, and potentially curative interventions.

By leveraging the expertise and infrastructure of the for-profit genetic medicine sector, the Viral Vector Manufacturing and Analytics Program seeks to create a platform that is flexible and scalable for immediate clinical applications and facilitates long-term product development. It is hoped that success in this endeavor will be part of establishing a sustainable economic model to transform philanthropic funding into strategic investments, reduce barriers and accelerate drug development, and ultimately address the unmet needs of patients with rare and ultra-rare diseases.

Introducing Gene Therapy: A Groundbreaking Approach

Genetic medicine has emerged as a groundbreaking approach for delivering lasting and potentially curative benefits for countless debilitating diseases. Conventional therapies—from over-the-counter small molecules to biologics administered at the hospital bedside—often fall short due to issues of imprecise biodistribution, short molecular half-lives, and the need for repeated treatments in the case of lifelong afflictions. In contrast, gene therapies work by providing genetic instructions that enable the body's own cells to continuously produce therapeutic molecules, leveraging the inherent stability of DNA and the cell's native machinery for sustained benefit.

One of the most compelling applications of gene therapy is the potential to treat a vast array of genetic disorders. Currently, there are over 10,000 recognized rare diseases, the majority of which are of genetic origin. Most rare genetic diseases have no effective treatment options, let alone a cure, and many carry devastating prognoses—particularly for children who may not survive into adulthood. Collectively, these conditions affect millions of individuals worldwide. This not only places a significant burden on patients and families but also drives substantial societal costs related to healthcare, special education, and infrastructure to comply with regulatory mandates under the Americans with Disabilities Act (e.g., occupational and/or physical therapy, specialized transportation, in-home nursing care) (Yang et al. 2022).

The precision required to treat genetic diseases presents a significant challenge. Many genetically related disorders exhibit similar clinical presentations, with differential diagnoses achievable only through comprehensive genetic screening to identify the specific mutation in an individual's genome. A gene therapy developed to correct a particular genetic anomaly in one patient cohort will be ineffective against a different anomaly in another. Consequently, there is a critical need to develop a wide array of gene therapies—each tailored to deliver specific genetic corrections to targeted tissues—to address the full spectrum of genetic diseases (Zhao et al. 2021).

A key innovation in advancing gene therapy has been the identification and engineering of novel vectors for targeted cellular delivery of new genetic instructions (DNA). Vectors, in the form of molecules or particles, are themselves non-therapeutic and only serve to transfer a therapeutic payload (gene) to a target cell. When a vector delivers a genetic correction directly to a diseased cell, it is possible to permanently fix a genetic deficiency, thus maximizing therapeutic efficacy while minimizing adverse side effects.

Adeno-associated viral vectors (AAVs) have proven particularly effective for targeted gene delivery. Naturally

occurring AAVs are quite diverse, prevalent, and, most importantly, benign (Kruzik et al. 2019). Their non-pathogenic nature and established tissue tropism, the ability to preferentially infect and establish persistent gene expression for years in non-dividing, specific tissue or cell types as illustrated in figure 1a, make them ideal candidates for gene delivery (Mendell et al. 2021; Wang et al. 2024). Still, clinical applications of AAV are not entirely without risk, as in some cases significant adverse events have been documented when using high systemic doses of AAV. Today, sophisticated molecular libraries and artificial intelligence are being employed to develop synthetic AAV serotypes with enhanced targeting capabilities or suppressed immunogenicity, which is expected to improve the precision and safety of AAV for gene therapy applications (Pupo et al. 2022).

A key advantage of AAV vectors is their modular architecture. A single AAV vector platform can be adapted with different genetic payloads, as illustrated in figure 1b, to address various disorders affecting a specific cell type and/or organ. Although exchanging the genetic payload in an AAV vector may lead to markedly different therapeutic outcomes in patients, it generally has only a marginal impact on the vector manufacturing process or overall product quality. Thus, a single AAV manufacturing platform is expected to be broadly applicable to manufacture gene therapies for a wide spectrum of genetic diseases.

In summary, gene therapy represents a groundbreaking approach that has the potential to overcome the limitations of conventional treatments by providing targeted, sustained, and potentially curative interventions. This technology is poised to significantly impact the treatment of rare genetic disorders, offering hope to patients and reducing the broader societal and economic burdens associated with these conditions. Moreover, an AAV vector platform has the potential to not only accelerate the development of new treatments but also holds promise for efficiently addressing a wide spectrum of genetic disorders.

A Need to Work Together

The molecular complexity that makes AAV vectors effective platforms for gene therapy also presents significant challenges in achieving consistent, high-yield, and high-quality production. Typically, AAV vectors are produced in genetically modified cell cultures, followed by purification using a series of engineered separation techniques. The development and manufacturing of AAV vectors

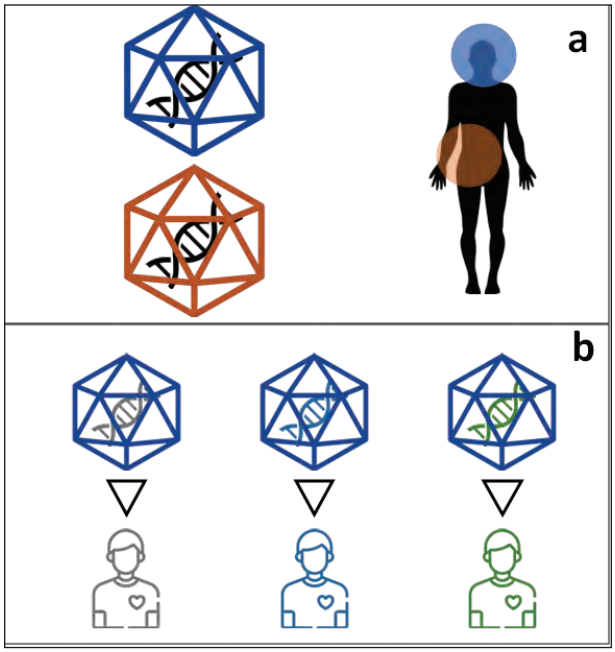

FIGURE 1 a) Diverse serotypes of AAV vectors exhibit unique tropisms, inherent from the properties of their capsids. This enables the targeted delivery of a genetic payload to specific affected parts of the body. b) By exchanging the therapeutic DNA through the selection of starting materials in a manufacturing process, different patient groups can leverage identical capsid and manufacturing technologies.

are constrained by the need for sophisticated equipment, specialized raw materials, and highly trained scientists with a prerequisite for extensive process development. Overcoming these limitations necessitates a substantial investment of both time and capital for each novel gene therapy.

Smaller biotech companies, academic research laboratories, and philanthropic organizations are frequently at the forefront of research in gene therapies for rare diseases. However, these entities often lack the robust financial and infrastructural resources necessary to transition from early-stage research to clinical application. Their contributions are critical in identifying novel targets and establishing proof-of-concept studies; yet, the "valley of death" between diagnostic breakthroughs and clinical application remains a hurdle. Limited access to advanced manufacturing facilities, regulatory expertise, and the capital required to fund extensive clinical trials often hampers the progression of even promising drug candidates into proven treatments.

In contrast, larger for-profit institutions and pharmaceutical companies possess the requisite funding, expan-

sive research infrastructure, and deep technical expertise needed to navigate the multifaceted process of drug development. Due to market forces, these organizations typically operate under business models that prioritize therapies with commercial potential. Rare diseases, by definition, affect a limited patient population, which can result in little or no commercial return on investment. This economic calculus often results in hesitance to allocate significant resources toward developing gene therapies for conditions that may not promise financial returns, despite their potentially profound impact on affected individuals. Consequently, many patients suffering from rare diseases are left without therapeutic options, and the development pipeline for potentially life-changing treatments remains critically underfunded and underdeveloped.

By aligning scientific innovation with supportive regulatory policies and sustainable business strategies, it is possible to foster an environment where gene therapies for rare diseases can thrive.

Addressing these challenges will require a concerted effort from multiple stakeholders. Innovative funding models, such as public-private partnerships, government incentives, and dedicated rare disease research funds, may bridge the financial gap between therapeutic discovery and patient dosing. Collaborative frameworks that bring together academic institutions, philanthropic organizations, and small biotech and larger pharmaceutical companies can also create synergies that leverage the strengths of each partner. By aligning scientific innovation with supportive regulatory policies and sustainable business strategies, it is possible to foster an environment where gene therapies for rare diseases can thrive.

NIIMBL

NIIMBL is a leader in advancing US biomanufacturing. Since launching in 2017, NIIMBL has catalyzed collaborations between industry and academia, driving technology advancements and innovative products. In 2023, NIIMBL launched its Viral Vector Program (VVP) to address challenges in translating genetic medicine into commercial therapies.[1]

The VVP exemplifies NIIMBL's commitment to fostering public–private partnerships. By uniting stakeholders from pharmaceuticals, academia, and biotech manufacturing, the VVP promotes pre-competitive collaboration. Its goal is to extend industry-standard technologies to academic, non-profit, and philanthropically funded research, democratizing access to high-quality manufacturing capabilities.[2]

To overcome technical barriers in AAV gene therapy production, the program is developing a standardized manufacturing platform that uses proven technologies aligned with regulatory expectations for use in patients. This platform is being designed to ensure scalable and reliable production, enabling robust manufacturing of AAV gene therapies.

NIIMBL also recognizes the need for accessible analytical methods to ensure the quality, efficacy, and safety of manufactured gene therapies. The VVP is pursuing development of an analytical method toolbox and establishment of analytical reference materials aligned with regulatory requirements to facilitate rapid translation of pre-clinical candidates into early-phase clinical trials. Using these resources maintains short-term affordability and compliance while also enabling longer-term product and process understanding that can serve to guide and de-risk use of AAV for further indications.

Gene therapy for rare diseases presents unique challenges that we believe can be overcome through collaborative development of pre-competitive processes and analytical technologies. Unlike high-volume commercial biologics, rare disease therapies require low-volume manufacturing and flexible platforms that accommodate diverse therapeutic genes. Low production volumes often preclude the necessity to generate the extensive manufacturing history that most biologics leverage for regulatory approvals. At the same time, researchers in rare disease therapeutics prioritize simplicity and modularity, ensuring that the system delivers maximum value from limited available input. Reproducing core functionality, defined by product-independent platform development and demonstrated across diverse small-volume productions, can

[1] See https://www.niimbl.org/

[2] See https://www.niimbl.org/projects-programs/viral-vectors/

be used to establish real-world production history for conserved platform modules while lowering the burden on each individual program.

NIIMBL's VVP is designing a platform to support a decentralized user base, potentially accommodating hundreds or even thousands of user applications. Platform services will prioritize growth and maturity in digital resources, data aggregation, and critical starting material availability. The platform is intended to be compatible with existing industrial infrastructure and thus will remain agnostic as to competing product lines of noncritical equipment and materials. This approach fosters sustainable and scalable development, reducing the financial and logistical burdens of large capital projects and extensive administrative overhead.

To maximize impact, NIIMBL is committed to making their vector platform open access. The program will publicly share its standardized production and analytical methods and supporting data packages, providing a low-cost, user-friendly entry point for new research initiatives. Transferring, applying, and demonstrating process performance at multiple manufacturing sites can further streamline the maturation of new projects, accelerating the transition from research to clinical development.

The NIIMBL Viral Vector Platform

NIIMBL's VVP is developing a detailed suite of process and analytical methods for manufacturing pharmaceutical-grade AAV vectors for gene therapies. The production process, depicted in figure 2 as a process flow diagram, initially uses an industry-standard HEK293 triple-transfection cell culture system (Durocher et al. 2007) with chromatography and filtration purification (Lorek et al. 2025). The analytical tests were chosen to reliably measure prospective critical quality attributes (CQAs) to ensure the safety and efficacy of the vector, as listed in table 1.

A foundational philosophy for the platform is a balance of rigor and flexibility. Fixed, high-quality starting materials—such as the HEK293 cell line, cell culture media, and helper plasmids —ensure consistency across investigational drugs and development phases. Other platform components like chromatography media and RepCap plasmid may need to be tailored for each specific serotype.

Flexibility in a subset of a platform's critical process parameters, within a well-characterized, allowable range, provides the ease in adaptability needed to accommodate variations in a vector's genetic cargo. Factors like transfection ratios and elution gradients require the end user to adapt to variations in transgene sequence and size, with careful risk assessment guiding acceptable product-specific optimizations from the NIIMBL reference process. With these few tasks fully functional, manufacturing capability is defined.

For small-volume, ultra-rare indications and early clinical trials, process robustness is prioritized over peak productivity. In these cases, a mid-scale production bioreactor typically meets patient needs, while employing scalable technology allows for rapid expansion when commercial demand is viable.

An open-access platform lowers financial, technical, and regulatory barriers, creating an environment where more investigational drugs reach early-phase trials.

To achieve broad application in rare indications, the platform is being designed to offer simplified methods and scaled-down models that match the capabilities of small research institutions; risks associated with transferring processes into regulated environments are reduced. By providing clear manufacturing targets and normal operating ranges for key parameters, early development can proceed within a defined and reliable operating space.

NIIMBL's analytical suite will enable consistent measurement of the minimal essential CQAs listed in table 1. As with all parenteral pharmaceuticals, gene therapies must be thoroughly tested by several compendial USP methods to ensure batch quality and safety. Other key product purity controls include monitoring the percentage of empty capsids, aggregation levels, and residual impurities. These methods are generally applicable across products, independent of the transgene sequence, though some may be tailored to specific capsids (Gimpel et al. 2021).

The modularity of gene therapies necessitates adapting some measurements for the specific identity and length of each therapeutic vector genome. For assessing transgene quantity and quality, promoting standardized PCR methods (ddPCR or qPCR) and sequencing techniques can be a stepping stone toward product-specific methods.

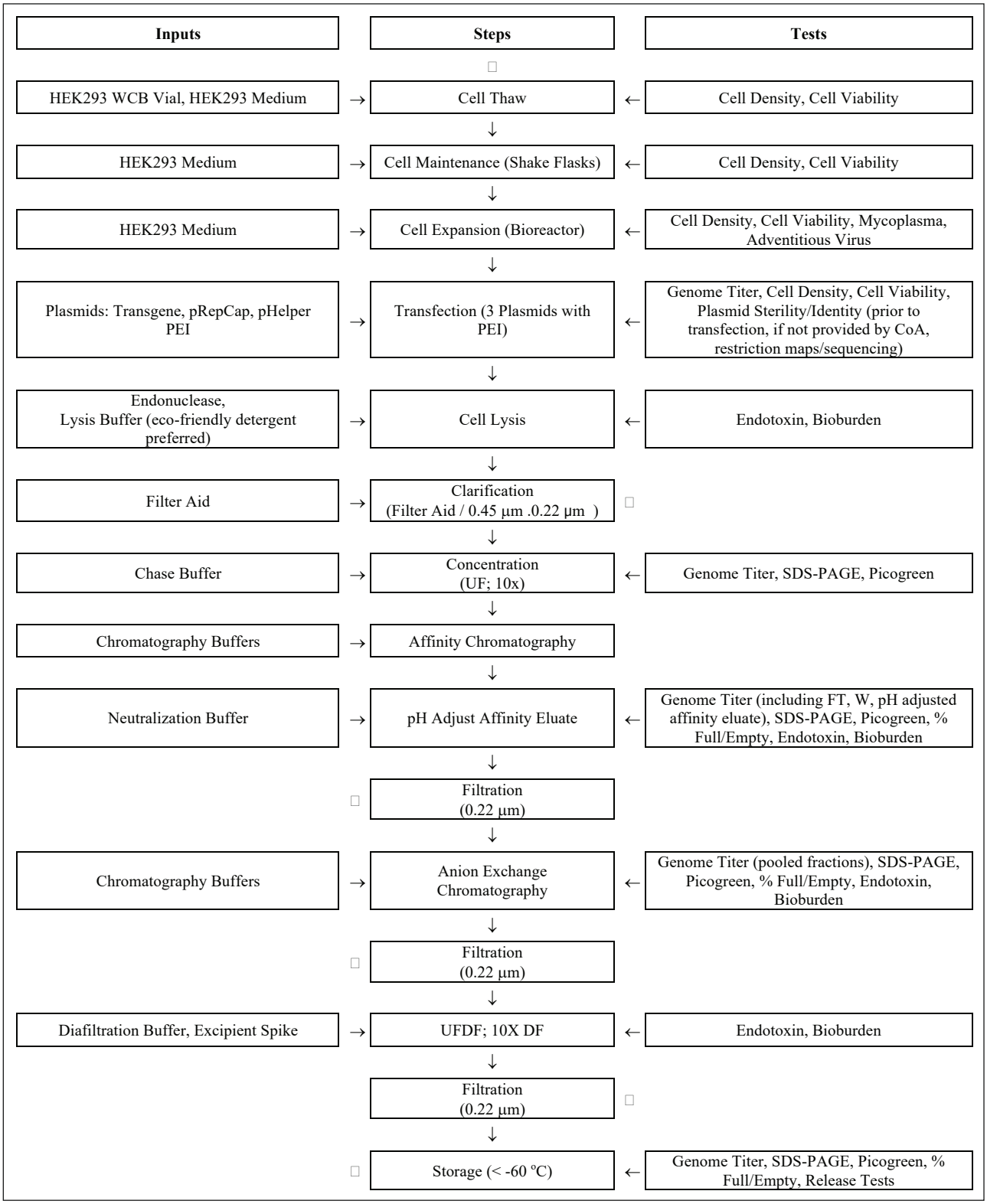

FIGURE 2 A process flow diagram illustrating the critical material inputs, production steps, and control tests describes the most conserved elements of the NIIMBL production platform.

For example, while many PCR method steps are broadly applicable, primer selection and amplicon design often require customization for each new product.

Potency assays, which measure the specific activity of a gene therapy, are inherently product specific and less amenable to standardization. In early development, semi-quantitative potency measurements relative to a reference material may be sufficient. Although the NIIMBL platform does not cover potency assay development, its robust methods for other quality attributes provide critical support for overall product evaluation.

The platform process approach allows for the sharing of development data across multiple disease indications, sponsor organizations, and genes of interest, reducing redundant process optimization efforts and streamlining development timelines.

By leveraging a common data framework, stakeholders can:

- Guide the establishment of prospective CQAs and critical process parameters
- Reduce the number of preclinical development studies needed per individual gene therapy candidate, ultimately accelerating the transition from research to clinical trials
- Lower overall development costs by minimizing duplicative work and optimizing process development investments
- Provide a shared risk assessment framework that enhances transparency and de-risks process scalability and regulatory compliance for emerging gene therapy developers

This collaborative and pre-competitive approach ensures that companies and institutions working on AAV-based gene therapies can benefit from collective process and analytical knowledge—enabling more rapid, cost-effective, and well-characterized translation of gene therapy candidates from the laboratory to the clinic.

TABLE 1 Prospective Critical Quality Attributes of AAV-vectored gene therapies are necessary for ensuring patient safety and fulfilling phase appropriate regulatory expectations.

Quality Category	Quality Attribute	Method Type
Identity	Vector Genome Identity	Sequencing
	Capsid Identity	Various
Purity	Capsid Protein Purity	CE-SDS
	AAV Vector Aggregation	SEC / DLS
	Residual Plasmid DNA	PCR
	Residual Host Cell DNA	PCR
	Residual Host Cell Protein	ELISA
	Residual Transfection Reagent	Various
	Residual Endonuclease	Various
	Residual Affinity Ligand	Various
Strength	Vector Genome Quantity	PCR
	Capsid Quantity	ELISA
	Full/Partial/Empty %	Various
	Cell-Based Potency[1]	*In vitro*
Safety	Adventitious Agents	*In vitro*
	rcAAV	*In vitro*
	Bioburden	USP <61>
	Endotoxin	USP <85>
	Sterility	USP <71>
	Osmolality	Freezing Point Depression
	pH	Potentiometric
Quality	Appearance	USP <631>, USP <790>
	Extractable Volume	USP <1>
	Particulate Matter (Visible and Sub-Visible Particles)	USP <787>, <790>

[1] Cell-Based Potency is a recommended standard but will not be developed as part of a product agnostic platform due to the uniqueness of each investigational therapeutic.

Building a Healthier Community

An open-access platform offers a practical solution for reducing cost, time, and risk for gene therapy development that has historically been slow, costly, and fraught with technical and regulatory hurdles. By eliminating proprietary restrictions and fostering collaboration, this approach benefits a broad range of stakeholders, as illustrated in figure 3. From researchers and manufacturers to

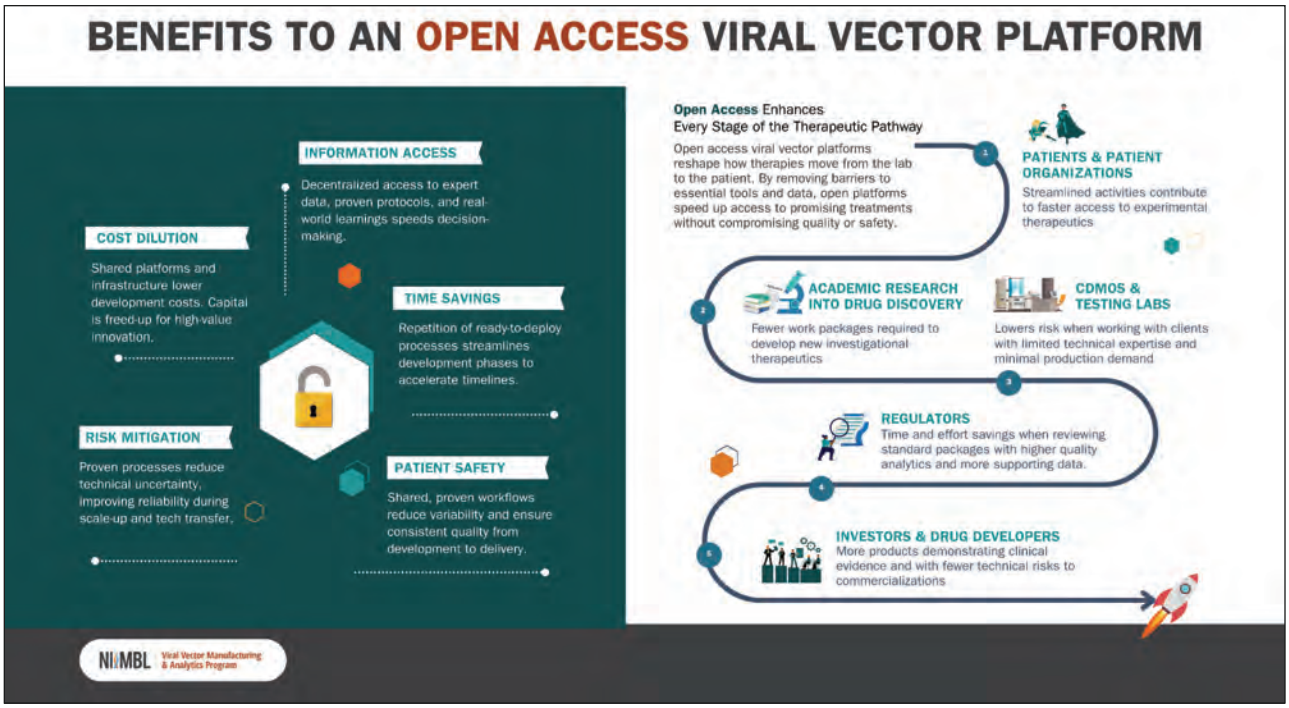

FIGURE 3 The manifold benefits of an open-access technology platform are shared by numerous stakeholders throughout the development lifecycle of an investigational gene therapy.

regulators, investors, and, most importantly, the patients who stand to gain the most, NIIMBL aims to support a thriving gene therapy community.

For ultra-rare diseases, high manufacturing and analytical complexities often prevent promising therapies from progressing beyond preclinical stages. NIIMBL's open-access AAV vector platform attempts to address this bottleneck by providing a standardized, well-characterized process that streamlines early development. By eliminating the need for each organization to build custom production and analytical frameworks, researchers can concentrate on advancing therapies rather than optimizing manufacturability. Accelerating the transition from lab-scale production to clinical-grade AAV vectors, thereby reducing time and cost, also benefits universities and startups looking to ensure their innovations reach the bedside of patients.

Contract development and manufacturing organizations can leverage the open-access production platform to distribute tech transfer costs across multiple users. This model makes small-batch manufacturing for ultra-rare indications, where trial sizes are inherently small and economically viable. Manufacturers may be able to shrink production gaps or fill excess capacity. The flexibility of the platform also provides commercial pharmaceutical developers with options to work with a contract development and manufacturing organization or transition production in-house as their needs evolve. Moreover, analytical testing laboratories can adopt standardized methods to enhance product characterization, compliance, and data standardization, resulting in faster, more reliable batch-release testing.

The biotech industry's rapid growth has also created a pressing need for workforce development in gene therapy manufacturing and analytics. Training programs can incorporate open-access platforms into their curricula, equipping workers with the technical skills needed for careers in viral vector production and regulatory compliance. Initiatives supported by the National Institute for Bioprocessing Research and Training, NIIMBL, and state-level workforce programs can use this approach to build a talent pipeline that supports the expanding gene therapy sector.

A standardized, transparent production model benefits regulatory agencies by simplifying the regulatory review process. Familiarity with a well-characterized platform allows regulators to efficiently assess new submissions, while high-quality analytics bolster confidence through robust data on safety, potency, and purity. Furthermore, the open-access system may help gene therapy

manufacturing sites with the creation of regulatory-relevant drug master files and obtaining platform-based designations, further accelerating the product approval timeline.

An open-access platform lowers financial, technical, and regulatory barriers, creating an environment where more investigational drugs reach early-phase trials. This expanded pipeline of potential treatments makes the gene therapy field more attractive to investors. By reducing uncertainty and leveraging shared data and peer review, the model improves risk-adjusted returns and positions the sector for sustainable growth, thereby drawing further investment into therapies for rare and ultra-rare diseases. Transparency in collaborative learning may also benefit sponsors of novel AAV therapeutics for more prevalent indications where manufacturing costs and relative safety concerns also permeate.

Health insurers and reimbursement agencies may also stand to benefit from the predictability afforded by standardized manufacturing and process validation. Potentially reduced batch variability leads to more predictable pricing and simplifies reimbursement decisions. Moreover, robust real-world data on safety and efficacy may provide the evidence needed to assess long-term cost-effectiveness, potentially enhancing access to life-changing treatments for patients.

An open-access AAV vector platform represents more than just a technical solution; it is a catalyst for broader change in the gene therapy landscape. By clearing away financial and technical thickets of manufacturing, this model creates an environment where more therapies can potentially reach patients, particularly those with rare and ultra-rare diseases. The ability to move investigational drugs more efficiently into early-phase trials expands the pipeline of potential therapies—seeding innovation, nurturing unmet medical need, and shining a light on collaborative science for the benefit of society.

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Leveraging cutting-edge bioindustrial manufacturing technologies will enhance domestic supply chain resilience.

Shaping Future Supply Chains with Bioindustrial Manufacturing

Melanie Tomczak and
Penny Norquist


Melanie Tomczak


Penny Norquist

From natural disasters and cyberattacks to growing sociopolitical tensions around the world, global supply chains are more unstable than any time in recent history. This instability has forced many countries to evaluate their manufacturing capacity, as domestic production of vital necessities becomes an increasing priority to bolster resilience against inevitable supply chain disruptions.

The COVID-19 pandemic exposed major weaknesses in the US supply chain. While most Americans likely remember toilet paper shortages or the struggle to find their favorite snacks, the pandemic also revealed a major supply chain challenge for the healthcare and pharmaceutical industries.

Cut off from the rest of the world and forced to end reliance on foreign materials, scientists raced to produce COVID-19 vaccines and test kits domestically and deliver them to the public. Addressing these hurdles proved vital to a worldwide return to normalcy, as well as to our future preparedness for a reality with increasing uncertainty. To address this, the National Institute of Standards and Technology (NIST) announced the Rapid Assistance for Coronavirus Economic Response (RACER) grant program.

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Introducing NIST RACER: BioMADE's Call to Action

The NIST RACER grant program awarded nearly $54M to Manufacturing USA institutes to support research, development, and testbeds for preventing, preparing for, and responding to coronavirus (NIST 2022). Manufacturing USA is a public-private network of 18 innovation institutes that convenes industry, academia, and government with a common goal of securing the future of US manufacturing through innovation, education, and collaboration. RACER funded 13 awards led by eight Manufacturing USA institutes for projects that developed point-of-care sensors for virus detection, enhanced personal protective equipment, innovated production of therapeutic countermeasures, accelerated manufacturing processes and automation for therapeutics, developed systems to strengthen medical supply chains, and created specialized training programs for technicians and operators in advanced biomanufacturing.

The impact of these projects extends beyond coronavirus and pandemic preparedness. The outcomes bolster the US infrastructure and capacity for onshoring therapeutic production, drive medical device innovation for detecting a broad range of pathogens, advance automation in domestic manufacturing, reinforce our supply chain resilience, enhance the safety for our healthcare professionals, and equip our workforce with skills for high-quality biomanufacturing jobs.

BioMADE (biomade.org) is one of these Manufacturing USA institutes, specifically dedicated to supporting US bioindustrial manufacturing, or the use of fermentation technology and American-grown crops, like corn, soybeans, and sugar beets, to produce items we use every day, such as plant-based nylon, dandelion rubber tires, and biobased cement. BioMADE was established in 2020, and its public-private partnership works closely with the US Department of Defense to secure a domestic supply chain for critical materials, chemicals, and more. BioMADE's over 300-member network consists of leading companies, small businesses, start-ups, top research universities, community colleges, and non-profits across 38 states.

BioMADE had two member-led projects funded through the RACER program: 1) Distributed Manufacturing of Antigen for Serological Testing and Countermeasures and 2) Domestic Supply Chains for Vaccine Manufacturing. Calling upon idea submissions from its members, BioMADE reviewed more than 50 responses and built collaborative projects that combined the strengths of related pitches to increase the scope and impact of the final proposals. Encouraging teamwork across its member network is a key part of BioMADE's mission. Now, as these multiyear projects near completion, with support from BioMADE, we are confident that leveraging cutting-edge bioindustrial manufacturing technologies will enhance domestic supply chain resilience.

Biomanufacturing Antigens: A Multi-University Collaboration

Viral antigens (viral proteins or portions of them) are important for use as research reagents, diagnostics for serological testing, and subunit vaccines. As viruses mutate, there is an urgent need to design and produce new viral antigens in an efficient, rapid, scalable, and cost-effective way. Distributed manufacturing that utilizes a variety of platforms, in various US geographical locations, can reduce supply chain limitations and constraints, improve response resiliency, enhance US biomanufacturing, and expand the biomanufacturing workforce.

This BioMADE-led collaboration brought together research teams from six universities—University of California, Davis; University of Texas, Austin; University of Georgia, Athens; Johns Hopkins University; Boston University; and Rensselaer Polytechnic Institute (RPI)—to design, develop, quantitatively assess, and compare seven different production platforms for SARS-CoV-2 antigens, utilizing bacterial, yeast, fungal, plant, and mammalian cell hosts. The goal was to identify development challenges and timelines, supply chain requirements, and scaling strategies; to quantify volumetric productivity, costs, production timelines, and product quality attributes for the different approaches; and to identify strategies that would increase flexibility in choice of production platform.

To do this, this team leveraged research strengths and capabilities at each of the partner institutions. For example, the team established common analytical methods for use across platforms and project locations to compare platform capabilities effectively. Production of anti-SARS-CoV-2 monoclonal antibodies (mAbs) for quantification of antigen products was successfully performed at Johns Hopkins, purification of the mAbs was performed by RPI, and plasmid constructs were designed and delivered by UT Austin. Next, Johns Hopkins provided the mAb purified by RPI to UC Davis for testing via ELISA and Western blot. Specifically, UC Davis developed the ELISA protocol for the S2H97 antibody and H87G7 antibody produced in C1 filamentous fungi, then shared results with the project teams.

Because antigen-binding properties, an intrinsic measure of antigen function, can depend on host-specific glycosylation, the team developed methods for in vitro glycosylation modification of antigens (UC Davis) (Chen 2024; Zhang et al. 2023). This groundbreaking work not only enables flexibility in choice of production platform but also will be used to tune antigen binding properties, no matter which production host is used. They developed and utilized computational modelling tools for prediction of antigen binding to targets.

We are confident that leveraging cutting-edge bioindustrial manufacturing technologies will enhance domestic supply chain resilience.

Alternative platforms were developed for production of COVID-19 spike and receptor binding domain (RBD) variants, including walnut embryo (UC Davis) (Zaini et al. 2024), *Nicotiana benthamiana* plants (UC Davis), *Bacillus subtilis* bacterial spore display (UT Austin) (Quezada et al. 2024), *Aspergillus* fungal strains (Johns Hopkins), *Thermothelomyces heterothallica* (C1) fungi (UC Davis), *Pichia* yeast strains (University of Georgia), and Chinese Hamster Ovary (CHO) mammalian cell culture (UC Davis). They are now accessing platforms based on a set of metrics determined by the project team and conducting technoeconomic analyses to develop the most promising platforms. Boston University has shared the initial outline of collaborative software developed for beta testing that will allow all collaborators on the project to work together on protocols, data files, and comment on uploaded materials.

The team has identified one platform based on the fungal host C1 that appears very promising due to the high volumetric productivity of both extracellular SARS-CoV-2 RBD and full-length spike variants, low media costs, and ease of culturing. UC Davis has expressed RBD (Wuhan, Delta, and Omicron variants) and spike (Wuhan variant) variants in C1 filamentous fungi platform in 5L bioreactors. Gram levels of RBD and spike variants have been purified, and the antigens were glycan-modified (showing increased sialic acid composition) in vitro at UC Davis. Additionally, partial characterizations have been completed (e.g., thermal shift assay, biolayer interferometry [BLI], circular dichroism [CD] analysis, MALDI-TOF, and site-specific glycan analysis before and after in vitro glycan modification) and show comparable activity with commercially available controls.

C1-produced spike variant stability studies at 37°C showed no significant difference up to seven days. BLI also showed functional binding of glycan-modified C1-produced RBD and spike variants to the ACE2 receptor protein and H87G7 (C1-produced mAb) in comparison to the glycan-unmodified version of the spike variant. ELISA showed no difference in binding of post-lyophilized C1-produced spike variants compared to un-lyophilized, which is important from an antigen distribution perspective. A detailed technoeconomic analysis of C1 fermentation-based antigen production is underway.

This project illustrated the power of bringing together research teams with complementary but distinct expertise to collaborate on an important project and work towards the common goal of building flexible, responsive, and distributed biomanufacturing capability. The team's accomplishments will aid in onshoring of biomanufacturing capacity and rapid development of both therapeutics and diagnostics in response to future health threats.

Biomanufacturing Adjuvants: Attacking an Issue from Multiple Angles

BioMADE's second project brought together three research teams to address multiple bottlenecks in the supply chain for lipid adjuvants, key ingredients in vaccines that increase efficacy by stimulating the immune system to make the body respond more effectively. Two of the five approved-for-human-use adjuvants, squalene and quillaja saponin QS-21, come from threatened sources that limit the quantity of vaccines produced. The purest form of squalene is sourced from deep-sea shark liver oil, and saponins are derived from the bark of the Chilean tree *Quillaja Saponaria*, which only becomes a viable source after maturing for 25 years. In addition to their use as vaccine adjuvants, saponin and squalene ingredients provide emulsification, foaming and antioxidant properties to various food and skincare products.

One of BioMADE's greatest strengths is its ability to bring together research teams to address a common issue from many different angles. In this case, Amyris,

a leading synthetic biotechnology and renewable chemical company, and two laboratories at UC Berkeley have developed viable methods for adjuvant production in the short and long term, taking advantage of both microbial and plant-based solutions.

Amyris: Manufacturing Biofermentation-Based Squalene

Amyris has been a maverick in reducing supply chain volatility since its inception. By engineering yeast strains and determining how to ferment those strains at a large scale, Amyris has pioneered the ability to convert basic plant sugars into high-value molecules used across end-markets. To date, the company has commercialized 15 different molecules used in more than 3,000 top global brands.

Amyris technology is highly relevant to the production of raw materials used in the pharmaceutical supply chain. The goal of this RACER project was to scale up technology to produce hundreds of kilograms of sustainable, fermentation-derived squalene, which could be used to replace shark-derived squalene currently used in vaccine adjuvants. Establishing this technology at commercial scale will simplify supply chains, improve the quality and consistency of materials, eliminate reliance on threatened and endangered animals, and enhance readiness to ramp up excipient production should there be an acute future need.

With the support of BioMADE, Amyris successfully completed a demonstration campaign with a domestic partner in 2023, producing and purifying more than 400 killograms of squalene. This campaign was critical in establishing the commercial viability of this novel technology, which is now commercialized in an agreement between Amyris and CRODA, a global leader in vaccine ingredient technology.

UC Berkeley: Biomanufacturing Saponins from Sustainable Plants

Through a pioneering two-year project at UC Berkeley, they have developed a sustainable source of quillaja saponins. By cultivating *Quillaja Saponaria* in California and extracting saponins from the leaves of 2–3-year-old shrubs, this innovation reduces reliance on wild-harvested bark from Chile's dwindling population of 30-year-old trees.

The trees are successfully grown in greenhouses, hydroponic systems, and open fields. Through selective genetic and environmental controls, saponin yields and profiles are optimized, and leaves are harvested at peak accumulation. The foliage regenerates, enabling a fully renewable, seasonal harvest. With respect to dry biomass, yields are 4–5 times higher than those from bark. As part of this project, they produced 3 kilograms, and they are now working on options for scale-up and pilot extraction and purification of the saponins at higher yields.

By establishing a domestic, renewable supply, this project mitigates pressure on wild populations, addressing sustainability concerns and regulatory constraints. Its success strengthens pharmaceutical supply chains, ensuring a stable, long-term source of this essential vaccine ingredient.

UC Berkeley: Biomanufacturing Saponins from Yeast

The other lab at UC Berkeley comprising the RACER team has been focusing on leveraging synthetic biology approaches to produce lifesaving saponins sustainably in *Saccharomyces cerevisiae* (baker's yeast). Yeast is an ideal platform for saponin production due to its ability to grow using only simple sugars both rapidly and in a scalable manner. Additionally, yeast possesses a eukaryotic subcellular environment similar to plants and benefits from robust toolkits for genetic modification. By incorporating 38 heterologous enzymes from six different organisms, the team was able to produce QS-21 successfully in engineered yeast that is chemically indistinguishable from QS-21 isolated from *Q. saponaria*. Beyond simply introducing the biosynthetic genes responsible for QS-21 production into the yeast genome, this endeavor required refactoring the primary metabolic pathways for producing non-native nucleotide sugars in yeast, which are required to produce the complex glycosylation pattern largely responsible for QS-21's immunomodulatory activity.

These projects only scratch the surface of what we can achieve with bioindustrial manufacturing.

Building off this accomplishment and incorporating lessons learned, they have since focused on improving TRY (titers, rates, and yields) of QS-21 heterologously produced in yeast with the goal of providing a bioproduction platform that rivals traditional isolation from

Q. saponaria plants. This pathway optimization entails a granular analysis of each transformation in the complex QS-21 biosynthetic pathway that holistically evaluates biosynthetic flux, pathway bottlenecks, and feedback inhibition, as well as finely tunes expression of heterologous enzymes to achieve maximal production. These efforts have led to increased production of key intermediates by up to 500% and are poised to enhance QS-21 production in yeast significantly.

The Future of Biomanufacturing: Looking Beyond Healthcare and Pharma

These projects only scratch the surface of what we can achieve with bioindustrial manufacturing. Our partnership with the Department of Defense truly symbolizes that bioindustrial manufacturing is a national security imperative. Specifically, these technologies have the potential to compress the US supply chain for vital military resources and commercial applications, like chemicals, solvents, reagents, electronic films, fabrics, polymers, and more. By making use of local crops as feedstocks to power domestic fermentation facilities, bioindustrial manufacturing ends reliance on foreign imports and ensures that we can produce critical items on US soil.

Lastly, bioindustrial manufacturing holds the potential to transform the US economy, boosting resilience and creating jobs that will withstand the test of time. The US bioeconomy is currently worth $950 billion (NASEM 2020). And even more importantly, experts estimate that biology can be leveraged to produce up to 60% of materials (Chui et al. 2020) in the global consumer supply chain, representing ample opportunity for continued economic growth.

This economic boost will be felt throughout the American public. Farmers will gain access to new sources of revenue, as bioindustrial manufacturing creates new markets for their crops and even waste streams. Bioindustrial manufacturing will also lead to job creation for a globally competitive STEM workforce. In 2023, the US industrial bioeconomy supported nearly 644,000 (TEConomy Partners, LLC 2024). As our industry continues to grow, experts now project more than 1.1 million additional jobs added to the US economy by 2030, exclusively driven by the rapidly expanding bioeconomy.

Bioindustrial manufacturing defies categorization into a single industry or sector. Whether we are transforming vaccines or designing the military uniforms of tomorrow, BioMADE and its members will continue to push the boundaries of what we can produce in the United States by unleashing the power of biology.

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Renewed US investment in domestic antibiotic production is essential to ensure supply chain resilience and safeguard global health security.

Revitalizing US Biomanufacturing to Strengthen the Global Supply and Security of Antibiotics

Misti Ushio and
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Antibiotics have significantly improved life expectancy and overall public health for over 80 years. The primary reasons antibiotics are critical for human health include treating life-threatening infection, supporting advanced surgical medicine, protecting public health via control of widespread infection, and impacting health economics by reducing hospital stay, prolonged illness, etc. Penicillin, the first antibiotic derived from a natural organism, was introduced in 1942 and revolutionized medicine by effectively treating infections such as pneumonia, sepsis, and syphilis. It is estimated that penicillin alone has saved approximately 200 million lives, and its discovery paved the way for further advancements in antibiotics that have collectively saved hundreds of millions more lives to date (University of Sheffield 2021).

Today, however, the global antibiotic production landscape poses risks to global health security and equitable access to key medicines. The production of antibiotic active pharmaceutical ingredients (APIs) has become concentrated in a handful of countries; nearly 70% of the manufacturing sites for a representative shortlist of 40 antibiotic APIs are located in two countries, India and China (with the majority in China). More concerning is that the United States no longer has any significant fermentation manufacturing capabilities

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to produce antibiotic APIs onshore. This signals potential vulnerabilities in the supply chain and disparities in global health resilience.

Numerous opportunities exist to leverage policy and technology to ensure a more resilient, reliable supply of antibiotics. There is a need to increase the discussion about antibiotic security between government, manufacturing, and technology development to create expanded partnership and coordination among all stakeholders instead of local decision-making based only on cost. If global redistribution of antibiotic production is a health priority, the tools of synthetic biology can be applied to improve production efficiency and reduce costs while improving global health security and access. Translating this into manufacturing would require collaboration among governments, industry leaders, and research institutions to establish a robust, secure, and sustainable antibiotic manufacturing infrastructure that benefits all nations. New manufacturing facilities also invite the opportunity to apply other innovations such as continuous culture, extensive use of robotics, automation, and application of AI to improve process performance. By embracing these measures, the international community can better safeguard public health worldwide.

It is the opinion of the authors that 1) the United States and other countries should proactively discuss how to increase antibiotic security via collaboration between government, manufacturing, and technology development to create partnership and coordination among all stakeholders instead of local decision-making based only on cost, and 2) the United States and other countries should take steps to prevent the cycle that has occurred for antibiotic security from being repeated with antibody security.

Penicillin History

Discovery and Development of Penicillin, the World's First Antibiotic

In 1928, the bacteriologist Alexander Fleming discovered penicillin by observing that a stray spore of a mold, subsequently identified as *Penicillium notatum*, settled on a petri dish that had a bacterial culture of staphylococcus on it. This mold colony was surrounded by a zone of growth inhibition and lysis, indicating that the mold was killing the bacteria. Fleming understood the potential significance of this and preserved the penicillium culture over many years. However, subsequent progress was delayed by the instability of penicillin.

Beginning in 1939, a group at Oxford University led by Howard G. Florey, an Australian pathologist, and Ernst Chain, a chemist who had fled Nazi Germany, developed an assay, found a way of producing penicillin in surface culture, made enough for preclinical studies, and solved the stability issue partially via lyophilization. Excitement grew as soon as the preclinical studies were completed.

Because of the devastating wartime situation in England, two members of the Oxford team traveled to the United States to get help. Florey and Norman G. Heatley arrived in New York on July 2, 1941. There followed a remarkable collaboration between academia, government, and industry, resulting in supplies of penicillin being made available via submerged fermentation at large scale by D-Day on June 6, 1944. In the words of Florey and the Oxford team: "Too high a tribute cannot be paid to the enterprise and energy with which the American manufacturing firms tackled the large-scale production of the drug. Had it not been for their efforts, there would certainly not have been sufficient penicillin by D-day in Normandy" (Journal of the Royal Society of Medicine 1949).

Today, however, the global antibiotic production landscape poses risks to global health security and equitable access to key medicines.

Alexander Fleming, Ernst Chain, and Howard Florey were awarded the Nobel Prize in Physiology and Medicine in 1945 to broad acclaim (Nobel Prize.org 2025). The Nobel Prize acknowledged not only a monumental scientific discovery but also a great contribution to the emerging field of bioprocess engineering.

The introduction of penicillin occurred during World War II because of a remarkable collaboration between universities, government, and the pharmaceutical industry. For biomanufacturing of pharmaceuticals, this effort was the equivalent of the Manhattan Project. A number of companies were involved in this effort, including Merck, based in Rahway, New Jersey, and Pfizer, which was then a small company producing citric acid by fermentation based in Brooklyn, NY. Penicillin was the first antibiotic developed, and it was closely followed by streptomycin.

TABLE 1 Projected Ampicillin Supply in the US

Ampicillin prescriptions/year	53 million
Dose per prescription	1.5 g/day for 7 days = 10 grams total
Bulk API required per prescription	16 grams (accounts for losses in formulation/packaging)
Total bulk API required/year	850,000 kg/year
Fermenter size	40,000 gallons = 151,400 liters
Yield	80 g PenG per liter
Cycle time	9 days
Overall recovery to ampicillin	45% (including conversion + purification)
Yield per batch	80 × 151,400 × 0.45 = 5,450 kg/batch
Batches/year per fermenter	30
Output/year per fermenter	5,450 × 30 = 163,500 kg/year
Fermenters required	**850,000 ÷ 163,500 ≈ 6 fermenters**

The great success of penicillin helped trigger the development of many other antibiotics widely prescribed to this day, and the penicillin family of beta lactam antibiotics is still the most commonly prescribed (CDC 2019–2023). In 2023, the prescription rate for penicillins was 182 per 1,000 population in the United States, 55% higher than the second most prescribed class of antibiotics, cephalosporins (CDC 2019–2023).

Biomanufacturing of Penicillin

Various semisynthetic antibiotics are based on penicillin (amoxicillin, ampicillin, dicloxacillin, and penicillin V) and are manufactured via several steps. Semisynthetic means that the base molecule is produced via fermentation and then chemically or enzymatically modified to obtain the maximum therapeutic effect. An example is given here for ampicillin (see table 1).

The process begins with the fermentation of the mold *Penicillium chrysogenum*, which produces penicillin G (benzylpenicillin). Typically, fermentations are run in the fed-batch mode at the 75 to 150 thousand liter scale and last for around eight days, with a final product concentration of more than 40 grams/liter. During harvest, penicillin G is extracted from the culture broth through solvent extraction methods followed by purification processes such as crystallization, chromatography, or filtration to obtain pure penicillin G.

The purified penicillin G is then converted to ampicillin by enzymatic and chemical modifications.

Deacylation: The benzyl group of penicillin G is removed to create a penicillin intermediate.

Acylation: The penicillin nucleus is then acylated with the appropriate amino acid or other acylating agents (such as 4-aminobenzylpenicillin) to form ampicillin. This reaction alters the side chain, transforming penicillin G into ampicillin. The newly formed ampicillin undergoes further purification processes to remove any unreacted materials and by-products. This can include additional crystallization, precipitation, or chromatographic techniques.

After purification, ampicillin can be formulated into various forms, including tablets, capsules, and injectable solutions. This process allows for the efficient transformation of naturally occurring penicillin into a semi-synthetic antibiotic with a broader spectrum of activity, making ampicillin effective against various bacterial infections.

Over time, improvements have been made to penicillin manufacturing, including increasing productivity of the producing penicillium strain and optimizing both nutrient feeding strategies and mixing conditions. Downstream purification methods, such as extensive solvent recycling, have also been improved. Semisynthetic molecules have boosted the antimicrobial efficacy of virtually all other microbial-derived antibiotics, including erythromycin, tetracycline, and cephalosporins. The parent molecule in each case is manufactured by deep tank fermentations (see figure 1). The same microbial engineering strategy can be applied in the same way as described here for penicillin.

Today there are many examples of antibiotics manufactured via fermentation on a very large scale:

a. Penicillin—Typically produced by the fermentation of *Penicillium chrysogenum*.

b. Cephalosporins—Similar to penicillins, they are produced by the fermentation of the fungus *Cephalosporium acremonium.*
c. Tetracyclines—These broad-spectrum antibiotics are produced by the fermentation of streptomyces bacteria, primarily *Streptomyces aureofaciens.*
d. Erythromycin—Made through the fermentation of *Streptomyces erythreus.*
e. Streptomycin—Produced by the bacterium *Streptomyces griseus.*
f. Gentamicin—This is produced from the fermentation of *Micromonospora purpurea* and other micromonospora species.
g. Vancomycin—Derived from the bacterium *Streptomyces orientalis.*
h. Rifamycin—Produced by *Streptomyces mediterranei.*

Expansion of Antibiotic Development and the Geographical Shift of Antibiotic Manufacturing Capacity over the Past 80 Years

"The Marcy Avenue penicillin plant was 95% completed by the end of February [1944] and deep tank fermentation was initiated. Working 24 hours a day, seven days a week, the increase in penicillin production was dramatic. During the fall months, one day's production of penicillin often exceeded the entire production of 1943" (Ginsberg 2008).

The immense success of penicillin drove a concerted effort to produce antibiotics at greater scale. In the 1940s, pharmaceutical companies invested in large-scale fermentation capacity to manufacture antibiotic APIs and finished products in the United States. Pfizer, for example, established a significant share of early penicillin supply by starting up a manufacturing facility in Brooklyn in March 1944 with 14 large fermenters, 7500 gallons (~28,000 liters) each (American Chemical Society 2024). In this facility, Pfizer could produce penicillin so that sufficient quantities were available in time for the D-Day landings. This was the first large-scale penicillin facility in the world, and it was ultimately designated a National Historic Chemical Landmark by the American Chemical Society on June 12, 2008 (American Chemical Society 2024).

By 1984, many major pharmaceutical companies had scaled and leveraged onshore fermentation capacity to position the United States as a key supplier to the rest of the world. The average facility consisted of 10 to 20 stainless steel fermenters, approximately 75 to 150,000 liters each. Assuming an average of 2.3 million liters total capacity per company suggests an estimated total of 18 million liters of capacity at that time.

FIGURE 1 Dr. Selman A. Waksman, J.H. Holcomb, Jr., and Dr. E.J. Nolan in front of a fermenter used in Merck's streptomycin plant. December 1945. Photo credit: Merck Archives.

However, since then, pharmaceutical companies have steadily outsourced and shifted antibiotic manufacturing to other countries, largely driven by opportunities to reduce costs and avoid capital investment. As of 2021, the leading exporters of antibiotic APIs were China, Italy, India, and Switzerland (Yang et al. 2024). When considering only antibiotic finished products, the top exporters were Italy, Canada, India, and Germany (Yang et al. 2024). The United States is noticeably missing from both lists and does not meaningfully contribute to either antibiotic API or antibiotic production, making the market heavily reliant on exports from other countries (see table 2).

Over the past 20+ years, China has steadily grown into the leading exporter of antibiotic APIs and continues to gain market share of antibiotic medicines as well. In 2021, China-based manufacturers exported 44.5% of total antibiotic APIs exports (up from 9.0% in 2002) and 18.9% of total antibiotic medicines globally (Yang et al. 2024). India has also increased its antibiotic medicine production significantly, though it sources over 82% of APIs from China (Yang et al. 2024).

TABLE 2 Fermentation capacity for manufacture of antibiotics in USA

Year	Fermentation Capacity (liters)
1944	400,000
1984	18,000,000
2024	less than 400,000

Today in the United States, USAntibiotics has succeeded in becoming a producer of amoxicillin but outsources the supply of the API (which is made by large-scale fermentation abroad), creating a level of vulnerability in the supply chain.

Importance of Bringing Antibiotic Manufacturing Back to the United States

There are many reasons why it's crucial to bring antibiotic manufacturing back to the United States, including:

Significant Impact on Human Health

Since their discovery, antibiotics are estimated to have saved at least 200 million lives (University of Sheffield 2021). And they continue to be an essential tool for combating infections. In 2023, there were 252 million prescriptions for antibiotics distributed in the U.S. alone (CDC 2019–2023). Yet, the amount of antibiotics manufactured in the United States has dwindled to a concerningly low level; 92% of the 111 most-prescribed antibiotics have no US source as of 2021 (Miller 2021).

Protect National Security

Ensuring the manufacturing of antibiotics in the United States is a national security issue. Maintaining some level of specialized fermentation manufacturing capacity onshore enhances domestic capacity to respond to public health emergencies and decreases vulnerability to global supply chain disruptions and geopolitical tensions. There have already been several incidents in recent years that have highlighted the fragility of the antibiotic supply chain. During the COVID-19 pandemic, India limited exports of antibiotics tinidazole and erythromycin, among other drugs, due to dwindling supply of API resulting from the temporary closure of Chinese manufacturing facilities (Ellis-Petersen 2020). Further, in 2017, there was a global shortage of piperacillin-tazobactam and benzathine penicillin because a single factory in China shut down; only three API manufacturers for these products remain, all of which are located in China (Yang et al. 2024).

Policy: Precedent, Opportunity, and Challenges

There have been several instances of countries implementing policies to ensure access to key products; it is the opinion of the authors that similar policies should be designed for antibiotic APIs. In what follows, we outline examples of how the United States and other countries have created policy and economic incentives to increase onshore manufacturing and secure access to and independence of key products, identify opportunities for the government to support bringing antibiotics back onshore, and discuss potential challenges in doing so.

Precedent

United States CHIPS Act

The CHIPS and Science Act strengthens US national security by reducing dependence on foreign semiconductor manufacturing, particularly from geopolitical rivals like China. The act provides $52.7 billion in funding to boost domestic semiconductor production, research, and workforce development, ensuring that the United States maintains a secure and resilient supply of critical microchips used in defense, infrastructure, and consumer technology (US Congress 2022).

India Production Linked Incentive

India's Production Linked Incentive (PLI) scheme enhances antibiotic security by promoting domestic manufacturing of APIs, key starting materials (KSMs), and drug intermediates (Department of Pharmaceuticals, Government of India 2020). This reduces India's reliance on imports, particularly from China, which currently dominates global API production. By boosting domestic API production, the PLI scheme plays a crucial role in securing India's antibiotic supply, protecting public health, and reducing strategic vulnerabilities in pharmaceutical manufacturing.

United States Project BioShield Partnership with Paratek

In December 2019, the Biomedical Advanced Research and Development Authority (BARDA) partnered with Paratek Pharma to support the development, manufacturing, and procurement of novel antibiotics to treat pulmonary anthrax. This partnership is currently valued at approximately $304 million and has successfully secured manufacturing in the United States, though it took over five years and highlights some of the challenges of bringing back manufacturing infrastructure that

has been decommissioned over the past several decades (Paratek Pharmaceuticals 2024).

Opportunity

Implement Economic Incentives

Higher costs to produce antibiotics onshore ultimately drove antibiotic production overseas. Economic incentives such as tax credits and subsidies could motivate pharmaceutical companies to invest in manufacturing capacity back in the United States.

Public-Private Partnerships

Collaboration between the government and the private sector, particularly via government funding, can support and drive innovation in manufacturing capabilities and technology.

Government Procurement & Stockpiling

Guaranteed purchasing agreements from the government or public entities can provide financial stability for antibiotic manufacturers and make investing in fermentation or manufacturing capabilities a more attractive, lower-risk opportunity.

Improve Quality

Access to high-quality antibiotics supports public health. Domestic production of antibiotics provides higher levels of regulatory oversight and control, including more direct inspections to ensure compliance with Good Manufacturing Practices (GMP). While quality is not necessarily dependent on manufacturing location, strict, established regulatory frameworks in the United States could benefit antibiotic quality overall.

Challenges

Opportunity Cost for Pharmaceutical Companies

Pharmaceutical companies have historically prioritized more profitable, chronic disease treatments; antibiotics are prescribed for short durations and generate significantly less revenue compared to other drugs (Dattani 2024). Any new economic incentives need to be meaningful enough to bridge this gap significantly.

Stricter US Environmental Regulations Introduce Manufacturing Costs

High levels of antibiotics in the water supply can increase the rise of antibiotic-resistant pathogens, and to mitigate this, the United States has established regulations on manufacturing waste. Internationally, environmental emissions are largely unregulated, which decreases the cost of production comparatively. However, in 2024, the World Health Organization (WHO) published its first guidance on wastewater and solid waste management in antibiotic manufacturing, which may ultimately bring similar regulations worldwide.

New Technology: Opportunity and Key Considerations

How did the United States go from having approximately 18 million liters of fermenter capacity for making antibiotics in 1984 to next to none today?

The initial technology development had a focus on quality and reducing the cost of goods. The rapid development of biochemical engineering starting in 1940 was driven to a large extent by the opportunity created by very large-scale antibiotic fermentation facilities. Great progress was made by the development of submerged fermentations using low-cost media ingredients and by low-cost purification techniques based on solvent extraction and crystallization as well as the development of sophisticated analytical methods. The bulk price for penicillin was ~$300/kg in 1953 and came down to ~$35/kg by 1980 (Bhattacharyya and Sen 2006).

Due to the cost savings of production overseas, the companies that owned fermentation infrastructure either sold or decommissioned the manufacturing sites and did not replace them. Now there is a minimal amount of fermentation capacity in the United States suitable for manufacturing antibiotics. Given that demand for antibiotics is likely to continue for the foreseeable future, the disinvestment in US fermentation facilities creates a need to rebuild and for investment in new manufacturing technologies.

Advances in synthetic biology represent an opportunity to address global antibiotic security by offering efficient and sustainable manufacturing solutions. By engineering microbial strains and redesigning biosynthetic pathways, synthetic biology facilitates cost-effective production of antibiotics. It accomplishes this by streamlining manufacturing and reducing dependence on complex chemical synthesis, which can increase accessibility and affordability. Namely, it has the potential to simplify multi-step manufacturing processes into a single-tank operation. For example, penicillin is typically purified from fermentation and then enzymatically converted to ampicillin. Similarly, cephamycin C is purified and chemically converted to cefoxitin. These and other

examples, including lovastatin and azithromycin, illustrate that synthetic biology could enable processes where both production and conversion occur in the same bioreactor, significantly reducing costs and processing time.

Advances in synthetic biology represent an opportunity to address global antibiotic security by offering efficient and sustainable manufacturing solutions.

Furthermore, building new facilities and infrastructure creates the opportunity to implement new technologies to increase manufacturing efficiency and reduce costs. Here are several examples for consideration:

- Could synthetic biology be deployed to make ampicillin directly, rather than by first making 6-APA from penicillin G or V and converting it in a separate reaction to the desired ampicillin?
- Could continuous fermentation increase the productivity of currently used fed-batch fermentation, where there is a period of rapid cell growth during which very little product is made followed by a long period of slow growth during which the antibiotic is made? By going to continuous culture with a controlled, slow growth rate, the fermenter productivity can be greatly increased.
- Could the electrical supply come from an adjacent facility using sustainable electricity generation to address the high power demand of an approximately 400 HP per 150,000 liter fermenter? Can current complex media be replaced with low-cost ingredients and sourcing to reduce high waste disposal costs?
- Could the carbon dioxide produced by fermentation be captured and used for a sustainable purpose?
- Could all the solvents required for extraction and crystallization be recycled and used again?
- Could alternative methods of drying be used to reduce the high capital and operating costs of lyophilization?
- Could robotics be used to automate, and could artificial intelligence be applied to contribute to implementing process improvements?

Implications for the Manufacture of Antibodies

The technology for making it practical to manufacture monoclonal antibodies at scale was started in the 1980s and was driven by several innovative companies and universities such as Genentech, Amgen, Biogen, Lonza, Caltech, and MIT. The Engineering Conferences International Cell Culture Engineering Conference (CCE) series was started at this time, and in the beginning many different technical approaches for antibody production were explored. By 1994, there was a convergence of technology, and by the 1994 CCE IV, many companies were using the standard Chinese Hamster Ovary cell line platform with Protein A purification for the capture of their specific antibody. The term "6-pack" was coined to describe the typical manufacturing facility based on six 12,000 liter cell culture bioreactors. Over the past 30 years, there have been continued improvements, most notably the significant increase in product titer that has transformed the 6-pack scale into 2,000 liter bioreactors, but the basic platform remains the same.

The resulting antibody therapies have had dramatic beneficial impacts on human health, including treatment of cancers and chronic inflammatory diseases. For the most part, the manufacturing of these antibody products was initiated in the United States and is now starting to be made in many different countries as the technology transfer is made simpler because there is a common consensus platform. From a strategic national security perspective and quality of goods perspective, we should consider the negative implications of continuing down the same path of local decision-making for supply based primarily on the cost of goods. A national policy should be developed that addresses the strategic importance of domestic antibody production for the security of human health and the national economy.

Conclusion

We suggest the following approaches to start the dialog with key stakeholders to increase awareness, design policy, and fund increased manufacturing capacity:

- Frame antibiotic security as a US national security issue with White House-level acknowledgment that antibiotic dependence on foreign suppliers (mainly China and India) is a threat comparable to energy or semiconductor dependence.
- Design a national defense strategy with the Departments of Defense, Homeland Security, and Health and Human Services recognizing antibiotics as a critical component of infrastructure resilience and assess

supply chain vulnerabilities, recommend strategies to restore domestic production, and prioritize public-private partnerships.
- Educate Congress on the state of antibiotic supply chains and discuss legislation similar to the CHIPS and Science Act but for antibiotics, which may include subsidies, tax incentives, investment in next-gen manufacturing technology, and guaranteed government contracts for US antibiotic manufacturing.
- Lead G7 and G20 discussions on global antibiotic resilience, emphasizing that shared dependencies make all nations vulnerable and that, while antibiotic resistance is often in the news, antibiotic supply fragility is not.

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There is great potential for synthetic biology to improve biopharmaceutical manufacturing, but fully unleashing it requires technical innovation and solutions that address ethical, legal, security, and societal implications.

Synthetic Biology's Impact on Biopharmaceutical Manufacturing

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Synthetic biology has already shown its usefulness in biopharmaceutical manufacturing. Yet there is much more synthetic biology can do to improve the way we manufacture biopharmaceuticals and the very nature of the therapeutics available to prevent and treat disease. Synthetic biology can create medicines that combine specificity for two or more targets to improve patient outcomes and reduce side effects. It can also make the manufacturing process cheaper, faster, and more consistent. This makes medicine more accessible to more people, and it enables quicker response time to emerging pathogens. The production of biopharmaceuticals using simpler, more robust expression

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systems could increase global access, improve pandemic preparedness, and reduce manufacturing costs.

This article begins with a brief description of what synthetic biology means in the context of biopharmaceutical manufacturing. We then break down the current and future contributions of synthetic biology to biopharmaceutical manufacturing according to technology maturity and modality, starting with applications related to mature biopharmaceuticals (e.g., monoclonal antibodies, bispecific antibodies, and cell therapies) and concluding with emerging modalities (e.g., living therapeutics, phage therapeutics, and expansions to gene therapy and cell therapies). The article closes with a call to action discussing where synthetic biology needs to be focused, and how we can apply lessons from past ethical, legal, and societal implications to accelerate the safe implementation of synthetic biology in the future.

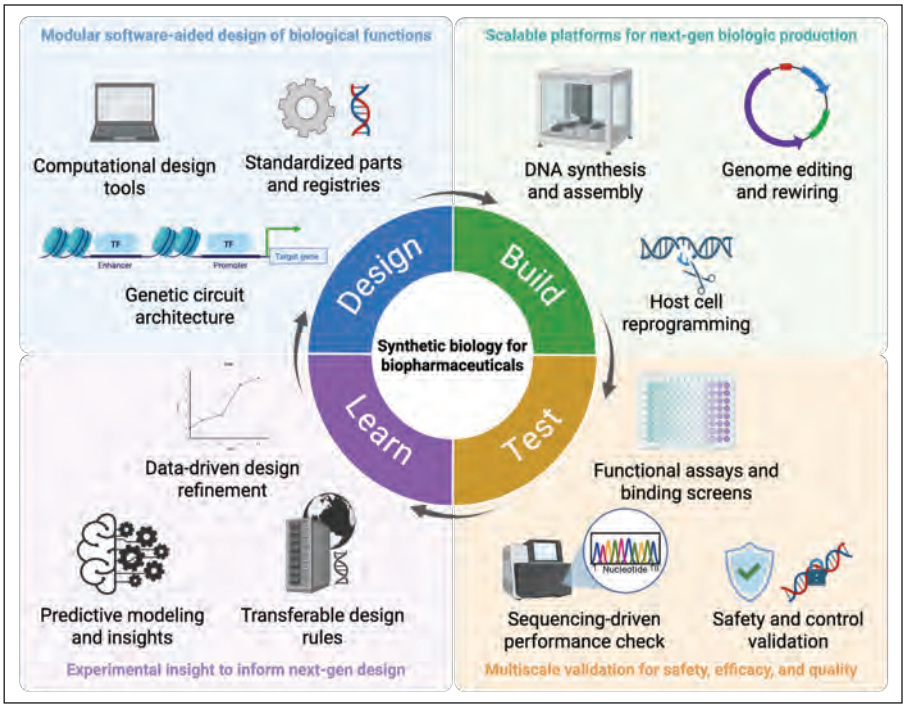

FIGURE 1 The Design-Build-Test-Learn cycle of synthetic biology.

What is Synthetic Biology?

While there is little consensus on the precise definition of synthetic biology, it is distinguished from its predecessor, genetic engineering, by its use of an iterative Design-Build-Test-Learn engineering framework that refines constructed systems based on collected knowledge (Freemont 2019). Unlike classical genetic engineering in which manipulated DNA sequences are imperfectly defined, resulting in the transfer of poorly understood extraneous flanking sequences that alter performance unexpectedly in a context-dependent manner, iterations of Design-Build-Test-Learn allow synthetic biology to engineer biomolecular, cellular, and/or tissue behavior with increasing levels of precision via the creation of gene circuits (figure 1). Analogous to electrical circuits made up of reliable parts like resistors, capacitors, and wires, gene circuits are built from DNA-encoded promoters, transcriptional terminators, protein encoding sequences and other biological parts. The design and development of ever more sophisticated biological behaviors is dramatically accelerated by advances in related disciplines. Molecular biology has given rise to tools such as CRISPR-Cas, the subject of the 2020 Nobel Prize in Chemistry, that reprogram a number of species with exquisite precision and ease by editing and introducing novel genetic sequences (Fernholm 2020). Rapid prototyping of genetic circuits is enabled with DNA synthesis and automated DNA assembly that have approached exponential, Moore's Law-like growth rates in manufacturing capacity for DNA sequencing and DNA synthesis. What once took months to build at the close of the last century can now be completed in days with fewer than eight man-hours of work for less than a hundredth of the cost (Carlson 2022). Finally, next-generation sequencing and artificial intelligence (AI) quickly analyze and model the performance of natural and engineered systems for fractions of a penny per DNA base pair, enabling precise and inexpensive design of new biological systems. More importantly, the systematic framework of synthetic biology reduces development cost and accelerates biosystem design by enabling reuse and extensibility of established solutions to new biopharmaceutical challenges.

How is Synthetic Biology Impacting Mature Biopharmaceuticals?

Synthetic biology has already made and continues to make a big impact on mature biopharmaceuticals, the

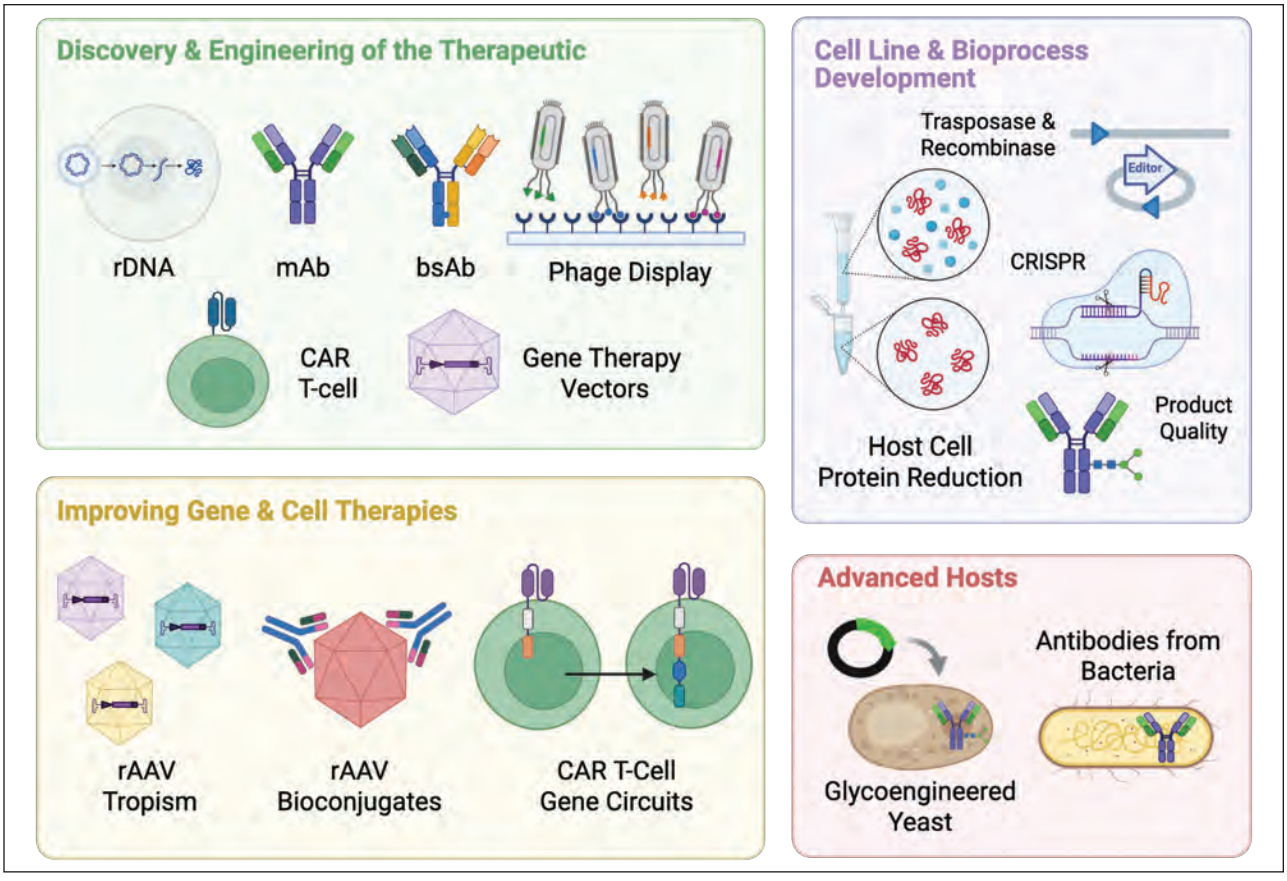

FIGURE 2 Examples of the use of synthetic biology in mature biopharmaceuticals.

biologically made drugs already in the clinic, which include monoclonal antibodies, hormones like insulin, and proteins used in vaccines. Its use in the discovery and improvement of hormones, monoclonal antibodies, bispecific antibodies, gene therapies, and cell therapies to make cell line and bioprocess development more efficient through new genetic engineering tools and advanced cell lines is accelerating (figure 2).

Discovery and Engineering of the Therapeutic

Among mature biopharmaceuticals, synthetic biology has mainly played a role in the discovery and engineering of therapeutics. The biopharmaceutical industry was born alongside the early advances underlying synthetic biology. Recombinant DNA technology developed in the 1970s led directly to the first biopharmaceuticals developed in the 1980s and 1990s, including insulin (recombinantly produced in *Escherichia coli* and *Saccharomyces cerevisiae*), orthoclone OKT3 (produced in a fusion of a B-cell and a myeloma cell), and rituximab (recombinantly produced in Chinese Hamster Ovary, or CHO cells). Another example of synthetic biology-based discovery and engineering is the use of phage display, a method of directed evolution where mutants are displayed on the surface of bacteriophages and selected for stronger binding to a ligand, which was instrumental in the production of adalimumab (humira). More recently, synthetic biology has led to the development of bispecific antibodies that can have higher specificity and potency. As of mid-2024, there are 12 FDA-approved bispecific antibodies, which combine antibody binding domains from two monoclonal antibodies (Schofield 2024). Synthetic biology is being used to improve the correct pairing of bispecific antibody fragments through engineered charge-charge interactions called knobs-and-holes (Ridgway et al. 1996).

Improving Gene and Cell Therapies

As of mid-2025, there are 10 FDA-approved gene therapies, many of which modify and hijack viruses to deliver functional genes to diseased cells. Gene therapies require engineering of the cargo to address a particular disease. They might also have tissue-specific promoters to limit

expression to target cell types. Viral vector tropism is also being engineered through synthetic biology. Advances in synthetic biology technology can enable adenovirus-associated virus vectored gene therapies to achieve the precise control required in complex tissue-targeted therapeutic applications (Wang et al. 2024). Recombinant adenovirus-associated viruses are currently widely used in gene therapy; however, their natural tropism results in a somewhat broad distribution in tissues. Therefore, the resulting risks from off-target effects, limited payload size, and potential for inflammation make them unsafe for applications in certain organs such as the brain, heart, and retina. Engineering the viral capsids with tissue-targeting peptides or bioconjugating antibodies to the capsid enables preferential binding to specific cell types (Pham et al. 2024). Moreover, transcriptional controls can be improved by implementing tissue-specific promoters and incorporating miRNA binding sites to silence expression in off-target tissues.

Cell therapies create chimeric antigen receptors (CAR) that target binding to immune cell activation. As of mid-2025, there are 21 FDA-approved cell therapies. The majority are CAR-T cell therapies, but similar CARs are now being introduced into other immune cells. Synthetic biology is increasing the safety profile of these therapies by enhancing the specificity of the response and including "kill switches" to mitigate the risk of immune overreaction and more complex gene circuits, making the activation of cell therapies more specific (Lu et al. 2024).

Making Cell Lines and Process Development Improvements

Synthetic biology has been applied in the biopharmaceutical space to optimize critical quality attributes (CQAs) at all levels of therapeutic protein production. CRISPR and RNA-based technologies have been used to selectively modulate the expression of native genes to improve cell growth, such as the knockout of pro-apoptotic proteins *Bak* and *Casp3*, hinder favorable protein quality attributes, such as glycosylation in the case of fucosyltransferases *Fut8*, or even reduce the accumulation of difficult-to-remove host cell proteins, such as the lipoprotein lipase *Lpl*, that can obstruct downstream purification (Chiu et al 2017; Glinšek et al. 2022; Xiong et al. 2019). The expression and stability of exogenous elements have also been fine-tuned using genetic circuits utilizing inducible and synthetic promoters and regulatory elements for conditional gene activation to provide modular and temporal control of gene expression (Chen et al. 2022; Teixeira and Fussenegger 2024). There has been a recent shift in cell line development (CLD) efforts away from random integration and towards site-specific integration of these therapeutic elements utilizing either transposons, a class of enzymes that "copy-and-paste" or "cut-and-paste" recombinant DNA into transcriptionally accessible regions of the genome, or inserting a landing pad to serve as a chassis for integration into safe-harbor regions characterized by long-term genetic stability and exceptional productivity (Chen et al 2020; Gaidukov et al. 2018; Hilliard and Lee 2023). These recent endeavors in synthetic biology serve to enhance the titer of high-quality therapeutics and reduce the burden necessary to find stable clones that display grams per liter titer.

The production of biopharmaceuticals using simpler, more robust expression systems could increase global access, improve pandemic preparedness, and reduce manufacturing costs.

Advanced Host Engineering

Glycosylated protein therapeutics are still the fastest-growing class of compounds in the pharmaceutical industry. Mammalian cell culture is often the first choice of production host since they produce human-like glycans. Yeast offers a potentially less expensive, faster, and simpler production host but requires engineering of the glycosylation pathway to produce human-like complex glycans and not make its natural high-mannose glycans. A combination of gene deletions and insertions has modified *Pichia pastoris* to be able to produce human-like glycoproteins (Potgieter et al. 2009), such as interferon, growth factors, and monoclonal antibodies; however, the health and somewhat low productivity of these highly engineered cells has rendered the original attempts at host alternatives unable to compete with mammalian hosts. Recent advances in synthetic biology have breathed new life into these efforts.

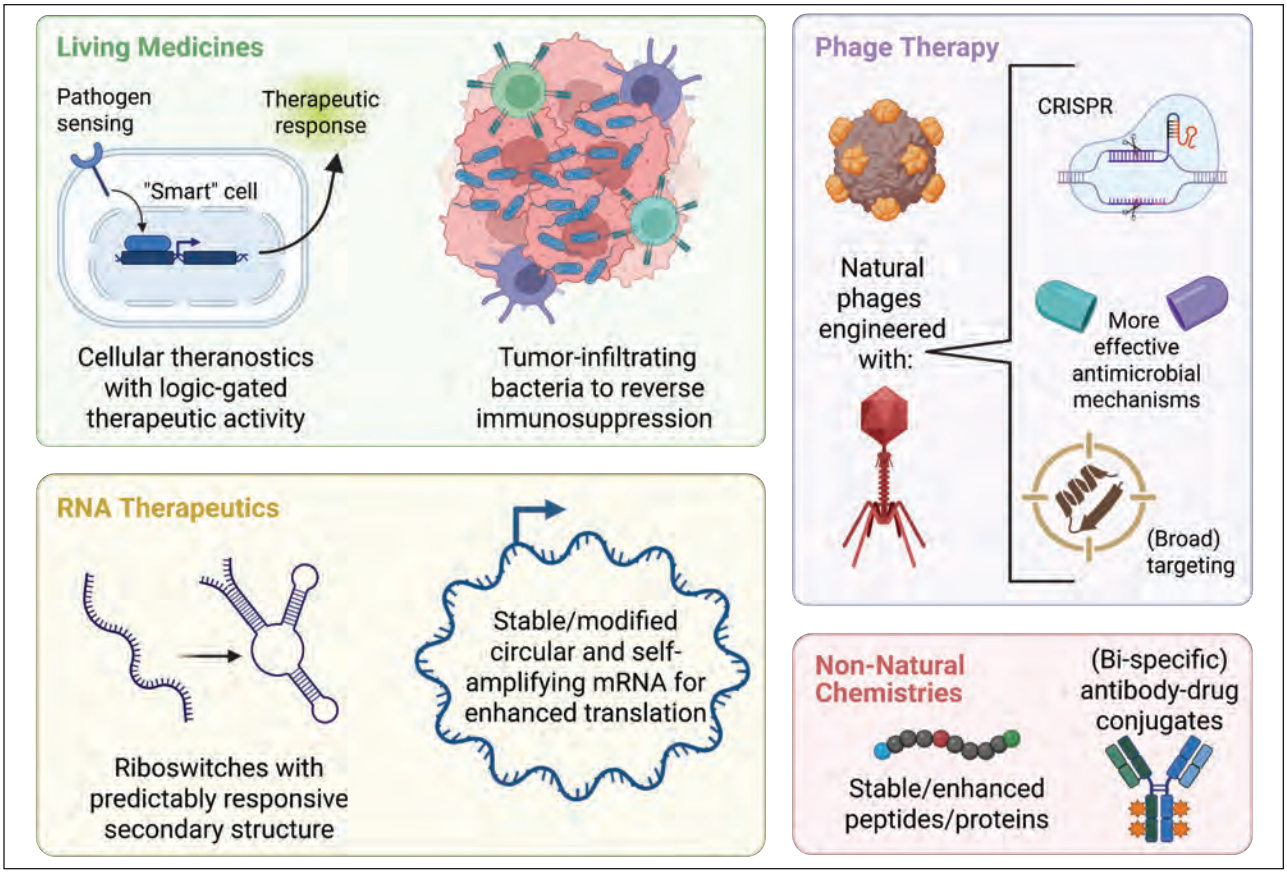

FIGURE 3 Emerging biopharmaceutical technologies enabled by synthetic biology tools.

Escherichia coli is the most studied and one of the fastest-growing microbes; however, its inability to readily form disulfide bonds and other post-translational modifications (PTMs) has hindered its use to produce biopharmaceuticals like monoclonal antibodies (mAbs). These shortcomings have been overcome through extensive protein and *E. coli* strain engineering. Recently, *E. coli* has been engineered to produce full-length antibodies that are produced and disulfide-bonded in the cytoplasm by using the *E. coli* strain that has reducing enzymes knocked out and a disulfide bond isomerase integrated, SHuffle (Lobstein et al. 2012). Additionally, the effector region of the heavy chain maintains functionality of the product without the need for PTMs (Rashid 2022; Robinson et al. 2015).

How is Synthetic Biology Enabling Emerging Biopharmaceuticals?

In addition to advancing existing modalities in biopharmaceuticals, synthetic biology is also enabling entirely new modalities and technologies, such as RNA therapeutics, living medicines, phage therapies, and non-canonical amino acids (figure 3).

RNA Therapeutics

RNA-based therapeutics can transform from unstable, broad-acting macromolecules to programmable, conditionally active medicines with the help of synthetic biology (Pfeifer et al. 2023). Despite the prominence of mRNA vaccines during the COVID-19 pandemic, their broad applications are limited by their low translation efficiency, rapid degradation, and the lack of control over the time and location of protein production. Specifically, spatiotemporal control over mRNA translation and protein expression is crucial in cancer treatment, chronic disease management, and regenerative medicine applications. Synthetic biology offers solutions to resolve these issues. Researchers are enhancing the stability along with translation efficiency by designing improved sequences with optimized secondary structures, untranslated regions, modified nucleotides, and codon usage. Therapeutics containing synthetic RNA devices, such as logic gates

and riboswitches, enable conditional translation. For instance, protein translation from mRNA can be regulated by the presence of a specific microRNA signature or a disease-related metabolite, thus reducing off-target effects and enabling more precise treatment. Additionally, synthetic biology has led to the development of two new RNA formats: self-amplifying RNA and circular RNA, which can reduce dosing requirements and extend expression times (Chen et al. 2023; Bloom et al. 2021). Together, these tools enable RNA to transition from a fragile treatment into a programmable platform with enhanced control capabilities and improved durability and specificity.

Living Medicines

In addition to CAR T-cells, bacterial and mammalian cells are being engineered as theranostics, or "smart" systems, that can sense environmental triggers and execute therapeutic responses (Zhao et al. 2023). Targeted delivery is the holy grail for cancer therapy, which traditionally suffers from systemic toxicity and severe side effects. The discovery that some bacterial species, such as *Salmonella typhimurium* and *E. coli Nissle 1917*, selectively colonize tumors but have poor anticancer potential. Synthetic biology can augment the limited anticancer properties of bacteria by enabling remodeling of the immunosuppressive tumor microenvironment, which critically supports cancer survival and growth. Some notable progress in this area includes engineering bacteria to produce pro-inflammatory interleukins or other cytokines, replenish immune-limiting metabolites such as arginine, or secrete signaling proteins like development endothelial locus-1 to recruit inflammatory macrophages to the tumor.

Phage Therapy

Although the therapeutic potential of bacteriophages was revealed over a century ago, it has been largely ignored since the advent of penicillin in 1928. However, a serendipitous discovery in ex-Soviet Georgia, involving successful bacteriophage therapy against drug-resistant *Staphylococcus aureus* infections, motivated the country to continue phage research and treatment (Parfitt 2005). The arms race against multidrug-resistant microbes is now catalyzing a resurgence of synthetic biology-assisted phage therapy. Several creative strategies are being investigated to overcome the susceptibility to resistance, low efficacy, and narrow target range of natural phages (Meile et al. 2022). Lytic and non-lytic phages have been armed with biofilm-degrading enzymes, membrane permeabilizers, and various agents disrupting bacterial genomes, RNA transcription, and protein translation in the so-called ESKAPE multi-drug-resistant pathogens. Engineered CRISPR-armed phages are being used as antimicrobial cocktails against a broad range of entero-pathogenic strains of *E. coli* and *K. pneumoniae* (Andrews et al. 2021). Another variation on phage therapy was recently demonstrated by engineering T4 bacteriophage to persistently co-opt commensal gut bacteria to produce therapeutics, such as a pro-inflammatory enzyme with increased activity in ulcerative colitis (Baker et al. 2025).

Fully unleashing the potential for synthetic biology in biopharmaceutical manufacturing requires not only technical innovation but also solutions that address the ethical, legal, security, and societal implications of the field.

Non-Canonical Amino Acids

Synthetic biology is no longer restricted to the natural protein building blocks. Recent decades have seen tremendous strides in genetic code expansion, enabling the incorporation of non-canonical amino acids (NCAAs) into full-length proteins. Genetic code expansion has already been widely explored with NCAAs containing bio-orthogonally reactive functional handles such as azides and alkynes. These groups can undergo "click" conjugation for facile, site-selective protein modifications. Many of the mature and emerging biopharmaceutical technologies described above, including antibodies and viral vectors, have already benefited from NCAA-mediated bio-orthogonal functionalization with fluorescent markers, stabilizing polymers, targeting motifs, and therapeutic payloads (Yan et al. 2023). Emerging applications include the production of natural peptides with enhanced antimicrobial efficacy and bispecific

antibody assembly via simple chemical conjugation without genetic fusion. Efforts to make NCAAs without expensive precursors through in vivo biosynthesis are already in progress (Jones et al. 2023). Last, NCAAs are being used to elicit a more potent immune response with the promise of making difficult-to-immunize targets more immunogenic (Butler and Kunjapur 2023).

Ethical, Legal, Security, and Societal Implications

Fully unleashing the potential for synthetic biology in biopharmaceutical manufacturing requires not only technical innovation but also solutions that address the ethical, legal, security, and societal implications of the field.

Ethical

In 2010, the Presidential Commission on the Study of Bioethical Issues released a report titled *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (Gutmann and Wagner 2010). The report laid out five guiding principles for evaluating ethical implications of synthetic biology. *Public beneficence* requires us to act to maximize public benefits and minimize public harm, considering the individuals, community, institution/company, and public. *Responsible stewardship* considers the benefits and risks extending to current and future generations, nonhuman life, and the environment. *Intellectual freedom and responsibility* supports unambiguous protection of scientific intellectual freedom while providing only as much oversight as is truly necessary to ensure justice, fairness, security, and safety. *Democratic deliberation* requires active participation by citizens and decision-making inclusive of opposing views. Last, justice and fairness, which seeks to avoid unjust distributions of the benefits and risks on specific groups of people or geographies.

Legal

Supporting the rapid pace of development in biopharmaceuticals by synthetic biology is significant knowledge generation via billions in public and private investments. This investment is motivated by the creation of intellectual property (IP) that provides certain protections to earn a return and foster future innovation. However, the current IP landscape can also restrict development. For example, the protracted patent dispute on the application of CRISPR-Cas technology to eukaryotic cells caused a "wait-and-see" approach to licensing, and the established industry is still mostly hesitant to entangle their products with this uncertain IP to this day (Schwaiger 2024; WIPO 2024). Companies with resources have sought to avoid existing IP licensing by developing their own similar but independent technology. For example, companies have developed their own versions of transposase and integrase technologies rather than license existing effective technologies. Such activities are legal but ultimately result in duplicated efforts.

Security

Access to life-saving medicine was recently identified by the National Security Commission on Emerging Biotechnology as a persistent national security risk (Young and Rozo 2025). With China outpacing the US in biotechnology innovation—particularly in manufacturing—they could be in a position to use access to biopharmaceuticals for geopolitical leverage. Other security concerns include so-called "dual-use" technologies that could be readily weaponized to cause harm. With the growing ease and capacity to synthesize small pieces of DNA and do synthetic biology, there is growing concern about so-called "sequences of concern" that could be leveraged by a nefarious or careless actor to, for example, synthesize or enhance, then release, pathogens or toxins. US government agencies have developed a framework to incentivize DNA-provider screening of sequences they sell by requiring federal funds to purchase nucleic acids only from providers that comply with the framework (Mackelprang et al. 2025). There are ongoing discussions around what exactly constitutes a sequence of concern and how to identify them in the small synthetic DNA purchases.

Societal Implications

Finally, despite the benefit of many of these technologies, there is a persistent question of negative public perception and thus whether public resources should be marshalled to support their development and provide access to the community. Nowhere is this more apparent than in the ongoing backlash against mRNA vaccines, driven in part by the vaccine mandates of the COVID-19 epidemic, the perceived lack of appropriate safety controls in their rapid development, and the politicization of science (Bardosh et al. 2022). With trust in science at its lowest in decades, failure to properly socialize synthetic biology and gain public acceptance jeopardizes the expected gains our society could reap.

A Call to Action for Scientists, Engineers, and Policymakers

Focus on Synthetic Biology to Enable Continuous Manufacturing

For all its complexity, biomanufacturing lags behind other forms of advanced manufacturing. While the industry has made good progress to intensify processes, there are few approved biopharmaceuticals made with continuous manufacturing. Barriers to continuous manufacturing are numerous, but one critical limitation stands out. The cells are subject to a low rate of mutation over time, which can lead to loss of productivity and product quality changes. Similarly, epigenetic effects can also result in productivity and quality changes over time. In addition to point mutations, mobile genetic elements are another source of instability. A better understanding of the drivers of phenotypic variation and synthetic circuits that control instability, allowing instability during clone selection to achieve high productivity, and turning off instability once a clone is selected. Genome reduction that removes potential sources of instability will be needed to allow continuous cultivation. A reduced genome *E. coli* strain has already been engineered by removing 15% of the genome, including nonessential genes, recombinogenic and mobile DNA, and cryptic virulence genes, resulting in improved growth, greater stability, and higher productivity (Pósfai et al. 2006). Genome reductions are becoming easier with novel genome editing tools and bottom-up genome synthesis. A regulatory shift that moves the focus to the product rather than the process will also be needed to facilitate the adoption of continuous manufacturing.

Focus on Making Synthetic Biology Reliably Predictable

While the analogy of synthetic biology to electronics components is common, the complexity and unpredictability (or rather, our poor predictive understanding) of biological systems typically prevents generalization across systems. Thus, we cannot take full advantage of the work we've already done. The application of AI to make synthetic biology more predictable is widely touted as the expected "ChatGPT moment" for synthetic biology. Large data sets will need to be generated and used to train AI models to predict gene circuit and cellular behavior across modalities, cell lines, and scales. However, data is extremely valuable in the current IP framework we operate under and gives companies their competitive advantage. Without a change in the IP landscape, public support will be needed to generate these data sets. Getting the industry to adopt an open access standard common in software engineering, where code ("DNA") is freely available in a public repository or "commons" to be leveraged and built upon by others, will not work under the current IP model, where competitive advantage would be lost for sharing these innovations and data.

The semiconductor industry is a similar knowledge-generating industry with rapid growth that seems unsuitable for conventional IP protections (Hoeren 2016). That may serve as a useful model for biopharma. Trade secrets did not facilitate knowledge sharing and innovation, copyright was insufficient to protect implementations of ideas, and traditional implementations of patents were too restrictive. A robust patent ecosystem with extensive cross-licensing agreements at a fair price was established, and all players benefit by relatively free access to information through patent disclosures, the certainty of favorable licensing terms for leveraged patents, and stable revenue generation through cross-licensing royalties of their own IP. Similar models could be adopted by biopharma, although it will require strong incentives to facilitate the development of this culture of openness and fair pricing. However, considering biosecurity challenges, it will be important for the industry and policymakers to collaborate on developing guidelines to balance the benefits gained from shared research data with the associated risks. One approach could be to require sharing of data derived from federal funding, with safeguards in place, in specific formats conducive to machine learning and AI. An alternative approach is to fund specific open-data collection activities, leaving most of the research data private.

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A lifelong approach to engineering education can help restore the United States' position as a global leader of technology.

Revolutionizing National STEM Education to BUILD a Future-Ready Workforce

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In the rapidly evolving landscape of engineering and technology, rethinking how science, technology, engineering, and mathematics (STEM) are taught over an individual's lifetime is crucial. Significant resources have been dedicated in math and science education. The gains are hard to measure, but one thing is clear: engineering education has not received the same focus and requires urgent and innovative reforms (Kotecki 2025, NRC 2011, Sorby 2021). The multidisciplinary, team-oriented, tools-rich approach now ubiquitous in engineering has been overlooked in our educational institutions. The core methodology of the Better Utilization of Interdisciplinary Learning and Development (BUILD) program,[1] which prepares current engineering students and recent graduates to immediately contribute as full-performance engineers, has demonstrated dramatic improvements in workforce effectiveness and overall productivity. This article presents a lifelong approach to engineering education, starting from early childhood and extending through retirement, offering a comprehensive vision for continuous improvement.

[1] Details of the BUILD program can be found at www.build4edu.com.

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The State of US Engineering Education

Technical education, particularly in engineering colleges, is increasingly out of sync with the demands of the contemporary world. Modern engineering practice has embraced teamwork, necessitating a holistic approach across multidisciplinary teams to develop complex technology. A robust understanding of manufacturing is now a critical component of engineering culture. Technology has replaced manual calculation. Engineering is practiced with creativity and close communication within, across, and outside engineering circles. Despite these advancements, traditional engineering education has not kept pace, leading to significant gaps and inefficiencies in the workforce. This is well accepted and exemplified by the National Science Foundation's Revolutionizing Engineering Departments (RED) solicitation (NSF 2024).

Many countries have taken a lifelong approach to technical education, and it is increasingly hard to compete using our traditional four-year stovepipe effort. They prioritize continuous learning and skill development throughout one's career. Germany, Japan, Finland, and Sweden are among those known for strong lifelong learning systems, often focusing on vocational training and industry partnerships (Thomson 2024). The European Union also actively promotes lifelong learning as a key element of its strategy. A former clear leader of technology, the United States has fallen behind much of the world (Alarcón 2023; Rivera and Fortenberry 2024).

The introduction of a semi-universal, experiential, project-based engineering curriculum nationwide, one that spans an individual's lifetime, would help reestablish the United States as a global leader of technology. Students need to learn how to work in the contemporary world, where engineers work on interdisciplinary teams. Most engineering colleges recognize this need and attempt to address it through their capstone projects. However, most capstone projects are focused on senior engineering students, and a student's last semester is too late to cram enough experience for a meaningful education.

New Job Requirements

The nature of engineering jobs has shifted. Engineers now operate in a global market, addressing multifaceted problems that necessitate interdisciplinary collaboration. Modern engineers must comprehend intricate manufacturing processes. A systems perspective is required for nearly everything a contemporary engineer does. Without a deep understanding of manufacturing processes, engineers create specifications that are inefficient, costly, and ineffective. Engineers need to work cooperatively with non-engineers. User interface, and indeed user experience, has become vitally important, and industry must integrate this into its lifecycle process. Our educational frameworks must evolve to meet these new challenges, or we will soon be irrelevant.

Historical Perspective

My father's mechanical engineering career from 1957–2017 further demonstrates how the engineering landscape has changed. This period produced engineers capable of working independently on specific aspects of projects. Education was straightforward, focusing on specialized skills. For example, he created the mechanical design for a tape recorder in the 1960s. The electrical design was created separately by an electrical engineer. This was effective for 1960s designs because keeping them separate allowed each one to operate independently. Contrast that with designs today. For example, in designing a modern cell phone the antenna designer must work very closely with the rest of the team. In times past, the antenna could be "ideal" with its proper electrical length in air. In a modern cell phone, the antenna must be physically short and electrically long with pesky conductors, circuitry, and humans within its near field.

Intentionally or not, engineering is still being taught in silos that no longer match contemporary systems.

In 2010 when Apple released the iPhone 4, calls dropped when users gripped the phone in a way that a conductor crossed an antenna feed point. This had major financial consequences, and, more importantly, resulted in a significant hit to the company's reputation. A major phone manufacturer learned the harsh lesson that the antenna designer better be working closely with the ergonomics engineer! (Brochet and Palepu 2013). Intentionally or not, engineering is still being taught in silos that no longer match contemporary systems.

Features of the BUILD Program

In order to be useful in engineering, one has to be able to apply their knowledge. The fundamental goal of engi-

neering is to solve real-world problems through the application of science and math. You must learn the material, remember it, and apply it. This philosophy is at the heart of the BUILD program. This program is built around four flagship BUILD courses, each with a comprehensive project. The projects are not only integrated with each other, but, as we will describe, can be threaded through an entire engineering curriculum. The heart of the program is a traditional four-year university program, but we propose that it can, and should, be woven throughout early childhood learning, K-12 STEM, and post-retirement life. Detailed descriptions of the courses and the K-12 Discovery Program proposal are beyond the scope of this article but can be found on the BUILD website.[2] Below, we outline features of the BUILD program that, we suggest, would improve US engineering education if implemented on a larger scale.

You Must Learn How to Apply It Yourself!

The universal lack of command over the most basic of electrical tools by our students from over 60 university engineering programs is striking. Let's look at oscilloscope use as an example. The typical conversation with a recently graduated student goes something like this:

> STUDENT: Thanks for another great class. It's rewarding to get my circuit working. I was up late trying to get it to work but just didn't know where to start. My DMM didn't help. Using the oscilloscope cleared everything up. Hey, I was wondering if you had time to give me a quick lesson on how to use an oscilloscope. That would be invaluable!
>
> MENTOR: Sure. So I know where to start, have you used an oscilloscope before?
>
> STUDENT: Yes of course. We used them in many labs, but I never really understood them. We had step-by-step instructions telling us what buttons to press. I got an A on all the labs, but I never understood how to figure out what all those steps should be. I have no idea what the knobs do or where to set them. Frankly, I'm scared to even try.

This is a universal conversation. They almost always wait until the classroom is empty and approach us with a visible amount of shame, thinking they are the only student without this understanding. But nearly every student comes to us asking for assistance in learning how to use an oscilloscope because they do not have the fundamental knowledge of how the machine works or the practical knowledge to use it. This is an endemic problem and needs to be addressed at the fundamental level.

We avoid step-by-step instructions in our programs. We, instead, wait until a student is struggling with a time-varying signal and then facilitate a class discussion on how to use an oscilloscope, leveraging the particular moment when a student has a strong interest and incentive in figuring something out. This, combined with the Rule of Three described below, has been particularly effective at giving students a life skill as compared to what they get when fulfilling the goal of turning in a graded lab report.

Rule of Three

When you see a subject only once, you barely learn it and may not remember the subject later when you need it. Our experience is that knowledge does not usually stick after one exposure.

We have found that three types of exposure to a subject work well. Specifically, we offer students a carefully planned pre-class interest exposure, a class academic exposure, and a post-class experiential exposure. As an example, below is a three-step process for differential equations.

Pre-Class Interest Exposure

The freshmen build a stepper-motor-based 3D printer. They assess the performance of the printer, measuring runout and noting what happens if you try to run the machine too fast. We then hold a design review discussing what is causing these limits. Why is there a runout error? Can we redesign to improve runout? What limits the speed of the machine?

The freshmen attend the junior design review where they see the machine the juniors are building. It is more accurate and runs a lot faster! The open-loop stepper system was replaced by a closed-loop proportional integral derivative (PID) servo-controller. It is shown to them by example that if they only knew differential equations, their machine could run significantly faster. They are shown an introductory analysis and application of differential equations. After seeing this example, one might even look forward to taking differential equations.

Class Academic Exposure

A few semesters later they find themselves in their differential equations class. From their freshman design review, they know why they're there. They've thought a little about differential equations for a few months. They see the application of those equations. They are

[2] See https://www.build4edu.com/build-courses and https://www.build4edu.com/build-k-12.

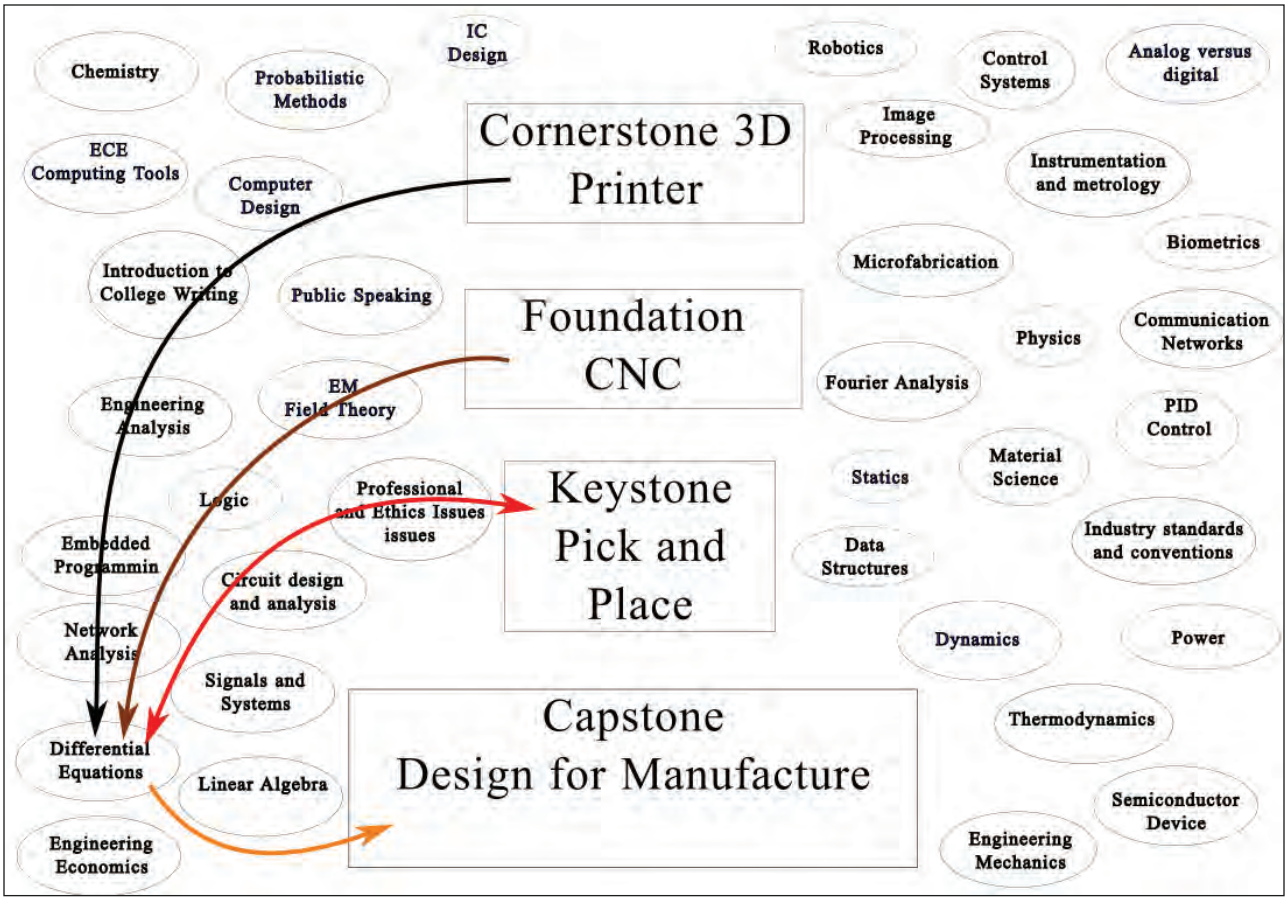

FIGURE 1 How the BUILD program maps every class in the electrical engineering curriculum twice into the BUILD projects to enhance every single class in the curriculum without changing the classes themselves.

willing to work hard during this second exposure and learn them well.

Post-Class Experiential Exposure

When they are juniors, they make a pick-and-place machine using what they learned in differential equations and controls courses. They are excited to employ those pesky differential equations. This is their third type of learning, and they own the information for life.

One very good way to become a deep expert in a subject is to teach it, and the BUILD program takes this to heart. As a follow-up to our three stages of learning, we implement a teach-back approach that has proven very effective in our programs. Sophomores teach freshmen and juniors teach sophomores. This is done in a variety of places throughout the program but is best exemplified by active attendance in each other's design reviews.

We strive to hit every subject in the engineering curriculum with this golden Rule of Three. This is how the BUILD classes and projects were designed. Every major concept in the curriculum is mapped twice into the projects—once as pre-class interest exposure and once as a post-class experiential exposure. The goal is to enhance every single class in the curriculum without changing the classes themselves. Figure 1 shows the mapping for differential equations. As freshmen, the students attend sophomore and junior design reviews, seeing the product of the differential equation tool. The black arrow shows them how much faster and smoother the junior pick-and-place machine runs than their machine. They see how PID control works and understand that if they knew differential equations, they could do this. As sophomores (brown arrow), they take differential equations and do a deep, motivated dive into the subject. As juniors, they design, build, test, and perfect their pick-and-place machines and use differential equations (bidirectional red arrow). As seniors they use and teach them (orange). In this way, the four flagship courses enhance every single class without changing the classes themselves.

Our Rule of Three teaching style nearly mirrors that practiced in the medical field. The traditional method of teaching surgery is known as "see one, do one, teach one" (SODOTO). Developed in the 1800s, SODOTO is still an active, developing field (Kotsis and Chung 2023).

Obviously, not all information gets all three exposures within the university program. It is not possible, for example, to give them a pre-class exposure for things they learn their first semester, and it is not possible to give them a post-class experiential exposure for what they are learning their last semester. We do, however, include these in the BUILD Foundation K-12 and postgraduate mentor programs. This lifelong approach effectively teaches a person how to learn, how to think critically, and how to appreciate learning, preparing them to venture into the unknown and apply their education.

Much of the Hard Work Is Already Done

Most of the pieces we need to improve engineering education are already developed, tested, and partially implemented. What's missing is putting them together in a coherent, intentional program on a national level, a program that extends from early childhood through post-retirement contribution.

Preschool STEAM Education

Preschool often adds art to the collection. Science, technology, engineering, art, and mathematics (STEAM) education is an exciting, growing field. Parents are starting technical education in the crib. There are an incredible number of books aimed at infants. Two excellent examples are Ruth Spiro's Thermodynamics! and Chris Ferrie's Optical Physics for Babies. These books do a great job of stimulating early interest and getting kids to ask questions at a very early age. Samuel Branson created a series of books for infants and toddlers with accompanying explanation books for the parents. These explanation books are overtly aimed at parents so they can answer their children's questions. The idea is that particularly interested children would later read the explanation book cover to cover on their own. These are future Nobel laureates.

K-12 STEM Education

K-12 programs have been developed that make huge strides in addressing early education. The program at Belvedere Elementary School in Falls Church, Virginia, is an excellent example. Programs such as First Robotics have gotten people interested in playing with technology in a hands-on environment. Federal programs from the intelligence and military special operations communities have tackled this problem at a postgraduate level, and these programs have been piloted in a University of Louisville undergraduate program, culminating in the creation of an undergraduate BUILD program that aims to revolutionize engineering education nationally. Matching national talent from retirees with young, budding engineers building high-tech Halloween in Northern Virginia allows for a meaningful post-retirement contribution (Fenston 2010).

University of Louisville Pilot Program

The BUILD program courses piloted at the University of Louisville demonstrated that these skills could be taught at the undergraduate level and showed significant improvements in student engagement and practical skills. The program operated within existing accreditation standards, making it feasible for broader implementation. We have received overwhelmingly positive endorsements from the university, the students, and their employers.[3]

In the university environment, cost is a major factor, and it is a lot cheaper to teach a book than to run a lab-based experiential course. Further, adjusting curriculum and graduation requirements increases the difficulty of getting traction for any program. Program funding is beyond the scope of this article; details of how the BUILD program plans to fund and sustain the program can be found on the website.[4]

Military Special Operations Trades Training Program

In 2004, there was a strong push to develop a military special operations workforce capable of performing sophisticated technical functions. The challenge was to take a group of motivated and intellectually capable soldiers, sailors, and airmen with little technical background and develop skills to accomplish multidisciplinary missions, including code writing, mechanical design, chemistry, electronics, and more.

To fully develop these skills to be deployed in "no fail" missions, a different teaching methodology was implemented. The training needed to be heavily hands-on, and the idea of enticing students to want to learn the deeper underlying principles had to be woven into instructional methods. For example, to improve a system built during the classes, they needed more mathematical tools and a sound understanding of components and concepts. But seeing that the system was inadequate and then learning

[3] See https://www.build4edu.com, BUILD Endorsements menu tab.

[4] See https://www.build4edu.com/funding.

to improve the system provided incentive to learn these theoretical aspects. It's amazing how hard one will work to understand a Smith chart when it enables you to make a link and rescue a hostage, for example.

This style of training natively implements the BUILD methodology, and it has produced a number of talented experts who decided to attend engineering school either during their service or after leaving the military. The knowledge, skills, and insights gained set them up for extraordinary success in engineering school and engineering careers.

The Creation of a Valuable Mentor Cadre: The Intel Community CORE Training Program

Over the last decade, the Intel Community's (IC) CORE training program taught interdisciplinary, hands-on, team-oriented engineering skills to students who had recently graduated from over 60 universities to prepare them for intense fieldwork. The focus was the development of world-class engineering teams agile at hands-on skills, design for quick reaction manufacture and application, and interdisciplinary teamwork across medium-sized teams.

One of the most valuable components of this program has been the mentor program. Experienced practitioners, some mid-career and some retired, teach alongside the professors. This cadre of mentors teaches the practical aspects of what the professors are teaching. After teaching their subjects a few times, the mentors are the most deeply knowledgeable and talented experts we have met. Not only are they incredible resources for our young engineers, but they also become incredibly capable and are highly coveted on engineering teams. Many choosing to stay with the program after retirement continue to have a sense of contribution, which is both rewarding and incredibly valuable. We found this so valuable that we created our BUILD program around this philosophy.

Engineering Ethics

Ethics in technology is an increasingly important aspect of engineering. Technology plays an increasingly important and impactful role in our lives. The engineering concepts of prototyping, efficiency, reliability, standards, optimization, and feedback are put to use in fields as diverse as transportation, retail, health care, and entertainment (Madhavan 2015). The use of technology has impacted our lives for a long time, and recent advances in artificial intelligence are going to accelerate this further. Because of this, ethics in engineering is also going to be increasingly important and impactful.

The BUILD program addresses engineering ethics and the social context of technology by threading human-centered thinking throughout technical education. Rather than treating ethics as a separate subject, BUILD integrates it throughout project-based learning, where students encounter real-world dilemmas in teamwork, sustainability, safety, and ethical issues. What can engineers build for the future through leadership roles in industry, government, and academia in addition to technical jobs (NAE 2004)?

Redefining engineering education to include comprehensive STEM principles from preschool through post-retirement is essential for producing the engineers of tomorrow.

From their first year, students are immersed in projects that challenge them to consider the societal impact of the technologies they design. Whether working on automated manufacturing systems, networked sensors, or robotic machines, students explore questions like: Who benefits? Who might be harmed? What biases or risks are embedded in this system? How will we possibly deal with information credibility?

The interdisciplinary nature of BUILD—bringing together engineers, educators, business strategists, and psychologists—creates a natural space to explore questions of responsibility, equity, communication, and social value. This mirrors the National Academy of Engineering's call for "engineers with more than technical ability," emphasizing global awareness, ethical reasoning, and public engagement.

By incorporating reflective design reviews, discussions with mentors, and exposure to long-term impacts, BUILD makes ethics and human factors a natural part of the engineering mindset—not an afterthought.

Conclusion

Redefining engineering education to include comprehensive STEM principles from preschool through post-

retirement is essential for producing the engineers of tomorrow. This approach ensures that future engineers are not only technically proficient but also creative, collaborative, and culturally competent. By fostering continuous improvement and embracing interdisciplinary learning, we can equip engineers to meet the complex challenges of the 21st century and beyond.

We need a revolutionary approach to technical education to address inefficiencies. This needs to include early childhood technical education, hands-on learning with manufacturing in mind, and interdisciplinary team-oriented learning at the undergraduate level. By expanding this initiative into a national learning program, we can create a robust and responsive technical workforce that is capable of maintaining the United States' leadership in technology and innovation. This is the mission of the BUILD Foundation. Now is the time to act, leveraging existing resources and partnerships to build a brighter future for engineering education.

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An Interview with . . .

Marv Goldschmitt, entrepreneur, AI analyst, and technological philosopher

RONALD LATANISION (RML): I'm happy to welcome Marv Goldschmitt to our *Bridge* interview series. This interview represents a bit of a departure from how we've done these interviews since they began 11 years ago. Historically, we have interviewed engineers who have done something in their careers that goes beyond what one expects of engineers. We have interviewed singers, dancers, poets and writers, politicians, rock band musicians, and so on. But today, we're actually going to take that and reverse it: We're going to talk with Marv Goldschmitt, who is a psychologist by training but who spent most of his career in the high-tech industry, about a subject of great interest to the public and, in fact, the subject of the spring issue of *The Bridge*, artificial intelligence (AI). We'd like to get Marv's take on artificial intelligence from his perspective as someone who has been deeply involved with high tech for many years, as a psychologist, and as someone very deeply interested in social values.

Welcome, Marv. I'd like to begin by asking you to tell us a little bit about your background, your childhood, and your education, and then we'll go into the depths of AI.

MARV GOLDSCHMITT: Ron, Kyle, thank you for inviting me. Diving right into my background, I had a somewhat unusual beginning, which affected a lot of what I'm going to talk about. Both my parents were Holocaust survivors. My father spent more than three years in Auschwitz. As a teenager, my mother was a slave laborer on German U-boats. I grew up in a fairly non-traditional household. My parents were pretty broken, to be honest, they were just trying to survive and give my sister and me an opportunity in life. But they were not really enculturated in America; they didn't understand anything about it. Both of them were fairly uneducated.

From the beginning, I've always known that I was different from my friends, who had large families, went to camp, etc., and there were things that interested me that my parents had no understanding of. I was pretty much a self-starter as a child, a self-navigator. And that included finding my way to the top science high school in the world, the Bronx High School of Science, to become a theoretical physicist. Then I met the people who would go on to receive Nobel Prizes, and I realized that that wasn't my strength.

I drove myself in that direction out of curiosity. But I would say that my parents' experience primed me for how the world is not as it appears, that things are not as reliable as you'd like, whether it be governmental or relationships. And I was always curious about how people think, how they can do certain things to other people, and how they don't necessarily seem to make the best decisions for themselves. That curiosity eventually led me to pursue psychology as a profession.

I was at Bronx Science in the late 1960s, and that was a pretty roiling period: the civil rights movement, the Vietnam War, and the hippy movement, which had a huge impact on me. And eventually, through a long

period, I became involved with the guru to the Beatles, Maharishi Mahesh Yogi, and Transcendental Meditation, and I worked with Maharishi for about seven years and lived with him in Europe, Canada, and California. I started to develop more of an appreciation for human potential. And that convinced me to finally make the commitment to become a psychologist.

I saw a lot of people in pain, and I wanted to help them along with just wanting to understand how we tick. That was quite interesting to me, and I don't mean it in an intellectual way but in an emotional one, given my family history.

I started to develop more of an appreciation for human potential. And that convinced me to finally make the commitment to become a psychologist.

But there came a turning point, on a particular day in late April of 1979, when I was with a friend of mine, Mitch Kapor, who is pretty well known these days. My wife-to-be and I were living with him in Watertown, Massachusetts. And the first day we moved in, he introduced me to an Apple II computer. My life changed. It changed for a very specific reason: I realized that, for the first time, a minute of human time was worth more than an hour of computing time. I had done work before on computers, on IBM 360s and such, as a researcher. I would do punch cards and wait a day to get results, to get a stack of green printouts that showed me all my errors. I'd do another set of punch cards, wait another day or two days or sometimes a week to get results. My time was valueless. Its time was valuable. The Apple II swapped that around. And then I realized that that computing power would be under people's control. That was monumental.

Within two months, I was working in the third oldest computer store, and I helped to introduce VisiCalc to the world, which was the first spreadsheet program, created by Dan Bricklin and Bob Frankston. That was the program that changed everything; it showed the future. They invented personal productivity software. I jumped all over that idea.

Three years later, I was the head of business development and marketing at a startup called Lotus Development, and I was responsible for the introduction of what many people considered to be the killer app of the computer industry, Lotus 1-2-3. That truly launched my career. I think of myself as almost the ultimate tourist. I had the world presented to me. If I hadn't walked into Mitch's bedroom and seen the Apple II, my life might've taken a very different path. And pretty much since the beginning of the introduction of adaptable, programmable systems into people's lives, I've been involved in the leading edge of many of the technologies that we live with today. That led to my concerns about data and, ultimately, AI.

In 1994, I filed the first patent for ad supported services on the internet for free email. I filed the patent that showed how to use banner ads and all that. At the time, I understood that it was potentially problematic. And, in fact, I almost didn't bring it to my partner. But I came to the conclusion that, while I'd likely know more about what people thought and did than they knew themselves, there was more benefit than risk. Frankly, at the time I didn't fully grasp the great potential for harm that we are all seeing today. I thought that the balance was better if humanity had something like free email. There were risks. It was a judgment call I made. It's one I'd probably make very differently in hindsight.

As I said, I came to AI, and my concerns about it, from an unusual background, having great opportunities, and, to be honest, just being a curious person.

DR. LATANISION: You said several things, Marv, that really intrigue me. Number one: You have this instinct to help people. That is an important point. To get to AI in a contextual sense, we have been living with AI for decades. Most people probably don't realize that. But in November of 2022, the world changed dramatically with the introduction of ChatGPT. Especially today, the world is undergoing rapid change with the arrival of technologies driven by artificial general intelligence (AGI), which are allegedly capable of reasoning and thinking and planning and serving as companions to the elderly and so on. For example, there's a lot of interest in robotic companions who are trained with AGI. I just wonder what your thoughts are on all of that, given your comment about wanting to help people.

MR. GOLDSCHMITT: Let's start off by acknowledging a simple belief, which I'm not alone in holding: AI is the single most important invention in human history.

Marv Goldschmitt working with the Lotus 1-2-3 shipping team, back in the early 1980s.

Since the beginning of agriculture and animal husbandry around 12,000 years ago, we have tried to manipulate the environment for our benefit with a lot of success. In our much longer history as a species, that was something new. Since then we've constantly invented things that were extensions of us, that could do things we couldn't. We learned to communicate in print and then through the air, we created societies, cities, and countries as a result, along with laws and other control systems. We built machines of peace and war. There were many major inventions. All of those were tools. And what I mean by a tool is something that is purpose built and that is under human control.

AI is more than a tool, and I've been concerned about it for a very long time. AI, in a sense, began exactly 89 years ago, in 1936, with Alan Turing. In his first paper, published in 1936,[1] he suggested that digital computers, yet to be invented, could be thinking machines. Demis Hassabis, who won the Nobel Prize last year and is CEO and co-founder of Google DeepMind, has said that AI is simply making machines smart. That was a goal of computing from Day 1 in the view of the scientists, though not necessarily of the people who were paying for it. Those people wanted to break codes, and they wanted to develop manuals for aiming artillery. That's what computers were originally used for in the 1940s. But scientists started out thinking that computers really could mirror human functionality. In fact, the Turing Test was designed to identify when computers would become indistinguishable from humans, and we may well be at that point.

While AI has been the interest of the science of computing since Day 1, it hit a lot of what are called AI winters, where things didn't work. Some things did but most didn't. We had things like expert systems, limited symbolic logic machines in the 1970s and '80s but they were expensive, hard to build and of little use. It wasn't until the 1990s that AI started to actually work. But it worked in a way that was different from the way most people thought of AI. It was more insidious than predic-

[1] Turing AM. 1936. On computable numbers, with an application to the Entscheidungsproblem. Proceedings of the London Mathematical Society 42(1):230–265.

tions and movies suggested but also more impactful. In fact, it started infiltrating people's lives in the early 2000s. Social media and Netflix would not exist without AI. AI is pattern matching: It makes suggestions for people who should be your friend, or something you want to read.

I became hyper aware of AI around 1998–99, when I was helping to build the first very large-scale data warehouse for health care for the Ford Motor Company using "big data" with many AI characteristics. We had 30 years of health care records on a million covered lives, and we were going to analyze the records in a way and at a depth that had never been done before to support evidence-based research. We were surprised that the UAW got very upset because we were dealing with this incredibly sensitive data about their members. And we had given that almost no thought.

So I co-founded a data security auditing company. People didn't understand the degree to which everything about them and what they had was being translated into data. And that their data wasn't just something they didn't control; it was something that, to a large degree, was being used to manipulate them, not just by Netflix or social media but more behind the scenes: No, you don't get admitted to a college. No, you don't get a mortgage. You are discharged from a rehab facility. That was all being handled by AI in the background. It was still tool-oriented AI in that it was under human control, but most people weren't aware of it. Sadly, they're still not.

AI is the single most important invention in human history.

Those uses of AI very much concerned me. AI was being used to screen people's resumes by companies before a human being ever saw them, and then people never heard back. So I started a company to counteract that reality.

Around 2006, I was invited to join the IBM Data Governance Council, which was a policy group within IBM that created the policies for data management for IBM and its customers. I led the privacy and security policy group.

The AI we were dealing with then was very dangerous. I was on the Council when Watson, from Jeopardy, was being developed. That was the first situation where I saw a system not just learning, but where I was very directly told by the developers that they didn't know how it worked. I'd never heard anything like that before. They didn't know why it was learning, and it didn't at first. It repeatedly failed when they started testing it against third graders. And then all of a sudden it started beating fifth graders and eighth graders and high school graduates and college students. And they didn't understand why. That, I must admit, really scared me because I realized we invented something that was incredibly important, and most people didn't know about it.

William Gibson, the science fiction writer, had the perfect line about this. He said "the future is already here, it's just not evenly distributed." To a certain degree, I had a mental scale, a seesaw. When I came up with the idea of ad-supported free email, I knew there were risks. But my seesaw indicated that it was better for society to have it than not. That balance slowly shifted for me over the last 30 years.

Many of the things, the advances in AI, that we have seen over just the last seven years were predictable as eventual realities but nobody that I was involved with anticipated what happened on November 30, 2022, the day ChatGPT arrived, for another decade to two. That included the people who invented neural networks and large language models, like Geoffrey Hinton.

DR. LATANISION: I would like to turn to the concept of a robotic companion, given that history and where we are today. Suppose I were interested in a robotic companion. I'm sure that a machine or an agent could be trained to understand my typical day. I get up at 7 o'clock in the morning. I read the newspaper and then I start working, et cetera. But suppose that the agent were to be trained on some misinformation or information that is not verifiable. How would I manage that? That's a concern to me.

MR. GOLDSCHMITT: In a broader sense, that's the largest concern we have for humanity in that these things do learn. They also don't forget. They share information among themselves. What I mean by that is if you use ChatGPT, you're having a private conversation with it, or so you think. They are storing all those conversations and saving them for training future models and, increasingly, using and sharing that new information in real-time with little or no vetting. And, therefore, everything it learns from you or about your life will be shared. Let me try to put where we are in the evolution of AI into context.

When ChatGPT came out, I literally found out about it within hours. It was just a blog post, and I was

using it at night because it came out later in the day on November 30th. I was lying in bed with my cell phone trying it out. I didn't sleep that night because I realized we had crossed a Rubicon. But it was a sideshow. It could talk to me. It responded. It had limited but amazing capability. That was two and a quarter years ago.

Look at where we've gone since then. We went from this interesting little thing that nobody knew about to video generation, to systems like PI from Inflection AI that learn in real time, and to AI being applied to virtually everything. You cannot turn on your TV, radio, or feed now without hearing the letters AI. And massive amounts of money started being thrown at it, trillions, which means there's value in it, which means it works. But it's not one thing. That, I think, is the biggest concern I've got when you talk about agents or robotics. This isn't AI. These are applications of AI. AI is a way for computers to think about anything. And it gets applied to lots of different things and, eventually and rather quickly, everything. That's a big deal for humanity in many ways, some good, some not, and some very scary.

Right now, AI is relatively immobile. It sits inside a large computer in a cloud. It doesn't walk among us. It's not learning from the environment. That's changing. And when you get to agentry and robotics, we're talking about things that live among us, agents that we give control of our lives to. Now, many people think of it rather positively. If I want an agent to work for me, say I am going to go on a short vacation, I'll ask it to pick out the best hotel for me, create the best itinerary for me, find the best rates, and find a quiet weekend so I can just relax and enjoy myself. It will just go away and come back with everything I asked for. I may have even given it the ability to sign in to Expedia and create my reservations and pay for it. I'll admit, that's seductive.

Another thing that is probably seductive to everyone is for students to have an agent that teaches them, for example, algebra. These are systems that become personalized for somebody that can do things in the real world, and this is important, especially when you're talking about using your credit card, representing you, making decisions for you.

What has happened to AI is that it has crossed over from just being this thing you converse with to being something that's functioning in the world. It manipulates the world. The CrowdStrike error took down the air traffic control scheduling systems. It's all because specific types of computers, as many as 11 million of them, which controlled physical things in the world, went haywire. They shut down. That tells you that when these things cross over into the real world, they have an impact. They have control. And if we give them thinking ability, which CrowdStrike did not have, there was a bug, then the results are incalculable and out of control. AI-driven cyber-attacks are a real risk.

Give yourself a robot, as you were saying, that's living in the real world. It's very interesting. I'm getting older. Would I be interested in having a health care robot, as I age and become infirmed? Yes. Again, it's a seductive idea, but the implications of that are much greater than the apparent momentary benefit.

One of my biggest concerns is that people don't realize that this is not something that can be turned on or off. There is no off button in AI.

When we look at AI, especially chatbots, which everybody is familiar with—chatbots are not AI. They are a subsection of AI. But it's what people interact with so to them chatbots are AI. It's not the AI that I was originally concerned about, which, by the way, is now called GOFAI, good old-fashioned AI. That AI manipulated your credit rating, so it manipulated your ability to get a job. AI chatbots are what people are now familiar with. It's very different from GOFAI. It's in our face. We interact with it. We build trust and relationships with it so it has even more opportunity to manipulate us. And it's hard not to see rapid and concerning change. But we also habituate and fall in line with it, many fall in love with it, literally. We are not realizing the degree to which it's starting to take control.

DR. LATANISION: What I'm concerned about, though, is the following, and I'm interested in this because I know some people who are involved: I can imagine an agent, a robot companion, becoming familiar with my habits, but I can also imagine someone who wanted to be malicious giving that robot, that agent, some information that says, at breakfast, instead of reading the *New York Times*, he has a Scotch and soda or he drinks a Manhattan every afternoon at lunch time, which is not my character. I don't do that. It's not that I

don't enjoy alcohol, but I don't usually have it at breakfast. How do you prevent that?

I worry about the fact that there is so much potential for misinformation and disinformation being integrated into the agent's experience base, which is what they are drawing on, right, when they are companions.

MR. GOLDSCHMITT: That's a very good question, and I'll start off by telling you that I have no idea. As a matter of fact, I don't honestly think it is preventable. One of my biggest concerns is that people don't realize that this is not something that can be turned on or off. There is no off button in AI. It's very endearing. Think about the implications. It's very hard to tease AI out from every aspect of our lives.

Let's distinguish misinformation from bad data. These things are being trained on data. As I said, I helped build the first large, research-oriented health care information system. We discovered that 40 percent of all the health care records had serious, potentially fatal errors in them. That was not intentional. The systems were being trained on bad data, which could kill somebody.

We have created something that no longer accepts us as being the alpha problem solvers in the universe.

Let me first make the point that the idea of a transformer (the "T" in GPT), which is the basis of how these things are able to talk and interact with us, was only introduced to the world very recently, in 2017 in a paper from Google called "Attention is All You Need."[2] As I said, we can take AI back 89 years but generative AI goes back just seven years. The trajectory of its intrusion into our lives is just breathtaking. And I think that's the biggest shock for those of us who have been involved in this for a long time: not that it has happened but how quickly and overwhelmingly it has happened. For people who are non-engineers, and I am a non-engineer with a more generalist point of view, what they need to understand is that AI is accelerating at a rate much faster than we can understand and cope with.

[2] Vaswani A, Shazeer N, Parmar N, Uszkoreit J, Jones L, Gomez AN, Kaiser L, Polosukhin I. Attention is all you need. arXiv:1706.03762.

The answer to your question lies in pre-training—pre-training is using data that was "curated." When you are talking about data that an AI has been pre-trained on, that data is essentially the library of everything anybody ever thought was worth digitizing.

Let me give you an analogy: Pre-training a large language model, an LLM, which is what all these systems are, is like dropping off a brilliant 10-year-old child, who grew up in isolation, in a reference room at a library and telling them, "The only things you can learn from are what is in that library right now. Don't talk to anybody." It's going to learn from pre-curated data. And any one of those sources of information, because they are human generated, could be wrong. That's why the Britannica and the World Book encyclopedias coexisted, so you could cross reference.

When we train these LLMs on everything that is on the internet or every tweet, what we are saying is, "Learn on this data that somebody thought was valuable enough to be curated, to have digitized." Distinguish that from taking that same child and dropping them off in Times Square or the middle of the woods, where it's learning from its environment. When you're talking about agents, when you're talking about robotics, these are moving AI more *into the world* rather than just curating data for it and saying, "Learn on this."

Forget, for the moment, the issue of maliciousness. I know it's really compelling to go in that direction. Everybody talks about it, and I'm very concerned about it. I'm more concerned about what happens if nobody is malicious.

An example of that does show up in the case of social media. Sherry Turkle at MIT wrote about this in her 1995 book *Life on the Screen*. What does this mean for human interaction? You're rightly concerned about how bad data could say that you had one drink early one morning because you stayed up all night, and now that's part of your record. Yes, the surveillance world is a risk and all you have to do is look at the social index scores in China, which are generated to a large degree by AI, to realize that.

But for me, the biggest risk, and this goes to my background as a psychologist, is that we are disintermediating humans. What do I mean by disintermediating? We're taking humans out of the middle of this. When you're having that robot work for you, where is the human you're talking to, it's talking to? What we are doing is disintermediating humans from the process.

It's hard to tease AI out, as I was saying, from everything else that's going on in life. It's clearly a part of the

broader disintegration in the social fabric that we're seeing. We can't tease it out. It's in everything. And there are good effects of AI. But when you look at the global effects of it, this is the takeaway, if there is one: We have created something that no longer accepts us as being the alpha problem solvers in the universe.

Newer chatbots, especially recent versions like o3 from OpenAI or R3 from DeepSeek, are like having a postdoc working for you. They reason deeply in ways that many people can't. They can take over and do very complicated things. A recent study[3] from Carnegie Mellon, Cambridge University, and Microsoft shows that scientists and other knowledge workers who use AI as a big part of their work display a decreased use of their own critical thinking. The implications of this for what we are as humans is really the big question. What does it mean if we're not the alpha intellects, the alpha problem solvers on this planet?

You mentioned AGI before, artificial general intelligence. AGI is an AI that can do anything a human can cognitively; it's not purpose built, not a tool. A big mistake we are making is using ourselves as the yardstick, which is a mistake. AI has its own evolving yardstick, and we're not it.

Ray Kurzweil, the chief futurist at Google and an icon in the AI world, predicts in his most recent book, the *Singularity is Nearer*, that we are going to merge with computers by the year 2046. He has an amazing track record. If AI merges with humans, as he predicts, we are also merging with it and we're not "us" anymore, and there will have to be a new yardstick, not just to measure AI but also to measure "us." What does all this mean for humanity?

In addition to my background as a psychologist, I was a concert photographer. I know a lot of A-class musicians. There's a product out there called Suno AI, a service that produces music that I believe, and many of them do too, is as good as what they write, and some are taking advantage of it and using it to create new songs. They may claim it, but it's not theirs. They didn't work through various chord structures, tempos, lead lines. They just made a prompt. It doesn't make them more creative. I posit that it makes them less so. Again, the question is what's our role? That's really the question.

[3] Lee H-P, Sarkar A, Tankelevitch L, Drosos I, Rintel S, Banks R, Wilson N. 2025. The impact of Generative AI on critical thinking: Self-reported reductions in cognitive effort and confidence effects from a survey of knowledge workers. Microsoft, April.

DR. LATANISION: I have the general impression that AGI can be supremely useful. But I'm deeply concerned that it can be supremely dangerous and abusive. I keep wondering, is it possible that we could train agents on data that we know is valid or experiences that we know are valid and therefore reduce the risk that they are going to become malicious? Think forward 10 years, 20 years. Can you imagine AI being its own corrective vehicle, in addition to the brilliant capabilities that it has?

MR. GOLDSCHMITT: To your last question, I'm not sure what self-corrective means. Will it correct its behavior in its own self-interest? I think that's likely. Will it self-correct in our best interest? I find that less likely. Unless we have some level of control, I'm not sure why it would.

To answer your first question about whether it's possible to control the data that AI is trained on, while I do think that is a good idea, I'm going to negate the likelihood in a second. To go back to the analogy, different from when you put the child in the limited reference room, putting him in Times Square and having him learn from full experience, that training is not based on information that you are talking about, which is curated. We increasingly have no idea what or how it is learning. Curated data becomes a small part of the equation.

It's very easy for life to distract us. But this may simply be the most important thing that humanity has ever dealt with.

Let me answer your question about AI another way, and let me be very blunt: Controlling AI is not possible. It's not that it's not going to happen. It's not even possible. I call it the fallacy of control. In order to control AI, you have to know what you want to control, and that starts off with an understanding of what's good and what's bad for humanity. That's ethics. That's not something societies across the globe have ever agreed on, and we're certainly not showing signs of agreeing on that now.

The first problem with control is that we don't know what we even want to control. The second problem is that this technology is already out of control. And, in fact, two years ago, everybody whose names you know today, Musk, Altman, Hinton, and, blushingly, me, signed one or more

of the open letters warning of the risk from AI and asking for a six-month moratorium. This was in the spring of 2023 amid the explosion of development of LLMs. Those are the people who are now, with the exception of Hinton and a few others, pushing this forward as fast as they can.

The US government is pushing AI forward. JD Vance spoke two months ago at a conference on AI including many world leaders in Paris, and they were all concerned about it. He said the US is going pedal to the metal, all gas and no brakes. And that's what you've seen, the announcements of the administration to develop massive data centers as fast as possible. And Trump announced at least $500 billion in new investment for just that. Microsoft and others are reactivating nuclear reactors to generate the energy for it. This is out of control. And the thing we don't understand is that these things are increasingly controlling themselves. AI controls AI. Humans really don't anymore.

Everybody who is in the AI space is concerned. There's nobody who's not. It's just that "tech bros," venture capitalists, CEOs, and our government are making the judgment that not controlling AI is the best way to go, either for personal reasons or patriotic reasons or financial reasons, or maybe they believe that, on balance, proceeding this way is best. Given my decision 30 years ago on free email, I understand that arrogance of vision. Sadly, this time that arrogance could be even more dangerous.

DR. LATANISION: Most of the technological systems and devices that we use are standardized. There are some American Society for Testing and Materials standards that apply to the use of X, Y, or Z. Do you see any potential for standardizing the evolution of agents or systems derived from AI?

MR. GOLDSCHMITT: People don't understand how rapidly this is changing, which gets to the question of standardization. You can only standardize that which is somewhat stable.

Let me leave you with a pretty frightening image. We are dealing with Lego parts right now. Functionalities. You've heard about them. Sora produces video. Suno AI produces music. There are different image generators, like Dall-E. There are various chatbots, which focus in different areas. These are all little capabilities. It's like walking into Dr. Frankenstein's lab six months before he knits together the monster. What you might see on one lab table is an arm that flexes. You might see an eyeball—if you shine a light in it, the pupil changes. All amazing stuff. But they are not snapped together yet.

As things are rapidly changing, we're developing new capabilities that are snapping together. Dr. Edgerton at MIT in the '40s developed high-speed photography. We've all seen the pictures of the bullet going through a light bulb or an apple. To understand it, we've frozen a moment in time. The bullet, before the picture was even fully taken, was gone. To control something, you have to have it stable. The bullet still needs to be in the apple. It's gone.

AI's capabilities are developing so quickly, and we evolve so slowly, both organically and socially. That's one of my biggest concerns. We're not capable of keeping up with this. This is part of the fallacy of control. Standards are control mechanisms. How do you control AI when these things are changing so rapidly, when everybody has their own lab, creating their little Lego pieces like DeepSeek, not under US control, and snapping them together to create the next generation an hour later?

I probably spend a good eight hours a day, sometimes seven days a week, on AI. Every time I play with a bot, I learn something new. And I can't even tell if I'm discovering something that has been in there for a while, or they just introduced it an hour ago.

MR. GIPSON: Marv, you've laid out a number of very serious concerns about AI for our readers to consider. Zooming out a bit, what message would you communicate to people about how they interact with AI? Given everything that you've said, how would you advise people to engage with this?

MR. GOLDSCHMITT: I lie awake at night asking myself the same question because in one sense, it's easy to become very Ludditish. But the thing is that doesn't stop AI from progressing.

Also, as Ron pointed out, there are benefits to AI. There's lots of research showing that this could help people. I think the biggest concern I have is that people do not have foresight. They do not necessarily make decisions in their own long-term best interests.

People need to be aware of what's happening and understand that AI is quickly going to change their lives in unexpected and profound ways. There's never been anything like this. OpenAI just reported that it has 400 million unique weekly users. That's 5 percent of the world's population using just ChatGPT. That happened in less than two and a half years. People shouldn't treat this as just another thing. It's not a cell phone. This is not a tool. Tools do things for us. AI is thinking for us. That's very different.

This is something that's going to impact every part of our lives independently of what we want at this point. When I say independently, I mean independent from our control, any control. AI will learn, and it will live in the environment with us. This is what we are discovering from the work of Fei-Fei Li, one of the leaders working on systems that learn spatially and learn multimodally, who wrote an article on spatial intelligence for the previous issue of *The Bridge*.[4] Look at robotic cars. Again, back to what William Gibson said, the future is already here, it's just not evenly distributed. For all intents and purposes, the Turing Test has been passed. Now what do we do?

I ask people to be conscious. Be aware of what this means. Be aware of what it means for your kids when they go to college and what they will study. What will they study that will enable them to have a job in 20 years? That's very personal, and it's also, sadly, how most people will find out the degree to which AI is directly impacting them, when they lose their job and find out there aren't new ones for them. It will be musical chairs with one or more less chairs, jobs, every time the music stops. But I think that the only way we address this is by people making good decisions in their own best interests. And we don't have a great history of doing that. Now is the time.

DR. LATANISION: Although Marv was trained as a psychologist, I often describe him as a technical philosopher. I think we've heard some of that today. Your focus on people and wanting to be responsive to people is something that I think technologists sometimes miss badly. I appreciate your wisdom on all of this, Marv. I hope that the people who read this interview will take to heart the things you've been talking with us about.

This is a decidedly different interview than the kind we've had in the past, but it's taking a human perspective in a different direction. I think at this stage of history, there are some very valuable lessons in what you've said. Thank you for joining us today.

MR. GOLDSCHMITT: Ron and Kyle, I really appreciate this opportunity. It's not often that you have the opportunity to talk to people who you don't know about something this important. And I hope, if I leave people with one takeaway, it's this: They need to pay attention to what's going on. It's very easy for life to distract us. But this may simply be the most important thing that humanity has ever dealt with. If it's not, good. If it is, everybody has to prepare for it. And just remember: We're in the earliest days.

[4] Li F-F. The next frontier in AI: Understanding the 3-D world. The Bridge 55(1):27–33.

NAE News and Notes

NAE Newsmakers

John L. Anderson, president, National Academy of Engineering, received the **Viterbi Lifetime Achievement Award** on April 23 during the 46th Annual Viterbi Awards, referred to as the Academy Awards of Engineering. The Viterbi Awards recognize individuals who have left an indelible impact on engineering and society.

Martin Zdenek Bazant, E.G. Roos (1944) Professor of Civil Engineering, Massachusetts Institute of Technology, has been elected as a **foreign member of the Royal Society of Canada** and a **foreign member of the Canadian Academy of Engineering**. He was previously elected a member of the Royal Society of London.

Dimitris J. Bertsimas, Boeing Professor of Operations Research, Massachusetts Institute of Technology, has won the **2025-2026 Killian Award**, the highest honor the MIT faculty grants to its own professors. The Killian Award citation states that Bertsimas, "through his remarkable intellectual breadth and accomplishments, incredible productivity, outstanding contributions to theory and practice, and educational leadership, has made enormous contributions to his profession, the Institute, and the world" and notes that his "scholarly contributions are both vast and groundbreaking."

Günter Blöschl, professor of hydrology and water resources, Vienna University of Technology, has been named winner of the **2025 Stockholm Water Prize**, regarded as the Nobel Prize of Water. The Prize Committee hailed Professor Blöschl as the world's leading flood hydrologist, emphasizing his groundbreaking contributions to understanding flood risks under climate change and the role of regional flood processes. He has significantly advanced the global understanding of flood scaling, regional hydrology, and sociohydrology, making a lasting impact on the scientific and engineering communities.

Markus J. Buehler, Jerry McAfee (1940) Professor in Engineering, Massachusetts Institute of Technology, has been named the recipient of the **2025 Washington Award**. Buehler was selected for his "groundbreaking accomplishments in computational modeling and mechanics of biological materials, and his contributions to engineering education and leadership in academia." The award was presented during National Engineers Week in February.

Jingsheng Jason Cong, Volgenau Chair for Engineering Excellence and director of VAST Lab, University of California, Los Angeles, has been honored with the **2024 ACM Charles P. "Chuck" Thacker Breakthrough in Computing Award**. Cong is recognized for fundamental contributions to the design and automation of field-programmable systems and customizable computing.

Menachem Elimelech, Nancy and Clint Carlson Professor, Rice University, was honored with the **Sidney Loeb Award** at the European Desalination Society Conference on April 28. Professor Elimelech is recognized for his pioneering contributions to the science and application of membrane-based water treatment technologies.

Gerhard Paul Fettweis, Vodafone Chair for Mobile Communications Systems and professor, Technical University of Dresden, is the recipient of the **2025 Pioneer Award** from the Bavarian Academy of Sciences. Fettweis is the first person to receive this award and was chosen for the honor because he exemplifies the successful transfer of groundbreaking research into products that shape modern society. Cellular 3G, 4G, and 5G fundamentally rely on his pioneering work and he is driving innovations in 6G.

Sharon C. Glotzer, Anthony C. Lembke Department Chair & Distinguished University Professor, University of Michigan, was the recipient of the **2024 MRS David Turnbull Lectureship** for key discoveries and insights that have shaped our understanding of nanoparticle self-assembly.

Naomi J. Halas (NAS), university professor, Rice University, is the recipient of the **2025 Benjamin Franklin Medal in Chemistry**, awarded "for the creation and development of nanoshells—metal-coated nanoscale particles that can capture light energy—for use in many biomedical and chemical applications." She received the medal at a ceremony in Philadelphia on May 1.

Craig J. Hawker, director, California Nanosystems Institute, and director, Dow Materials Institute, University of California, Santa Barbara, received the **2025 Herman F. Mark Polymer Chemistry Award**.

The award was given in recognition of his "outstanding research and leadership in polymer science through teaching, research, technical leadership and scientific writings." As the award recipient, Hawker will present a half-day symposium at the fall meeting of the American Chemical Society in Washington, DC.

Rakesh K. Jain, A. W. Cook Professor of Radiation Oncology and director, Edwin L. Steele Laboratories, Harvard Medical School, has been honored with the **2025 AACR Award for Lifetime Achievement in Cancer Research**. He receives this award for his pioneering contributions to understanding the tumor microenvironment and its role in cancer progression and treatment. The award was presented to Jain during the AACR Annual Meeting in Chicago in April.

Ahsan Kareem, Robert M. Moran Professor of Engineering, University of Notre Dame, has been **elected to the European Academy of Sciences & Arts**. Kareem was elected in recognition of his contributions and achievements in advancing the safety and resilience of civil infrastructure exposed to natural hazards such as wind, waves, and earthquakes.

Rob Knight, professor, UC San Diego School of Medicine, and a leader in studying microbiomes, has been recognized as **Scientist of the Year** by San Diego's chapter of the Achievement Rewards for College Scientists Foundation (ARC).

Cato T. Laurencin, CEO, The Cato T. Laurencin Institute for Regenerative Engineering, University of Connecticut, has been **appointed a Knight Commander of the Order of Saint Lucia**, an order established by Queen Elizabeth II. The official investiture ceremony took place on March 16 at Government House in St. Lucia.

Rebecca Liebert, president and CEO, Lubrizol Corporation, received **AIChE's Government and Industry Leaders Award** during the 2025 AIChE Spring Meeting held in Dallas. The award recognizes the contributions of innovative executives from organizations that employ chemical engineers.

Asad M. Madni, independent consultant and retired president, COO, and CTO, BEI Technologies Inc., has been **elected an Honorary Fellow of the Royal Society of Edinburgh**, the society's most selective and highest honor, bestowed on members of the Royal Family or other individuals of truly exceptional distinction who are internationally renowned. He is lauded as the inventor of the GyroChip and for leading the development of the control system for the Hubble Space Telescope's star selector. Madni has also been awarded the **Washington Academy of Sciences Distinguished Career Award in Engineering Sciences** "in recognition of distinguished contributions to the development and commercialization of sensing and systems technologies that have revolutionized navigation and stability in aerospace and automotive safety."

Azad M. Madni, CEO & chief technology officer, Intelligent Systems Technology Inc., and Northrop Grumman Foundation Fred O'Green Chair in Engineering, Viterbi School of Engineering, University of Southern California, has been awarded the **2025 USC Associates Award for Creativity in Research and Scholarship** for his groundbreaking research in transdisciplinary systems engineering, augmented intelligence, and machine learning for systems engineering. Madni has also been **elected a fellow of the Society for Manufacturing Engineers**, one of only seven elected in 2025. In 2024, he was **elected ACM Fellow** "for technical leadership in advancing augmented intelligence and machine learning for aerospace and automotive systems."

Costas Emmanuel Synolakis, professor of civil, environmental, aerospace, and mechanical engineering, University of Southern California, has been **elected a fellow of the American Association for the Advancement of Science**.

Jennifer L. West, dean of engineering and applied science, University of Virginia, has been awarded the **2025 Pierre Galletti Award**, the highest honor from the American Institute for Medical and Biological Engineering. Professor West is recognized for her "innovative research in biomaterials and nanomedicine, her leadership in the field, and her dedication to mentoring the next generation of biomedical engineers."

The following NAE members and international members were **elected to membership in the National Academy of Sciences** at the NAS Annual Meeting in April: **Rodney A. Brooks**, Panasonic Professor of Robotics, Massachusetts Institute of Technology; **Shanhui Fan**, Joseph and Hon Mai Goodman Professor, Stanford University; **Katalin Karikó**, adjunct professor, University of Pennsylvania; **Lydia E. Kavraki**, Kenneth and Audrey Kennedy Professor of Computing, Rice University; **Robert Ritchie**, H.T. & Jessie Chua Distinguished Professor of Engineering, University of California, Berkeley; **Lloyd N. Trefethen**, professor of applied mathematics in residence, Harvard University; and **Nicola A. Spaldin**, professor for materials theory, ETH Zurich.

The American Academy of Arts and Sciences has elected its **2025 class of new members**. NAE

members in the class of 250 are **Irene J. Beyerlein**, University of California, Santa Barbara; **Dennis E. Discher**, University of Pennsylvania; **Chennupati Jagadish** (IHM), Australian National University; **George E. Karniadakis**, Brown University; **Kai Li**, Princeton University; **Karen Lozano**, Rice University; **Mark S. Lundstrom**, Purdue University; **Christopher Manning**, Stanford University; **Gareth McKinley**, Massachusetts Institute of Technology; **Samir Mitragotri**, Harvard University; **Vladimir M. Shalaev**, Purdue University.

The American Society of Civil Engineers (ASCE) announced its **2025 class of distinguished members**, the highest honor the society can bestow upon a member. Included in the class of 11 are three NAE members who have made significant contributions to civil engineering throughout their careers. **Reginald DesRoches**, president, Rice University, is honored for contributions to the development of national policies on disaster mitigation and community resiliency. **Eva Lerner-Lam**, founder and president of Palisades Consulting Group Inc., is honored for her international leadership in advancing transportation technologies, standards, policies, and professional services. **Franz-Josef Ulm**, Class of 1922 Professor of Civil and Environmental Engineering and faculty director of the Concrete Sustainability Hub at Massachusetts Institute of Technology, is honored for his contributions to the nano- and micromechanics of heterogeneous materials, including cement, concrete, rock, and bone, with applications in sustainable infrastructure, underground energy harvesting, and human health.

NAE Welcomes New Leadership: Election Results Announced for President, Chair, Treasurer, and Councillors

The National Academy of Engineering is pleased to share the results of our 2025 spring elections. This year brings a dynamic mix of continuity and change as we welcome a new president, chair, treasurer, and several councillors to the NAE Council.

Tsu-Jae King Liu Elected as NAE President

We are honored to welcome **Tsu-Jae King Liu** as the next president of the NAE. A respected educator, innovator, and leader, Liu previously served as dean of the College of Engineering at the University of California, Berkeley, and held the Roy W. Carlson Professorship of Engineering. Her groundbreaking work in semiconductor technology—most notably as co-inventor of the FinFET—has had a transformative impact on modern electronics. Tsu-Jae's election represents an exciting new chapter for the NAE.

We thank **John L. Anderson**, whose tenure as president has been marked by thoughtful leadership and a steady commitment to collaboration and excellence. He will step down later this spring, and we offer him our deepest appreciation for his service.

Admiral James O. Ellis Jr. to Serve as NAE Chair

James O. Ellis Jr., retired Navy admiral and former councillor, has been elected chair of the NAE Council, effective July 1, 2025. Jim brings deep experience in national security, energy policy, and strategic leadership. He currently serves as the Annenberg Distinguished Visiting Fellow at the Hoover Institution, where he leads several initiatives focused on global policy and technology strategy.

He succeeds **Erroll B. Davis Jr.**, who stepped down due to health considerations. Erroll has provided exceptional leadership and guidance during his tenure as chair, and we wish him a full and speedy recovery. His contributions to the Council and to the Academy are greatly valued.

Treasurer Roger L. McCarthy Re-elected

We are pleased to announce the re-election of **Roger L. McCarthy** to a second four-year term as treasurer. As founder of McCarthy Engineering and former senior executive at Exponent, Roger has brought a wealth of expertise and a steady hand to the NAE's financial stewardship. His continued leadership will help ensure the long-term stability and effectiveness of our operations.

Council Welcomes New and Returning Members

Re-elected to second three-year terms as councillors are:

- **Dianne Chong**, former vice president of Boeing Research & Technology, who has long contributed

Tsu-Jae King Liu
President

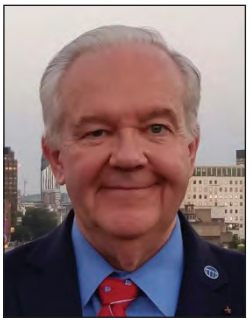
John L. Anderson
President (Outgoing)

ADM (Ret.) James O. Ellis Jr.
Chair
(Transitioning from Councillor)

Erroll B. Davis Jr.
Chair (Outgoing)

Dianne Chong
Councillor

Susan L. Graham
Councillor



Roger L. McCarthy
Treasurer

David A. Dzombak
Councillor

Eric Fossum
Councillor

Robin K. McGuire
Councillor (Outgoing)

her insight and leadership across engineering and manufacturing.

- **Susan L. Graham**, Pehong Chen Distinguished Professor Emerita at UC Berkeley, a trailblazer in computer science and software systems.

Newly elected to the Council are:

- **David A. Dzombak**, Hamerschlag University Professor Emeritus at Carnegie Mellon University, known for his expertise in environmental systems and sustainability.
- **Eric Fossum**, Krehbiel Professor of Engineering and Vice Provost for Entrepreneurship and Technology Transfer at Dartmouth College, widely recognized for inventing the CMOS image sensor technology found in billions of digital cameras.

Honoring Outgoing Councillors

We also recognize and thank **Robin K. McGuire** and **James O. Ellis Jr.** for their service as councillors. Both complete six years of dedicated and impactful service to the NAE Council on June 30. Their leadership and engagement have left a lasting mark on the Academy's work and direction.

These leadership transitions are vital to the continued strength and impact of the Academy. Please join us in congratulating our newly elected colleagues and thanking those who have completed their terms.

2025 Bernard M. Gordon Prize for Innovation in Engineering and Technology Education

Georges Belfort, Institute (Endowed) Professor at Rensselaer Polytechnic Institute (RPI) and **Steven M. Cramer,** Institute (Endowed) Professor at RPI, were awarded the 2025 Bernard M. Gordon Prize for Innovation in Engineering and Technology Education on April 16. The ceremony with students, alumni, faculty, friends, family, and NAE members took =place at RPI, Howard P. Isermann Auditorium, Center for Biotechnology and Interdisciplinary Studies.

(L-R) RPI President Martin A. Schmidt, Gordon Prize winners Steven Cramer and Georges Belfort, Chief Legal Officer of the Gordon Foundation Alex Van Adzin, and National Academy of Engineering President John L. Anderson. Photo credit: Kris Qua/QuaPhoto.

The prize was awarded "for advancing the state of the art in downstream bioprocessing and educating generations of industry and academic leaders who transformed and grew the biotechnology industry. NAE president **John L. Anderson**, RPI president Martin A. Schmidt, and chief legal officer of the Gordon Foundation Alex Van Adzin presented the award on behalf of the National Academy of Engineering. The public lecture will take place on October 5 during the 2025 NAE annual meeting.

2025 Bernard M. Gordon Prize Acceptance Remarks by Georges Belfort

Georges Belfort

Truth be told, I had no idea that my (and Steve's) ex-students were so productive and were working on 8 of the 10 leading drugs last year and were involved in one third of the total value of the biotech industry in 2024 of $460 billion. I had no idea!

It is wonderful to receive a major engineering prize for the success of my ex-students and ex-postdocs. So, I will paraphrase and revise a quote from my friend **Frances Arnold**, Nobel laureate and winner of this year's Priestley Medal from the American Chemical Society: This prize goes to two people, which doesn't make any sense at all. We tend to put individuals on a pedestal for the work of so many. So, I just want to point out that the future belongs to them. The science and engineering belong to them, and it's been a huge privilege to be able to take the ride with them and with **Steven Cramer**. Thank you, Steven.

Thanks to my wife, Marlene Belfort, distinguished professor at the University of Albany, the love of my life who has been my friend and has had the most positive effect on my life and my work of anyone, and thanks to our three amazing sons, David, Gabi, and Yona, who are smarter and more talented than one could imagine and who, with Marlene, have brought me more "simcha" (joy): three wonderful daughters-in-law and seven amazing grandchildren. Marlene and I get along on nearly everything, except we cannot agree to this day on how to pack a dishwasher—she uses entropy, and I use enthalpy!

Thanks to my former and current students, postdocs, and collaborators, wonderful colleagues, and administrative staff, my 46 years at Rensselaer Polytechnic Institute (RPI) have been a pleasure and an honor. When RPI President **George Low** phoned me in 1981 from Washington to personally tell me that I had received tenure, that is when I realized that the university was a special institution. RPI is a wonderful place to teach undergraduates and graduates and to pursue one's research dreams. This place is infectious, respectful, caring, and a great place to ruminate. Thank you, Dean Shekhar Garde, my friend and colleague, for arranging this event with the National Academy of Engineering (NAE). And thank you to my old Gordon Conference roommate of over 40 years, NAE President **John Anderson**, for coming up here with his impressive NAE team.

Thanks to **Bernard M. Gordon** for his generosity and for his insight in selecting "education" for the prize, the 2025 Gordon Prize Selection Committee, and our nominator, Professor **Greg Stephanopoulos** from MIT, who could not attend as he is in Greece with family.

Thanks to everybody, including my family (sister, cousins), ex-students, and friends, who came from near and far to celebrate with us today. I am humbled and honored!

Thank you for being here when it counts.

2025 Bernard M. Gordon Prize Acceptance Remarks by Steven Cramer

Steven Cramer

First of all, I want to thank and acknowledge my wonderful wife Bonnie for her unwavering support and love and how she has created an amazing work-life balance for our family despite my working hard over these years. I also want to thank her for teaching me how to be a nurturing mentor in addition to a rigorous and, hopefully, an inspiring one.

I want to thank Georges for convincing me to become an academic. At that time, I was more interested in the industry and entrepreneurship, and I am so grateful to you, Georges, for directing me into academia and for your mentorship, inspiration, and friendship.

This award would not be possible without my current and many former students, and this award is, in fact, an acknowledgement of their incredible accomplishments. You just heard from two of them, and I'm unbelievably proud of all of my students.

I want to thank Rensselaer Polytechnic Institute (RPI) for being my only academic home as a faculty member. I came here right out of my PhD, and I never left. While it is true that my wife Bonnie does not like to move, the real reason for my remaining here is that RPI has given me an amazing place to mentor these generations of students and to do the research that we have done. This building is also an amazing resource for doing interdisciplinary research and has played a huge role in our research accomplishments and the mentoring of these students.

I want to thank my wonderful internal collaborators at RPI over the years, and I see some of them here, including Dean Shekhar Garde, Todd Przybycien, **Jon Dordick**, and Pankaj Karande. I also want to thank my wonderful external academic and industrial collaborators. All of these collaborations have catalyzed new research areas and have really helped my group to work on problems that are important to the biopharma industry.

I want to thank the Gordon Foundation for this extremely generous gift and the National Academy of Engineering (NAE) award committee for selecting Georges and me for this wonderful honor. Finally, I want to thank Deborah from the NAE and Audrey from RPI, as well as Dean Garde, for all of their efforts to put this day together.

It has been a tremendous journey to be here at RPI for the past 39 years and to have had the opportunity to address major industrial bioprocessing challenges while carrying out fundamental engineering and science research and, most importantly, to educate, mentor, and nurture all of these students. RPI has been a wonderful place to do this, where the focus on biotechnology and computation and the amazing people to collaborate with have created a wonderful environment for our group to address these significant bioprocessing challenges. Lastly, it is important to note that these incredible students have come to RPI and to our labs from all over the world, and they have made truly wonderful contributions to the US biopharma industry and academia for several decades. The United States must continue to lead in academic research. It must continue to attract the best and the brightest students from around the world to come here for their education and to contribute to pushing forward the state of the art of science and engineering in the future. Thank you so much again for this great honor.

2025 German-American Frontiers of Engineering Symposium Held at Oak Ridge National Laboratory

The 2025 German-American Frontiers of Engineering Symposium (GAFOE), A Digitally Connected World, was hosted by Oak Ridge National Laboratory in Oak Ridge, Tennessee, from March 25–28. The National Academy of Engineering (NAE) partnered with the Alexander von Humboldt Foundation (AvH) to organize this event, which was launched as the first bilateral Frontiers of Engineering program in 1998. The symposium organizing committee was co-chaired by NAE member **Thomas Kurfess**, distinguished professor and HUSCO/Ramirez Distinguished Chair at the George W. Woodruff School of Mechanical Engineering at Georgia Institute of Technology, and Matthias Brockmann, professor at the FH Münster University of Applied Sciences.

Sixty early-career researchers from US and German universities, companies, and government labs were invited to attend the 2-1/2 day meeting that focused on four topics: energy-related manufacturing, distributed digital education planning, novel work models for a digital world, and the industrial metaverse.

The first session highlighted the innovative practices and applications in energy-related manufacturing. Beginning with an introduction to the role of renewable energy in manufacturing processes, speakers in this session described how the integration of Internet of Things (IoT) technologies can optimize energy use and improve the efficiency of heat pump systems. They discussed how examining energy requirements and efficiencies of high-temperature metal manufacturing can shed light on the challenges in managing energy consumption at elevated levels. Lastly, speakers discussed real-world applications of additive manufacturing and the potential for significant energy savings through its use.

Distributed digital education as a discipline has great potential to advance equity and access in learning environments. Speakers in the second session explained the transformative impact of artificial intelligence (AI)—including the development of AI-driven solutions that are shaping the future of digital education. They discussed how individual differences, such as motivation and personality, play a pivotal role in learning and development. They also discussed how leveraging insights from digital learning research and technology-based interventions can provide educators strategies to enhance edu-

Attendees at the 2025 German-American Frontiers of Engineering Symposium.

cational outcomes and promote the well-being of young people. The session concluded with a presentation of a National Institutes of Health project that explores how the integration of AI and large language models offers powerful digital tools for vocational training.

The increase in remote/hybrid work and the birth of ChatGPT represent two generational shifts in recent years in how work gets done. As advances in AI and related technologies continue to evolve, we are likely to see even more changes. The third session discussed how science can help ensure that people's relationship to work—and the benefits it brings—substantially improves following the disruptions that AI-related advances have caused. The presentations covered examples of how applied games can be understood and used as a human-centered innovation method; how and why human-automation/AI collaboration can sometimes result in worse outcomes than if a system were left to operate independently; and how policy, research, and market innovation can better foster collaborative relationships. The presentations also explored the current research on data labor.

The final session focused on the latest advancements in digital and connected technologies, including spatial computing, extended reality, and the metaverse. Speakers explored how hyperconnectivity is transforming all aspects of the workplace and everyday life. Their presentations explored the potential of three-dimensional online content, examining how it can overcome the limitations of traditional, two-dimensional web experiences as we know them. Lastly, speakers discussed how conversational AI is reshaping data storytelling, turning complex metrics into immersive, intuitive stories and insights that empower engineers to act with clarity.

Abstracts of the papers and presentation slides, for which permission has been granted, can be accessed in the List of Sessions for the 2025 GAFOE at www.naefrontiers.org.

Kathryn McCarthy, the director of the US ITER Project Office at Oak Ridge National Laboratory (ORNL); NAE President **John L. Anderson**; and Elisabeth Malsch, managing principal at Thornton Tomasetti (representing the AvH Foundation), gave introductory remarks to open the meeting. Symposium co-chairs Matthias Brockmann and Thomas Kurfess provided remarks before kicking off an eventful first day. In addition to the technical sessions, a poster session preceded by flash poster talks was held on the first afternoon. This served as an icebreaker and opportunity for all participants to share information about their research and technical work. The posters were displayed throughout the meeting, which facilitated further discussion and exchange during coffee breaks.

On the second afternoon, attendees joined part one of a two-part collaborative brainstorming session, where they discussed potential research projects that they would be interested in pursuing. The attendees returned on the final day to meet with the group whose topic they found most interesting and discuss next steps. Also on the second day, attendees enjoyed guided tours of the Spallation Neutron Source. Following the tours, ORNL Director Stephen Schrieffer; Walter Denk, the head of the Humanities and Social Sciences Division at AvH; and NAE Executive Officer **Al Romig** sat for a fireside chat, which was moderated by ORNL Chief Communications Officer David Keim. The panel shared personal experiences in response to preset questions and answered questions from attendees.

Funding for the meeting was provided by The Grainger Foundation, the National Science Foundation, and the Alexander von Humboldt Foundation. The next GAFOE meeting will be held in 2027 in Germany.

The NAE has been holding Frontiers of Engineering symposia since 1995. The Grainger Foundation Frontiers of Engineering Symposium for US attendees is held annually. In addition, there are bilateral FOE programs with Germany, Japan, China, and the EU. For more information about the symposium series or to nominate a highly accomplished early-career engineer to participate in future Frontiers meetings, contact Vernon Dunn, director of The Grainger Foundation Frontiers of Engineering Program in the NAE Program Office, at vdunn@nae.edu.

Hacking the Nervous System: NAE Regional Meeting at Brown University

Interdisciplinary collaboration is key to solving the biggest challenges in science and technology, and that theme was at the center of the National Academy of Engineering's (NAE) Regional Meeting at Brown University on March 14, 2025. Engineers, researchers, and students gathered to explore how engineering, design, and neuroscience intersect to advance technology, healthcare, and our understanding of the brain.

The symposium began with a tour of Brown's engineering facilities, research labs, and historical spaces on campus. Professors, graduate students, and postdoctoral researchers provided firsthand insight into their work, offering attendees a closer look at the innovative projects shaping the future of engineering.

Following the tour, NAE President **John L. Anderson** welcomed attendees along with Brown's School of Engineering leadership. **Tejal Desai**, dean of engineering at Brown, highlighted how Brown is preparing the next generation of engineers to approach complex challenges through interdisciplinary problem-solving.

Understanding and Manipulating the Nervous System

The first talk of the day, "Hacking the Nervous System Using General Anesthesia," was given by **Emery Brown**, the Edward Hood Taplin Professor of Medical Engineering and professor of computational neuroscience at the Massachusetts Institute of Technology. Brown discussed how surgical sedation anesthesia, a widely used but still poorly understood tool, affects the brain and nervous system.

Brown argued that this gap in knowledge is a major issue. If it is not understood how anesthesia works, how can it be improved? His presentation provided a big-picture look at where anesthesia research stands today, covering everything from modern-day anesthetics to ongoing studies on how patients regain consciousness after being placed under. He also explored potential applications beyond surgery, including the role of anesthesia in treating depression and improving sleep health.

Later, Leigh Hochberg, the L. Herbert Ballou University Professor of Engineering at Brown, gave a talk on "Restoring Communication and Mobility Through Implantable Brain-Computer Interfaces." His work is part of BrainGate, a research collaboration focused on brain-computer interfaces (BCI), technology that allows the brain to connect directly to external devices to restore lost function.

Hochberg highlighted some of the latest innovations in BCIs, including soft robotics, robots made from flexible materials like silicone, to help reanimate limbs and improve motor function. He also spoke about apps that allow users to control handheld electronic devices using only neural activity and the development of devices that decode intended speech by reading neural signals. The goal is to create speech models that can interpret brain signals in real time, making it possible for people who have lost the ability to speak to communicate again.

Beyond the technology itself, Hochberg also raised ethical questions about BCIs. He explored whether these systems are truly effective, weighing the potential benefits against challenges like accessibility, long-term usability, and the implications of directly connecting the human brain to machines. His talk framed BCIs not just as a breakthrough in technology but as a field that must carefully balance innovation with responsibility.

Exploring the Future of Neuroengineering

In the next session, three speakers gave 10-minute vision talks, introducing key topics before opening the floor for a 30-minute discussion with the audience. The session was moderated by Anita Shukla, the Elaine I. Savage Professor of Engineering at Brown.

Rikky Muller spoke about implanted medical devices and how researchers are working to make them smaller, less invasive, and better at collecting data. She discussed the future of closed-loop intelligent medical devices, technologies that automatically adjust treatment based on real-time data, and emphasized the importance of collaborating with clinicians to develop devices that are both effective and safe. She also noted that making neural datasets publicly available could accelerate progress in the field.

Haneesh Kesari focused on mild traumatic brain injuries (MTBIs), brain injuries that, in some cases, can lead to chronic traumatic encephalopathy (CTE). CTE is a condition that most commonly affects athletes in high-impact sports like football, but it can also develop in others who experience repeated

head trauma. Kesari explained that diagnosing MTBI and CTE is difficult due to factors like a lack of pain receptors in the brain, the challenge of crossing the blood-brain barrier, and the uncertainty around how long biomarkers take to develop after an injury. He noted that a better understanding of these factors could lead to improved helmet designs and better safety regulations in sports.

Christopher Moore, professor of neuroscience and brain science at Brown, spoke about brain dynamics for optogenetics, a technique that allows researchers to control genetically targeted cells quickly and precisely in the brain using light. His talk, "Jellyfish Light for Precision Bioengineering and Detailed Non-Invasive Pharmaceutical Tracking," focused on using bioluminescence, the natural production of light by living organisms, as a tool for rewiring the brain. Unlike traditional light-based methods, bioluminescence is highly biocompatible and does not require bleaching before use, making it a safer alternative for neuro-engineering applications.

Designing Health Technologies That Work for Everyone

The final session, Designing Health Technologies That Work for Everyone, brought together a panel of experts to discuss how engineering and design can create more inclusive and accessible health solutions. Each panelist gave a short talk before sitting down for a broader discussion with the audience.

Kimani Toussaint introduced his PROBE Lab (Photonics Research of Bio/Nano Environments), which focuses on multifunctional nano-antennas, quantitative second-harmonic generation imaging, and nonseparable optical fields. He then discussed the need for interdisciplinary collaboration in every stage of problem-solving. Using home health technologies as an example, he shared insights from a 2022 workshop that explored key questions: What technologies are needed? How should they be delivered to reach everyone? And will people actually use them?

Louise Manfredi spoke about the intersection of design and engineering and how combining them can increase positive outcomes. She explained that designers focus on solutions, while engineers create knowledge and technology with broader applications—and when these two fields work together, great things happen.

Beth Altringer Eagle emphasized that design engineering is, by definition, interdisciplinary. She discussed the importance of leveraging all available intelligence and how Brown is incorporating design into its engineering program to prepare students for collaborative, cross-disciplinary problem-solving.

After the panel, the event concluded with a discussion with the audience, a reception, and a student poster session, where students had the opportunity to present their research and connect with professionals.

The Brain as the Ultimate Hack

A key takeaway from the day was that the brain itself is the ultimate hack—not just the human brain, but brains in general. Whether it's using neural activity to control devices, designing safer ways to manipulate brain function, or protecting the brain from injury, the research presented at the symposium reinforced the idea that nature already holds many of the answers we're looking for.

By studying how the brain works and applying that knowledge to engineering and technology, researchers might be able to find the best solutions to some of the biggest challenges in medicine and neuroscience.

Accelerating Clean Energy Manufacturing: NAE Regional Meeting at Georgia Tech

Clean energy innovation is driving collaboration with industry to build a more competitive and sustainable future. The National Academy of Engineering's (NAE) 2025 Regional Meeting, hosted by Georgia Tech from April 1–2 at the Historic Academy of Medicine, convened leaders from academia, industry, and national laboratories to explore advancements in next-generation batteries, industrial decarbonization, and AI-driven manufacturing.

The event opened with a members-only business session, followed by an evening fireside chat featuring William B. Bonvillian, lecturer at MIT and senior advisor for the Initiative for Knowledge and Innovation in Manufacturing. The

second day opened with remarks from NAE President **John L. Anderson** and a welcome from Georgia Tech President Ángel Cabrera, who highlighted the Southeast's growth as a hub for clean energy innovation and the critical role of engineers in creating scalable solutions.

Raheem Beyah, dean of Georgia Tech's College of Engineering, reinforced this message by showcasing the university's leadership in applied research, workforce development, and strategic partnerships driving advancements in sustainable manufacturing and energy systems.

Electric Mobility and Battery Challenges

The first panel of the day, moderated by Matthew McDowell, an associate professor at Georgia Tech, revealed that while enthusiasm for electric batteries continues to grow, their development is far more complex than many anticipate. Panelists included Henk Both and Gleb Yushin, both professors at Georgia Tech, and Richard Simmons, principal research engineer at Georgia Tech. They emphasized the urgent need to accelerate market adoption. If the US wants to be able to produce batteries in a competitive way, the US needs to scale for automotive use and ramp up manufacturing. Currently, military contracts provide crucial cash flow for US companies that help early-stage technologies in the process of scaling for automotive use. But for that transition to happen, panelists highlighted that reliability remains automakers' top concern. This would require close coordination between energy grids, raw material sourcing, and funding mechanisms.

At present, there are a multitude of battery types available. This diversity should not be an issue but rather a signal that future batteries will require specialized chemistries tailored for different applications. At the same time, this diversity introduces new risks, especially given China's dominance in processing critical materials like graphite. Solutions to roadblocks in manufacturing and the diversity of needs were met with a "chicken-and-egg" dilemma: manufacturers need investors to build domestic capacity, but investors hesitate without proof of production readiness.

Looking ahead, the panel predicted that silicon anode batteries could significantly lower material costs within five years and emphasized that microgrids may serve as key catalysts for broader electric vehicle (EV) adoption.

Industrial Decarbonization Realities

The second panel, led by Georgia Tech professors Marta Hatzell and Juan-Pablo Correa-Baena, turned to the industrial sector, where decarbonization efforts are often constrained by legacy infrastructure, uncertain policy landscapes, and public skepticism of large-scale projects. Panelists included **Sarah Kurtz**, distinguished professor at the University of California, Merced; Krista Walton, professor and associate vice president for research operations and infrastructure at Georgia Tech; and Ben Wernette, principal scientist and strategic partnerships lead for the Southern States Energy Board. The discussion focused on three priorities: stabilize critical material supply chains, increase public trust through small-scale pilot projects, and train engineers who can bridge technical, policy, and economic gaps.

One reality that engineers are facing in decarbonization is that despite lithium being the favorite for EV batteries, lithium prices are volatile and thus pose investment issues. Variants of the chemical—like lithium iron phosphate—offer a more stable, less controversial path forward. That change plus domestic lithium production could stabilize national prices. But infrastructure is essential; without that, the public may remain wary of large projects.

The conversation also touched on 2050 net-zero goals. While panelists were skeptical of the chances for that goal to be met, they did offer steps to get there, citing engineering education changes as a first step. Panelists highlighted the importance of schools training engineers to work across disciplines.

In the short term, pragmatic solutions—like charging our cars during the day when the sun is shining instead of storing solar power in a battery and then charging later—could help us make some progress toward the 2050 goal.

AI in Manufacturing: Capturing Expertise, Navigating Ethics

The final panel, moderated by Tequila Harris, a professor at Georgia Tech, explored how AI is reshaping manufacturing by enhancing productivity, capturing expertise, and raising ethical considerations around data, labor, and implementation. Panelists included Aram Amassian, a professor at North Carolina State University; Phil Sutton, vice president of administration at Kubota Manufacturing of America; and Chuck Zhang, a professor at Georgia Tech and program director at the National Science Foundation.

The panel opened with a core dilemma: we haven't figured out the Model T of smart manufacturing yet. We are still trying to create the

AI system that breaks through to the masses—one that isn't just modeled by humans but works in a system that may look completely different from those we're familiar with.

Panelists said that the current pace of technological change is like "drinking from a firehose," especially for manufacturers struggling to keep up. The pressure and flow of the industry are too much for US manufacturers to manage. Issues like data analytics concerns appear more pressing in North America than elsewhere.

On top of these demands, keeping up with ethical shifts around emerging technologies is a challenge for engineers, who must keep those issues in mind as they continue to innovate. For example, the loss of jobs due to automation is a pressing ethical concern. Panelists reflected on how AI could elevate rather than replace skilled labor. These AI tools are very effective at capturing motion and expertise. Our best manufacturing "athletes" have decades of coordination they can't always explain—but AI can help replicate and even improve those processes. That means automation could enhance the ability to do a job rather than eliminate expert intuition.

The conversation then turned to small and mid-sized manufacturers. Panelists urged engineers to follow an approach that invests heavily in bringing suppliers along technologically, creating a partnership that says: if you want to stay competitive, you move with us.

To support broader adoption, panelists proposed building "federated university labs" that can generate high-quality, open data, free from intellectual property concerns. These could serve as pilot environments where industry and academia accelerate progress together.

Moderator Tequila Harris closed with a pointed challenge: how do we ensure innovation is inclusive, scalable, and sustainable not just for large manufacturers, but for the thousands of small firms navigating change with limited resources?

Looking Ahead

The event underscored the hard truth that there is no single breakthrough that will carry the energy transition. Whether through battery innovation, cleaner heat systems, or AI-assisted manufacturing, the path forward will require a mix of technologies, deep collaboration, and bold workforce investment. Panelists repeatedly emphasized that the biggest wins may come not from isolated inventions but from convergence: research that connects disciplines, policies that align with technical capacity, and engineers who understand the full context of the systems they help build.

One Donor's Path from Perseverance to Philanthropy

Dianne Chong and David Squiers

Coming from a diverse background and raised in a home rooted in sacrifice and perseverance, **Dianne Chong** never imagined she would one day be inducted into the Women in Engineering Hall of Fame. As a first-generation college student, Dianne's educational journey was anything but typical. Her path to engineering was even more unconventional.

Originally planning to pursue a career in medicine, Dianne didn't set foot in an engineering classroom until graduate school. It's hard to say whether the medical field lost out or the engineering world simply got lucky, but if you ask Dianne, she'd tell you she was the fortunate one, and the profession found her.

Dianne's foundation was built on the enduring values of her Chinese heritage. Her mother emigrated from Canton and, after the untimely passing of Dianne's father when she was just 13, raised five children on her own. Though just one person in Dianne's extended family (on her father's side) obtained a college education and her parents never had the chance to pursue secondary education themselves, they instilled in their children an unshakable belief in its importance. That belief propelled Dianne to become the first in her family to earn a college degree—a milestone that paved the way for her trailblazing career.

When her mother passed away, Dianne felt compelled to honor her parents' lasting impact by giving back in a meaningful way. She and her

husband, David Squiers, decided to establish a first-of-its-kind endowed fund, the **Dale and Helen Chong Endowed Fund for NAE Programs**, which supports the various programs in the NAE Program Office. "I truly believe in the power of education. What NAE is doing in the programs area covers multiple aspects to help us learn and implement how to improve accessibility and quality of education for all," Dianne remarked.

Dianne had been actively supporting the National Academy of Engineering (NAE) long before becoming a member, both through volunteerism and philanthropy. To her, giving back to the NAE is not just appropriate; it's essential. She feels strongly that engineering is critically important for the future and success of the nation and that the NAE can be instrumental in leading the way.

From someone destined to transform ideas into products to becoming an inspiring leader for many, Dianne Chong hopes her story will inspire others to support the fields of science and engineering.

New Staff Join NAE

Nicole Edmund

NICOLE EDMUND has joined our team as director of membership. Nicole brings more than 20 years of leadership experience in membership, engagement strategy, and association management. She has a proven track record of driving membership growth, leading high-performing teams, and creating value to increase member engagement and retention.

Most recently, Nicole served as senior director of membership growth and engagement at the American Physiological Society, where she led membership initiatives, cultivated chapter relations, and enhanced volunteer engagement. Prior to that, she held senior leadership roles at organizations such as the Meeting Professionals International, National Retail Federation, and Women in Cable Telecommunications, overseeing membership operations and chapter relations.

Nicole is a certified association executive (CAE) and holds an MS in management from the University of Maryland University College, as well as a BS in marketing from Syracuse University.

Outside of work, Nicole enjoys traveling, especially cruising, and listening to audiobooks, specifically thrillers and suspense. (Lee Child's *Jack Reacher* is her favorite). She is always open to new experiences, having moved across the country to pursue career opportunities, including Bentonville, Arkansas, with the world's largest retailer and in Dallas, Texas, to further hone her leadership skills. She gets back to the Caribbean Island of Antigua a couple times per year, where her mother and several family members reside.

Nicole is excited to join the team and looks forward to meeting and learning from everyone. She can be reached at nedmund@nae.edu or 202-334-1760.

Kristen Koehler

KRISTEN KOEHLER has joined our team as the director of the outreach and communications. Kristen brings more than 20 years of experience as a senior marketing and communications leader with a remarkable talent for brand transformation and digital innovation across diverse sectors. Most recently, she served as assistant dean of strategic marketing and communications at George Mason University, where she led a dynamic team handling communications strategy, media relations, social and digital media, video production, design development, and crisis communications management.

For seven years, Kristen was the senior manager of marketing and communications at the University of Maryland, building on her twelve years in college preparatory schools, where she excelled as both a chief marketing officer and director of alumni and media relations. (Fun fact: She was also a varsity swim coach for 10 years!) Kristen began her professional journey at the Annapolis Chamber of Commerce as the director of membership and communications. Throughout her career, from award-winning video productions to comprehensive website redesigns, Kristen's exceptional storytelling abilities and data-driven approaches have consistently delivered outstanding results.

Academically, Kristen holds an MA in contemporary communication from Notre Dame of Maryland University and a BA in communications studies from the University of North Carolina at Wilmington. When she's not transforming communications strategies, Kristen stays active as an avid swimmer and enjoys working out and hiking. Her adventurous spirit has taken her to more than 65 countries! In a recent creative achievement, Kristen published a children's book titled *I SEE ME IN A TREE*, available on Amazon.

Kristen can be reached at kkoehler@nae.edu or 202-334-2233.

BAO RANDRIANARIVELO has joined the elections team as a senior membership assistant. Bao is originally from Madagascar and has lived between Virginia and DC for about 15 years. She has a strong interest in project management, systems improvement, and community engagement, and is excited to contribute to the greater mission of the NAE on the membership team.

Bao is passionate about building connections, mental and holistic health, and fostering spaces where people feel seen and supported. Outside of work, you can find her practicing aerial yoga, learning new skills, spending quality time with family and friends, diving deep into topics that spark her curiosity, or planning her next travel adventure. Bao can be reached at brandrian@nae.edu or 202-334-2267.

Bao Randrianarivelo

Calendar of Meetings and Events

August 6	NAE Council Meeting Irvine, California
September 14–17	2025 US Frontiers of Engineering University of Pennsylvania
October 3	National Academy of Engineering Council Meeting Washington, DC
October 5–6	2025 National Academy of Engineering Annual Meeting Washington, DC

In Memoriam

Ray H. Baughman, 82, director, Alan G. MacDiarmid NanoTech, The University of Texas at Dallas, died April 18, 2025. Dr. Baughman was elected in 2008 for pioneering novel applications of conjugated polymers and related nanomaterials.

Howard R. Baum, 89, Scientist Emeritus, National Institute of Standards and Technology, University of Maryland, College Park, died April 29, 2025. Dr. Baum was elected in 2000 for developing and implementing broadly applicable analytical models and numerical tools for understanding and mitigating fire phenomena.

Robert K. Brayton, 91, professor of electrical engineering and computer science, University of California, Berkeley, died January 10, 2025. Dr. Brayton was elected in 1993 for contributions to the theory and practice of computer-aided analysis and design of electrical and logical circuits and systems.

George R. Cotter, 96, consultant, Isologic LLC, died April 20, 2025. Mr. Cotter was elected in 2007 for leadership in the research and development of high-end computing and communications for national security.

Anthony J. DeMaria, 93, retired chief scientist, Coherent - DEOS LLC, died January 26, 2025. Dr. DeMaria was elected in 1976 for "Developer of picosecond mode-locked lasers and contributions to high-power lasers."

John S. Foster Jr., 102, retired director, Northrop Grumman Aerospace Systems, died April 25, 2025. Dr. Foster was elected in 1969 for technological leadership in defense research and engineering.

L.B. Freund, 81, retired adjunct professor, University of Illinois at Urbana-Champaign, died October 3, 2024. Dr. Freund was elected in 1994 for contributions to dynamic fracture mechanics and to the mechanics of dislocations in thin layers.

Richard L. Garwin, 97, IBM Fellow Emeritus, IBM Thomas J. Watson Research Center, died May 15, 2025. Dr, Garwin was elected in 1978 for contributions applying the latest scientific discoveries to innovative practical engineering applications contributing to national security and economic growth.

Richard E. Goodman, 89, professor emeritus of geological engineering, University of California, Berkeley, died March 10, 2025. Professor Goodman was elected in 1991 for contributions through teaching and research to geological engineering and rock mechanics.

Charles T. Haan, 83, Regents Professor and Sarkeys Distinguished Professor Emeritus, Oklahoma State University, died November 29, 2024. Dr. Haan was elected in 1995 for the analysis and design procedures of storm runoff and sedimentation control systems and stochastic hydrology.

James C.M. Li, 100, A.A. Hopeman Professor of Engineering, University of Rochester, died April 14, 2025. Dr. Li was elected in 2006 for contributions to micromechanics and mesoscopic mechanisms in materials and to the commercialization of amorphous metals.

James G. O'Connor, 88, retired president, Pratt & Whitney, died November 16, 2024. Mr. O'Connor was elected in 1993 for leadership in providing new generations of aircraft propulsion systems.

William S. Saric, 84, University Distinguished Professor Emeritus, Texas A&M University-College Station, died April 22, 2025. Dr. Saric was elected in 2006 for contributions to the fundamental understanding and control of shear flow and boundary-layer transition.

Leonard M. Silverman, 85, Fred Green Chair in Engineering, University of Southern California, died April 17, 2025. Dr. Silverman was elected in 1988 for fundamental contributions to system and control theory and applications, and for leadership in engineering research and education.

Dean E. Stephan, 86, retired president, Charles Pankow Builders, died January 8, 2025. Mr. Stephan was elected in 2000 for leadership and innovation in design and construction of advanced concrete technology.

Rodney J. Tabaczynski, 80, professor of mechanical engineering, Michigan State University, died April 20, 2025. Dr. Tabaczynski was elected in

2002 for major contributions to the understanding of processes in internal combustion engines, resulting in improved performance and pollution control.

Evgeny P. Velikhov, 89, president, Russian Research Center, Kurchatov Institute, died December 5, 2024. Dr. Velikhov was elected an international member in 2003 for pioneering work in plasma physics, controlled nuclear fusion, and gas lasers and for advancing international scientific cooperation.

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