EBRC Engineering Biology Research Consortium

July 27, 2023

Dear Dr. Baru:

The Engineering Biology Research Consortium (EBRC) is pleased to submit the attached response to the National Science Foundation's Request for Information seeking comments on Developing a Roadmap for the Directorate for Technology, Innovation, and Partnerships at the National Science Foundation (as published in the Federal Register Vol. 88, No. 82 pg 26345-7, FR Doc. 2023-08995).

EBRC is a non-profit, public-private partnership dedicated to bringing together an inclusive community committed to advancing engineering biology to address national and global needs. EBRC members represent diverse perspectives within the engineering biology research community and include some of the nation's top scientists and engineers. At its core, EBRC's objective is to advance pre-competitive research in engineering biology through cross-sector coordination between industry, academia, and government.

The TIP Directorate is charged by Congress through the CHIPS and Science Act to advance U.S. competitiveness through investments to accelerate the development of key technologies and address pressing societal and economic challenges. We offer comments from our vantage point as a convener of academic, industry, and governmental perspectives in support of a continued pursuit of these broad objectives toward maximizing NSF's impact and suggest strategies the TIP Directorate may employ toward these ends.

We appreciate this opportunity to comment on key issues impacting the development of an effective Roadmap for the NSF TIP Directorate and look forward to the far-reaching, valuable impact that will result from its fulfillment.

Sincerely,

Wilson Sinclair

Wilson Sinclair, Ph.D.
Postdoctoral Scholar, EBRC

Enclosures:
Engineering Biology Research Consortium Response to Developing a Roadmap for the Directorate for Technology, Innovation, and Partnerships at the National Science Foundation

5885 Hollis Street, 4th Floor | Emeryville, CA 94608 | 510-871-3272 TEL | 510-245-2223 FAX | www.ebrc.org

Developing a Roadmap for the Directorate for Technology, Innovation, and Partnerships at the National Science Foundation

An EBRC Response to NSF RFI; 2023-08995

July 27, 2023

Q1. The TIP Directorate should prioritize critical use-inspired and translational research in ***key technology focus area 7: biotechnology, medical technology, genomics, and synthetic biology***. These topics, encompassed by the field of engineering biology, have the potential to be one of the most impactful and wide-reaching of the key technology focus areas that the TIP Directorate is considering. Engineering biology tools and techniques (funded in part by NSF) have laid the groundwork to solve major societal problems and are opening new avenues for economic growth and competitiveness. The TIP Directorate should build upon this investment and accelerate the impact of engineering biology with resources targeting its research, development, and implementation. TIP should work with stakeholders to couple fundamental research development with commercialization and patenting resources. Simultaneously, TIP should partner with other funding entities to work across silos and ensure coordination in technology areas where others already provide support, such as ARPA-H with medical technologies, USDA with genomics for agriculture, and DOE with computational capabilities. In this moment of opportunity at the precipice of a global expansion in engineering biology, the U.S., through the TIP Directorate, must support the growth and translation of foundational engineering biology technologies and capabilities into scalable, commercializable, and sustainable solutions as a cornerstone of U.S. competitiveness in the global bioeconomy.

A recent WHO report highlighted the importance of engineering biology to solving pressing global issues toward societal benefit and improved public health.[1] They evaluated and ranked technological innovations for their potential impact over a series of timeframes. Importantly, biotechnological innovations such as microbiome analytical tools, engineered vaccines, and synthetic genomes for biomaterial production were listed as top candidates with high to very high potential impact and high chance of adoption in under five years. Notably, though, these are global targets and could be reached by a number of international groups. The countries that invest the most effectively in these areas will be able to set a global standard and prioritization for how this technology will be used and where the innovation hubs and supply chains reside. As other countries are making massive investments in engineering biology research, development, and commercial translation, the TIP Directorate should be a leading competitive force by prioritizing investments toward focus area 7 (*i.e.* engineering biology), and driving integration of enabling technologies, to ensure U.S. geostrategic and national interests.

Engineering biology is complex, wide-reaching, and underlies powerful application spaces (climate, health, energy, food and agriculture, and manufacturing), so the Engineering Biology Research Consortium (EBRC; http://ebrc.org) has built an inclusive community of experts committed to advancing engineering biology to address national and global needs. EBRC has published five technical research roadmaps since 2019 that identify and detail potential engineering biology advancements with impact across many social and economic sectors. These roadmaps are created by academic and industry researchers and have been demonstrated to be highly valuable to policymakers, program leaders, and researchers alike by informing future research programs and initiatives and by educating the next generation of engineering biologists. The roadmaps, most of which have been created with funding support from NSF, cover engineering biology broadly,[2] microbiome engineering,[3] the intersection of materials science and engineering biology,[4] solutions and opportunities to address climate change and environmental sustainability,[5] and engineering biology for national defense strategies.[6] **The evidence of scientific progress in EBRC roadmaps setting accomplishable near- and long-term milestones can inform the TIP Directorate's program decisions and investments, particularly within key technology focus area 7.**

EBRC's first technical roadmap, *Engineering Biology: A Research Roadmap for the Next-Generation Bioeconomy*,[2] meticulously described tool and technology innovations needed to meet specific milestones agreed upon by leading experts in the field marked for the coming 2-, 5-, 10-, and 20-years (2021, 2024, 2029, and 2039, respectively) necessary to achieve significant technology breakthroughs and high-level goals of engineering biology to improve society and the world. Recently, EBRC published an assessment of the progress toward *Engineering Biology*'s first, 2-year milestones, tracking research and technology advancements from 2019 to 2021.[7] This assessment reports significant progress in the field and is evidence that *Engineering Biology* has, so far, been a useful indicator of the direction of engineering biology research and should continue to inform programmatic decision-making. Importantly, **engineering biology research is now at a pivotal point where discoveries over the last 15 years are primed for translation into scalable products that address societal, national, and geostrategic challenges**. However, to realize this opportunity, TIP investments are needed in use-inspired research, workforce training, and testing engineering biology-based prototypes in relevant environments and circumstances.

We are at an inflection point in the global bioeconomy and we are already seeing engineering biology commercialized products change the world.[8] Below are examples from EBRC technical roadmaps with approaching milestones within the TIP roadmap's time horizon where the Directorate's resources and programs could accelerate translational impact of engineering biology to address societal, national, and geostrategic challenges. These examples also highlight opportunities for investments in engineering biology to support and leverage other key technology focus areas such as AI/ML, robotics & automation, disaster prevention and mitigation, data management, advanced energy, and materials science.

- Microbiome engineering:[2] Large datasets are being constructed to report on physiological characteristics of complex communities of microbes. These datasets can be shared to inform other researchers and also used as machine learning training data to enhance the designed properties from the scale of single-cell microbes to entire novel microbiomes. Resulting biotechnologies can be targeted to cure human diseases, improve sustainable agricultural output, act as pathogen biosensors thus enhancing national security, and more. Yet environmental testing sites and programs to facilitate data sharing are necessary to harness this potential, which TIP can support.

- Climate and sustainability:[3] By building on fundamental research in engineering metabolic pathways, researchers can engineer plants and microorganisms to support a healthier environment through several strategic avenues including i) increasing the rate and efficiency of carbon sequestration from the environment; ii) transforming waste biomass and plastics into value-added commodity products; and iii) synthesizing commodity compounds that are currently harvested from nature. For these emerging capabilities to be translated, they need to be optimized outside the lab in testbed environments where their performance and impact can be measured for technical improvements toward scale-up and manufacturing readiness.

- Materials science:[4] New advances in metabolic engineering will allow for the biological synthesis of new chemical monomers and novel polymerization methods to generate adaptable and tunable materials with biosensing and regenerative properties that could transform industrial supply chains. Bio-inspired and bio-built materials need to be tested beyond the lab and to test parameters at environmentally-relevant scales in repetitive circumstances to establish material consistency and sustainability. A particular challenge for engineered biomaterials is engaging established materials science methods, techniques, and expertise with the inherently variable, adaptable, and dynamic nature of living systems, so collaborative partnerships within engineering biology and materials science are key to amplifying and translating this work.

- National security:[5] Engineered organismal biosensors and reporting systems will measure, respond to, and report on desired biological, chemical, and even physical signatures. Engineering biology will also better enable the United States to counteract such threats, whether through improvements to therapeutics and mRNA vaccines, biosequestration of toxins, or specialty fuels and chemical coatings. Engineered diagnostics, therapeutics, and vaccines will be more sustainable and adaptable to low-resource settings, dramatically improving supply chain resilience and cold-chain limitations of current capabilities. TIP-guided investments and coordination could ensure that such use-inspired research and development enhance U.S. competitiveness and geostrategic interests.

Q2. NSF awards, primarily through the Biological Sciences and Engineering Directorates, have generated a vast number of the fundamental capabilities and tools that fuel engineering biology research, including: i) high-throughput gene assembly, sequencing, and screening; ii) data-driven design and integration of macromolecules and circuits; and iii) contextual transformation and characterization of host cells. These discoveries in genetic and microbe engineering underpin the industrial processes of several companies, generate macromolecules using biology instead of fossil fuels, and optimize pharmaceutical delivery systems. Yet there is so much untapped potential, and TIP is poised to build upon NSF's history of investment and lead new programs and opportunities that catalyze the early-stage translation of tools and discoveries towards transformational, use-inspired technologies to strengthen the U.S. bioeconomy. There are two main approaches which align with the TIP mission that could accelerate and bridge the transformation of engineering biology discoveries into real-world products: **i) accessible infrastructure for testing new technologies before scale-up, and ii) cross-disciplinary, coordinated data sharing programs.**

Infrastructure: In just the last 5 years, notable technical advancements were achieved in DNA assembly and in genome engineering of model and non-model organisms that are now being deployed across diverse sectors of agriculture, health and medicine, and climate and sustainability applications.[6] The TIP Directorate should capitalize on this momentum by providing opportunities for researchers to explore potential smaller-scale real-world environments and determine utilization and constraints across many application sectors prior to other sources of commercialization investment.[9] Such support will enable research to go beyond the novelty or basic understanding of a system, pathway, or tool to explore and better understand the potential applications, real-world behaviors, and system-level impacts of engineered biology, in advance of establishing feasibility for market or commercial potential.[10] To realize this translational research capacity of engineering biology, TIP should consider investments toward the following approaches:

- TIP should **foster ecosystems** focusing on engineering biology (and its intersection with other key technology focus areas) through partnerships between academic institutions, industry, non-profits, and government to **create facilities with shared resources and knowledge**. Such open research spaces can enable engineering biologists to access platforms and technologies that might otherwise be untenable. These could be modeled after NSF-sponsored Engineering Research Centers and other centers such as Materials Research Science and Engineering Centers (MRSEC). New investment can expand access to the capabilities of these types of Centers, but should also work with stakeholders to identify specific remaining needs towards scale-up and commercialization. Notably, four of the nine MRSECs funded in 2023 will leverage the synergy and opportunity at the intersection of materials science and engineering biology.
- Some applications of engineering biology require deployment beyond a fermentation chamber, such as the engineering of drought-resistant crops, bioremediation, and the control of pathogen-carrying insects could help humanity respond to climate change, clean polluted soil and

water, and ensure food security.[4] Careful and gradual steps are important for engineering validation, safety, and efficacy when translating from a laboratory finding to more application-oriented or use-inspired research and transitioning to experimentation in application-specific environments. **Investment in nationally accessible animal, field, and water testing sites at incremental scales** would make it more feasible to establish functional profiles and understand the limitations and vulnerabilities of engineering biology products. These could take the form of scalable physical environments, similar to the U.S. Naval Research Laboratory's Laboratory for Autonomous Systems, or infrastructure like the Harvard Digestive Disease Center, which uses clean animal facilities to effectively test hypotheses of precisely constructed microbiota in animal models of disease and treatment. However, the vast majority of the research community does not have access to such resources. Equitable access to such resources would be highly valuable to academics and early-stage startups who want to see their discoveries developed into solutions to meet societal, national, and geostrategic challenges.

Data: With current -omics technologies, nearly all biological researchers are capable of generating a modest-sized dataset including novel microbial strain characteristics and engineered enzyme properties. These data could be useful if shared with others (and/or used to train machine learning models), but the information is typically accumulated in localized, unconnected databases, leading to redundant efforts ineffectively using limited funding and labor. Recent advances in engineering biology and data science have substantially accelerated biotechnological discoveries and translation. The hoarding of data, insufficient data acquisition, and poor data organization are hindering the translation across several areas of biology. Platforms to increase or improve sharing of real-world sampling and experimental data could build a more collective and cohesive picture of what is attainable using engineering biology and aid researchers across life science disciplines. Several data initiatives have been developed and/or sponsored by the U.S. government that TIP could collaborate with to better utilize the national expertise generating valuable data, including the National Laboratories National Microbiome Data Collaborative, NIH Common Fund Data Ecosystems and National Center for Biotechnology Information (NCBI), NSF CyVerse and Environmental Data Science Innovation and Inclusion Lab, and DOE Integrated Microbial Genomes and Microbiomes. The TIP Directorate should help harmonize and connect these efforts to foster a more cohesive and productive data sharing ecosystem in the following ways: **i) coordinate and communicate current resources to scientists; ii) develop national standards for collecting and formatting different types of life science data (partnering with NIST); iii) invest in the use-inspired computational tools, including AI, to be used by reporting systems, and iv) train the workforce on standards of data reporting within existing systems.**

Investigators and new companies carry an undue burden of building data sets from scratch that may already exist elsewhere and would benefit greatly from a unified (or federated) repository maintained at the federal level and accessible by all those who wish to analyze it. TIP's support would bridge that gap for new innovators attempting to translate their technologies toward bolstering U.S. competitiveness. Accessible, user-friendly, and secure digital infrastructure and computational tools, such as modeling and machine learning algorithms, could redistribute knowledge generation away from the coastal hubs. This not only would NSF diversify research and development opportunities, but also better support education and workforce equity across the U.S. to capitalize on local resources and communities and address the dearth of data scientists with experience working in scientific environments. Importantly, training in these scientific skills within a translational project context will be important for a robust and competitive economy built on new engineering biology discoveries.

Q3. Over the next 5 years, the U.S. bioeconomy is poised for tremendous growth with many opportunities to support a robust domestic workforce at all entrance levels and in communities where industry may currently be stagnant or declining. TIP should center investments toward equitable access to biotechnology education and opportunity to revitalize this stagnation and translate engineering biology discoveries and techniques to benefit society. While acknowledging that workforce initiatives have longer time horizons, focusing equitable programs to raise awareness, fostering mentorship opportunities, and supporting locally-targeted community programs in the next 1-5 years will lay essential infrastructure for successful entry into and mobility within the developing bioeconomy.

Engineering biology-related education and training can be extremely diverse in scope, content, and delivery method. As the field is emerging, a large portion of the potential workforce do not recognize that engineering biology jobs exist and are accessible to them. Awareness of careers and educational pathways within focus area 7 is a major challenge for existing training programs and also for workforce development more broadly. Investment is needed in organizations, programs, and partnerships that aim to improve awareness of biotechnology-related careers and the educational pathways to develop the necessary skills and knowledge to enter the workforce across all stages. The bioeconomy needs workers at entry level, skilled technicians across many different platforms and industries, and those in leadership positions with advanced degrees, meaning there are many different entry- and exit-points for learning and training in biotechnology. Additionally, students and workers across the country may desire to launch startups in their local communities and could use more training in translational research and application building off of or modeled after existing NSF I-Corps (and I-Corps-like) programs becoming more broadly available and integrated into the traditional educational pipeline. The TIP Directorate should also consider expanding funding opportunities for collaborative projects between academic institutions and startup companies.

Bioeconomy workforce education and jobs are interdisciplinary and many formal training programs for these careers do not yet exist sufficiently to support the current and future market. Because engineering biology melds many different fields (engineering, chemistry, data science, and biology, among others), educational pathways must be diverse and oriented around applied skills and critical thinking. TIP can support institutions (including community colleges, four-year colleges and universities, educational and training nonprofits, and community organizations) to develop interdisciplinary, skills-based programs designed around workforce needs. NSF funds several programs with these groups, including HBCUs and other minority-led institutions, and leveraging those connections is and will continue to be important for TIP's success.

Engineering biology training programs can be incredibly expensive with complex equipment and machinery with which each student needs to become familiar. Progressive skills-based experiences can enable a learner to continue or return to the educational pipeline at any time to build onto their abilities. This also requires incentives and investment for strong academic-industry partnerships to ensure that the educational training and skills being offered are applicable across the engineering biology landscape, but also, ideally, aligned with local industry needs and resources. This can be accomplished by expanding access to hands-on training, mentorship opportunities, and developing and sharing public programs, services, and materials. As TIP develops and funds programs and facilities, it should ensure funded projects maximize provided resources with requirements for educational/training use.

Mentorship can be a major component and contributor to a diverse and inclusive STEM education and workforce, particularly when mentors come from underrepresented demographics, backgrounds, and experiences. Traditionally, the lack of diversity in the advanced STEM workforce, including biotechnology, means that these mentors are rare, and those who do exist are often overburdened with the responsibility of representation. Resources and investments are needed to support these individuals, community groups, and organizations; organizations and platforms like LabCentral Ignite can provide examples of programs to support diversity and inclusion through mentorship, capacity building, and career development.

Q3a. As noted in a previous response to NSF's 2023 *Dear Colleague Letter: Request for Information on Future Topics for Workforce Development in Emerging Technology Career Pathways* (NSF 23-100), more targeted programs are needed to support the potential of the bioeconomy workforce. TIP should look to existing, creative biotechnology training programs at community colleges that have partnered with local industry as models. For example, NSF-funded programs such as InnovATE*BIO*, non-profit community programs like BioBuilder, and a growing number of 2-year, 4-year, and graduate-instruction institutions offer biotechnology-related education and training opportunities that are multi-disciplinary and support a diverse range of learners and skill sets, such as the CUNY Masters in Translational Medicine. Effective strategies consider local and regional opportunities and teach the required skills for those jobs, while also teaching basic, broadly applicable biotechnology skill sets and understanding. Supporting diversity and inclusivity requires activities and programs that are accessible to all, meaning that they must be low-cost, information about them must be widely-distributed, and they must be available geographically where the workforce can be developed (and hopefully, employed). High schools, minority-led institutions, and community colleges can offer training and education opportunities that reach wider audiences than the 4-year higher education institutions that have traditionally provided most biotechnology education. Models for such programs include the Biomanufacturing Training Program for High School Students at Shoreline Community College (Shoreline, WA), the resources provided by the North Carolina Community Colleges' BioNetwork, and the biotechnology certificate, diploma, and Associate's degree available through Southeast Community College (Lincoln, NE).

Q3b. The development of key technology focus areas cannot be undertaken solely by TIP and the Federal Government. Partners in local and regional governments should be made aware of investments and priorities of the TIP Directorate within their jurisdictions. This will help to incentivize and enable local governments and partners to increase awareness of biotechnology (or other key technology focus areas), bring targeted curriculum into the K-12 education system, ensure facilities and funded projects are informed by local and regional needs, and strengthen education and training pathways funded by different government and private investors. TIP could require that funding proposals include how proposers will engage with their local community and governments similar to how broader impacts are evaluated for the NSF Engines program, for example. Often, community engagement occurs too late, which discourages local governments and communities from listening and building their own pathways. Instead, by working together when generating programs and ideas, the Directorate will ultimately better inform local governments and achieve greater impacts in implementing workforce programs across the U.S.

Investments need to be made into training program infrastructure and administration to be able to share career opportunities and entry-points to education and industry. Training programs need support to partner with industry (locally and nationally) to learn about and coordinate on the skills and knowledge necessary for biotechnology workers to be successful. Likewise, industry needs to be incentivized to dedicate time and resources to these partnerships and engagement with educators and instructors. Frameworks and programs built through TIP and NSF should be shared with state, local, and tribal governments to communicate existing resources to raise awareness and inspire locally dedicated programs.

Q4. Engineering biology solutions are uniquely poised to **sustainably** address chronic issues in climate change, manufacturing, and national security. The U.S. is poised to be a global leader in biomanufacturing and engineering biology, but global competition is fierce at this scientifically pivotal moment. Circular economies are being built in diverse application sectors with engineering biology as the focal point. Engineering biology enables us to use and leverage local and regional resources (including workforce and bio-based feedstocks), thus securing supply chains and national prosperity.[11] The countries that invest the most in this technology will be able to set global standards and priorities for how this technology will be used. TIP investments in translating engineering biology research into economically viable, needed products over the next one to three years will lay critical groundwork, bringing a strategic advantage for a competitive U.S. bioeconomy. In order to utilize this technology effectively to address environmental challenges, industrial productivity, and national security concerns, the TIP Directorate should prioritize engineering biology to support national and societal interests.

Climate Change and Engineering Biology: Engineering biology has significant applications in sustainable and circular agriculture, manufacturing, and climate change remediation.[5] With investments in engineering biology, the TIP Directorate can simultaneously i) increase manufacturing efficiency by moving manufacturing inputs closer to the assembly of the final product (e.g., domestic sugar/corn vs. imported oil as inputs for commodity chemical synthesis); ii) improve sustainability of manufacturing within the U.S. by using microbial-driven point-of-source carbon capture, conversion, and sequestration at manufacturing facilities; and iii) reduce negative outcomes associated with climate change by reducing carbon emissions through the use of high-density renewable bio-based fuels.

Reducing agriculture-associated climate impacts: Engineering biology and related biotechnologies have the potential to reduce greenhouse gas emissions and environmental pollutants due to agriculture and livestock farming. For example, synthetic nitrogen fertilizers generate emissions as they are produced and can cause environmental problems as they run-off into waterways. Engineering biology is enabling the optimization of microorganisms for fixing nitrogen. TIP-funded test sites where researchers could control air carbon dioxide and nitrogen concentrations could enable more precise measurement of the efficacy of such biofertilizers both now and as higher atmospheric carbon dioxide levels impact other elements of plant growth and productivity. Similarly, as described in EBRC's *Engineering Biology for Climate and Sustainability*,[5] "rice cultivation usually includes a period of time where fields are intentionally flooded, creating an environment where methanogens thrive. Methane from rice production accounts for approximately 11% of annual anthropogenic methane emission."[12] In test environments as described above, where ambient gas composition can be controlled and monitored, the impact of "rice engineered to maintain high yields with minimal flood time, or an engineered microbiome that suppresses methanogen activity during flooding"[13,14] could be measured, improved upon, and moved into commonly grown rice varieties.

TIP could also invest in the development of facilities to transfer engineered climate friendly agricultural traits from a single variety of a plant into many relevant agronomic varieties. At present, proofs-of-concept in a model species may not receive the funding or may face technical challenges in being transferred into commercially relevant varieties grown around the world. Providing the funding and use-inspired technical expertise and facilities for the transfer of such traits and their testing may help to address climate change and environmental sustainability challenges.

Sustainable and nationalized supply chains: Engineering biology enables a more sustainable mode of production for many industrial processes and materials. Manufacturing with engineering biology is based primarily, but not universally, around fermentation processes which can be carried out at various scales and at decentralized, nationally-dispersed production plants. This enables production of chemicals, pharmaceuticals, fuels, and consumer products in the regions in which relevant bio-based feedstocks are available and/or where biomaterial products are needed. Bioindustrial manufacturing can replace, augment, or supplement existing chemical synthesis processes, which can require high heat, pressure, and leave environmentally unfriendly waste products. Metabolic engineering to valorize waste (e.g., plastic upcycling using hybrid or biological processes) will contribute to solving climate change issues by reducing pollution and replacing petroleum-based products. Doing so will decrease the climate impacts of many of the chemicals and materials that enable our everyday lives. Investments from the TIP Directorate can enable more sustainable nationalized supply chains in the following areas:

- Recently, advances in capturing carbon and gas fermentation at high-emission point-sources have successfully sequestered carbon and converted it into valuable products, creating or bolstering national production capabilities.
- Through engineering biology, materials such as concrete, adhesives, and mycelium-based insulation can be grown rather than constructed using typical industrial techniques. These bio-based approaches can be more sustainable than currently used energy-intensive chemical conversion of fossil fuel derivatives.

- Living materials may be more sustainable as a result of self-repairing and self-replicating properties of bacteria.
- Engineered microorganisms can also be leveraged to create a circular bioeconomy, for example in synthesizing bioplastics and also breaking down plastic waste streams for source material.

Supply chain security is important both for the economy and for the health and welfare of a population. There are notable risks to sourcing important products internationally, or in relying on a limited number of domestic manufacturers. Domestic manufacturing of many biological and chemical products is possible through engineering biology; however, it's also challenging: both biosynthesis and downstream processing and purification of desired compounds require extensive troubleshooting and fine-tuning at each step of scale-up. Researchers struggle to scale up biological processes while ensuring their economic viability. TIP need not focus on addressing this entire challenge as others (e.g., BioMADE) are making progress toward solutions to these challenges and making pilot-scale infrastructure accessible. However, TIP could invest in facilities with 10 to 100 liter bioreactors and fermentation chambers and different capabilities for purification. These facilities would enable researchers to more regularly test their strains and processes in lower-stakes initial scale-up that allows for iterations through the design-build-test-learn cycle. By investing in very early transitions of fundamental research toward biomanufacturing, TIP can build resilience into U.S. supply chains and promote robust domestic production of critical products.

National Security and Engineering Biology: Engineering biology provides significant opportunities for advancements serving national security interests by detecting environmental threats, preventing and treating disease in human and animal populations, improving domestic supply chain resiliency and independence, and by ensuring the quality of basic necessities such as air and water.

Pandemic Preparedness: The COVID-19 pandemic reaffirmed the knowledge that pandemic preparedness is critical to national security. Preparedness includes surveillance of environmental indicators and vectors of disease outbreak. Engineering biology researchers have developed biosensors for detecting contaminants and pathogens in water supplies.[15] They are working to multiplex these sensors to detect a wide range of chemical and biological contaminants.[16] Furthermore, engineering biology enables the creation of rapid disease screening at scales to meet metropolitan demand and using technology that can be used in low resource environments (such as Stemloop products). After detection, engineering biology drives the advancement of therapeutics, most recently with mRNA vaccines and engineered antibody treatments. Technology such as mRNA vaccines have also begun to be applied to cancer.[17] Engineering biology researchers continue to demonstrate the power of new technologies, but will need testing capabilities for their durability and transportability (e.g., activity in different environmental conditions, cold-chain needs, stability in different packaging conditions, etc.)

Health Security: Engineering biology can also enable domestic, regionally distributed manufacturing using agricultural feed stocks and fermentation to create chemical products, medicines, and other economic necessities. A prime example of where this should be used is in the production of heparin, a very commonly used blood thinner. Heparin is largely sourced from China where it is produced from the intestines of pigs. In 2008, contaminated heparin from China resulted in dozens of deaths and left hundreds injured.[18] Additionally, swine flu outbreaks reduce the availability of healthy pigs for heparin production. By creating heparin in cultured cells using engineering biology, the U.S. would avoid this unnecessary risk to a crucial pharmaceutical. By investing in engineering biology, TIP invests in safeguarding the health and preparedness of the U.S.

Securing Basic Necessities: Security of basic necessities such as clean air and drinking water, is a top priority for the U.S. While the security of these is taken for granted in most instances, contamination of air and water is common. Water contaminants introduced in the past century, including industrial chemicals and heavy metals, are still present in underserved communities and in areas near the EPA's National Priorities List (i.e.: Superfund sites). Furthermore, recent reports from the U.S. Geological

Survey indicate that nearly half of all drinking water in the U.S. contains per- and polyfluoroalkyl substances (PFAS), of which the health ramifications are uncertain.[19] Through engineering biology, researchers have developed the ability to transport and deploy sensors that can detect water contamination without the use of large machinery or cold chain storage.[15] Further engineering biology efforts can be used to detect water quality dynamically. Measuring air quality is also an important application of this technology due to particulate matter and carcinogens being released by industrial processes or wildfires. Such sensors for air and water quality are highly useful means to ensure the health and safety of a population. By investing in technology to address concerns around water and air quality, TIP creates a safer and more aware U.S.

Finally, engineering biology and enabling technologies are crucial to the economic security of the U.S. and our position as a world leader in science and technology. Other countries, such as China, are investing heavily in a bio-based economy.[20] As the U.S. looks to strengthen its supply chains for pharmaceuticals and materials and secure its position as a norm- and standard-setting global leader, it should recognize that if we are not actively investing in a strong domestic and international bioeconomy, we will cede leadership to others.

Q6. Cross-cutting investment and interdisciplinary collaboration can yield rapid growth due to complementary advancements. Engineering biology thrives on its inherently cross-disciplinary nature and researchers' motivations to deploy engineering biology towards real-world problems. Due to this, there is no shortage of cross-cutting applications of engineering biology where TIP can make investments in translational research. Engineering biology paired with AI, materials science, and advanced robotics and manufacturing are three areas where cross-cutting investment could generate rapid innovation, create an adaptable workforce, and translate impact across sectors. The NSF Convergence Accelerator shares these same principles, so future project tracks could build off engineering biology's transdisciplinarity, like Track M, "Bio-inspired Design Innovations."

Acceleration of AI and Engineering Biology: Engineering biology and AI are mutually enabling and accelerating. A notable example is the incredible advancement in protein structure prediction by the DeepMind model, AlphaFold. AI models used large protein databases that were previously compiled and publicly available to enable the creation of AlphaFold. And we are seeing, in real time, how AlphaFold is in turn being used in engineering biology to help engineer proteins for real world applications far faster than previously thought possible. Investing in the **creation and curation of large databases** for metabolic data would streamline the creation of AI for metabolic engineering and enable the AI design of organisms to, for example, sustainably manufacture chemical products using engineering biology. AI/ML approaches for protein design and engineering are developing much faster than AI/ML approaches for metabolic pathway design. A major contributing factor to this gap is the availability of standardized training data (protein structure data is more uniformly organized and stored). Cross-disciplinary teams in AI/ML and engineering biology should imagine together how data can best be stored and used to train the computational algorithms that will significantly accelerate the logical use of biological data. As another example, investing in database creation and curation of pathogenic and potential zoonotic spillover viral sequences could enable the AI prediction of future viral outbreaks and support engineering biology efforts to design therapeutics sooner, such as was seen with mRNA vaccines investments.[21] These efforts also create significant opportunities for advancement in data storage, as metabolic and viral information is vast, thus requiring advances in data storage to support these databases.

Advanced Materials Science and Engineering Biology:[4] Engineering biology can create commercially important materials, such as plastics and adhesives, using sustainable starting materials that do not rely upon non-replenishable fossil fuel supply chains. TIP should invest in technologies that allow for the **high-throughput design, generation, and environmental testing of biomaterials** that will create the mutually beneficial advancements that enable the merging of these technologies to generate sustainable and robust supply chains. Engineering biology can also modify materials to grant them properties associated with biology, such as self-repair and morphing of material characteristics based on local conditions. Sustainable materials created using engineering biology, with the imbued ability to change and adapt based on their environment, could be especially beneficial for adapting to dynamic or unstable environmental conditions due to climate change. Additionally, engineering biology supports chemical manufacturing by reducing reliance upon global supply chains and by creating domestic manufacturing hubs. In a robust bioeconomy, chemical inputs can be derived from regional feedstocks through the use of enzymatic synthesis and/or fermentation.

Biosensing Robotics and Advanced Manufacturing: Engineering biology researchers and robotics researchers both endeavor to design and build systems that dynamically and continuously receive inputs and "sense" their environment and react accordingly. **Investment in biological-electronic interface technology and biosensing capabilities** will mutually enable engineering biology and robotics. Combined investment in these technologies for biosensing could, for example, enable the detection of particulates in air and water and respond appropriately based upon this information. Robotics combined with engineered biosensors can survey their environments to detect pollutants, disease, and hazardous materials and react to provide remediation or notification safely to human users. With regards to advanced manufacturing, engineering biology provides sustainable solutions for domestic manufacturing hubs.

Cross-cutting Workforce Development: Finally, TIP should **provide opportunities for cross-disciplinary collaborations** to enable engineering biology researchers to partner and engage with economists, environmental scientists, social scientists and other nontechnical experts to explore the impacts of their technology development, particularly early-on as research project ideas are being generated.[8] This can be complemented by entrepreneurial education for all researchers, to build stronger foundations for transforming research towards application. Additionally, bio-inspired companies and products are likely to be regionally distributed across pilot and production facilities built near biofeedstocks, such as corn and other agricultural products. This will provide high-impact, well-paying job opportunities for folks in the middle of the country in rural economies. Diversity of research teams also fosters the diversity of individuals contributing to discovery and innovation, a necessity for building a robust, equitable bioeconomy.

Q7. Engineering biology will play a crucial role and provide parallel strategies to tackle global and national issues toward improving societal and planetary well-being. Importantly, engineering biology investment in these cross-disciplinary fields is increasing dedicated funding internationally, so leaving engineering biology (i.e. key technology focus area 7) out as an arm within other key technology focus areas could stall U.S. leadership and economic competitiveness in critical sectors, should their funding and supply chains be bolstered overseas. Finally, it is important to note that several of the technologies that could change the economic and technological landscape would benefit greatly from TIP investment to go beyond proof-of-concept and demonstrate scale up and commercialization potential to continue U.S. leadership at the forefront of the global bioeconomic revolution.

References:

1. 2023 Emerging technologies and scientific innovations: a global public health perspective. (2023) Geneva: World Health Organization; (WHO global health foresight series).
2. Engineering Biology Research Consortium (2019). *Engineering Biology: A Research Roadmap for the Next-Generation Bioeconomy.* Retrieved from http://roadmap.ebrc.org. doi: 10.25498/E4159B.
3. Engineering Biology Research Consortium (2020). *Microbiome Engineering: A Research Roadmap for the Next-Generation Bioeconomy.* Retrieved from http://roadmap.ebrc.org. doi: 10.25498/E4QP4T.
4. Engineering Biology Research Consortium (2021). *Engineering Biology & Materials Science: A Research Roadmap for Interdisciplinary Innovation.* Retrieved from http://roadmap.ebrc.org. doi: 10.25498/E4F592.
5. Engineering Biology Research Consortium (2022). *Engineering Biology for Climate & Sustainability: A Research Roadmap for a Cleaner Future.* Retrieved from http://roadmap.ebrc.org. doi: 10.25498/E4SG64.
6. Engineering Biology Research Consortium (2020). *Enabling Defense Applications Through Engineering Biology: A Technical Roadmap.* doi: 10.25498/E49G6S. Note: This material is based upon work supported by the United States Air Force under Contract No. FA8650-15-D5405. This roadmap is an independent study and does not confer U.S. Department of Defense endorsement.
7. Engineering Biology Research Consortium (2023). *An Assessment of Short-Term Milestones in EBRC's 2019 Roadmap, Engineering Biology.* Retrieved from http://roadmap.ebrc.org. doi: 10.25498/E4NP46.
8. Voigt, C.A. (2020). Synthetic biology 2020–2030: Six commercially-available products that are changing our world. *Nature Communications* 11, 6379. https://doi.org/10.1038/s41467-020-20122-2.
9. Engineering Biology Research Consortium; Compiled and edited by Emily R. Aurand (2022). *Translational Research for Breakthrough Technologies: Advancing Engineering Biology to Address Societal Needs at NSF.* doi: 10.25498/E4201W.
10. Engineering Biology Research Consortium; Compiled and edited by Wilson Sinclair and Becky Mackelprang (2023). *Microbiome Research Strategy: Infrastructure, Computation, and Discovery.* https://ebrc.org/publications-2022eo-microbiome/.
11. Langholtz, M.H.; Stokes, B.J.; Eaton, L.M. (2016). 2016 Billion-ton report: Advancing domestic resources for a thriving bioeconomy, Volume 1: Economic availability of feedstock. *U.S. Department of Energy.* ORNL/TM-2016/160. Oak Ridge National Laboratory, Oak Ridge, TN. 411p. An updated Billion-ton report is expected in September 2023.
12. Jiang, Y. et al. (2019). Acclimation of methane emissions from rice paddy fields to straw addition. *Science advances*. 5(1). eaau9038. https://doi.org/10.1126/sciadv.aau9038.
13. Kumar, A. et al. (2014). Breeding high-yielding drought-tolerant rice: Genetic variations and conventional and molecular approaches. *Journal of Experimental Botany*, 65(21), 6265–6278. https://doi.org/10.1093/jxb/eru363.
14. Scholz, V. V. et al. (2020). Cable bacteria reduce methane emissions from rice-vegetated soils. *Nature Communications*, 11(1), 1878. https://doi.org/10.1038/s41467-020-15812-w.
15. Jung, J. K. et al. (2020). Cell-free biosensors for rapid detection of water contaminants. *Nature Biotechnology*, 38(12), 1451–1459. https://doi.org/10.1038/s41587-020-0571-7.
16. Thavarajah, W. et al. (2021). RNA engineering for public health: Innovations in RNA-based diagnostics and therapeutics. *Annual Review of Chemical and Biomolecular Engineering*, 12(1), 263-286. doi: 10.1146/annurev-chembioeng-101420-014055.
17. Reinhard, K. et al. (2020). An RNA vaccine drives expansion and efficacy of claudin-CAR-T cells against solid tumors. *Science*. 367(6476), 446-453. doi: 10.1126/science.aay5967

18. Hedlund, K. D. et al. (2013). The heparin recall of 2008. *Perfusion*. 28(1), 61-65. doi: 10.1177/0267659112462274
19. Smalling, K. et al. (2023). Per- and polyfluoroalkyl substances (PFAS) in United States tapwater: Comparison of underserved private-well and public-supply exposures and associated health implications. *Environment International*. 178, 108033. https://doi.org/10.1016/j.envint.2023.108033.
20. Zhang, X. et al. (2022). The roadmap of bioeconomy in China. *Engineering Biology*. 6(4), 71-81. https://doi.org/10.1049/enb2.12026.
21. Ramachandran, A., Lumetta, S., Chen, D. (2023). PandoGen: Generating complete instances of future SARS-CoV2 sequences using deep learning. *bioRxiv*. https://doi.org/10.1101/2023.05.10.540124.