Innovative Genomics Institute

Re: RFI Response: Biotechnology and Biomanufacturing Initiative

January 20, 2023

Office of Science and
Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Ave
Washington, D.C. 20504
(202) 456-4444
biotech@ostp.eop.gov

Dear Sir or Madam,

The Innovative Genomics Institute is pleased to submit the below comments in response to the Request for Information on the Biotechnology and Biomanufacturing Initiative.

The Innovative Genomics Institute (IGI) is a public, academic research organization formed through a partnership between the University of California, Berkeley and the University of California, San Francisco, two of the world's leading scientific research institutions. After making the transformational breakthrough discovery of bacterial genome editing systems known as CRISPR that can be applied to human, plant, animal, and bacterial cells, Dr. Jennifer Doudna founded the IGI with the goal of bringing together scientists and innovators from diverse disciplines to unlock the potential of CRISPR to solve some of humanity's greatest challenges.

We drive academic research in agriculture, biomedicine, microbiology, and biotechnology development. In addition, the IGI has a dedicated Public Impact team that focuses on matters of science policy, regulation, and societal engagement to ensure the responsible, ethical, and equitable deployment of CRISPR technologies.

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We included varied academic perspectives in our comments from several IGI and IGI-affiliated researchers and experts (see **Contributors** on page 7). We are grateful for the opportunity to provide input and recommendations to the Office of Science and Technology Policy and, by extension, relevant government agencies on how to best support the U.S. bioeconomy.

The IGI stands ready to further lend its expertise and answer any questions that may arise about the comments below.

On behalf of the Innovative Genomics Institute,

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Innovative Genomics Institute

There is tremendous potential to solve societal problems through biotechnological innovation and the Innovative Genomics Institute and its affiliated researchers and advisors are thrilled about the Biden Administration's leadership in this arena. Rapid advances in cell and gene therapy have had outsized impacts on health, such as the pivotal success of mRNA vaccines in the fight against the COVID-19 pandemic, highlighting that we have entered a new era of modern medicine. Agricultural crop plants can be genome edited with relative ease to increase yield, confer pest, drought, and flood resistance, and remove toxins from staple foods. An enhanced understanding of microbial life is revealing biological processes that can be leveraged to produce innovative solutions to climate change. Below we outline opportunities for the federal government to help realize the promise that biotechnology holds.

Investment in Research and Development - Qs.1b and 1c

In the biomedical space, developers and clinicians of cell and gene therapies face two primary problems with manufacturing capacity: wait times for raw materials and GMP requirements. The federal government is well situated to propel the necessary research, expansion of capacity, and workforce development.

- Robust funding of NSF and NIH has led to rapid advances in basic and preclinical discoveries in biomedicine. NIH also funds clinical trials; however, there is great need for substantial investment in translational research projects that will ensure support of basic research leads to real-world impacts.

- Biomanufacturing to good manufacturing practice (GMP) standards requires highly specialized personnel, equipment, and Quality Systems infrastructure; without more competition in the space, the capacity to produce at greater scales, and improvements in manufacturing methods, we cannot expect to see the type of transformation that is needed to reap the potential benefits of our biotechnological discoveries. Currently, biomanufacturing is difficult to access for academic institutions and smaller biotechnology companies. This is due to the limited available capacity, a rise in the number of biopharmaceutical products, and the very high prices being charged by existing contract development and manufacturing organizations (CDMOs). Because CDMOs manufacture products across the range of regulatory standards, they are often set up to meet the highest standard. That, in turn, increases the cost and wait times for products that do not need to be manufactured to the same level of quality control (see **Regulatory Needs** for further discussion of phase-appropriate GMP standards). It is particularly challenging for academic institutions and non-profit research organizations to compete with for-profits for manufacturing capacity. A lack of capacity means that discoveries made with federal research dollars cannot be tested for their translational value.

  Recognizing these limits, the California Institute for Regenerative Medicine (CIRM), a state-funded initiative, is looking to support infrastructure projects that will expand biomanufacturing for novel clinical trials. The work of CIRM presents a framework for investment upon which the federal government can build (also **Q.8**). Expanding capacity that prioritizes manufacturing for early-phase academic or non-profit trials is a smart and time-saving way to enable more novel biologics to be tested in Phase I trials. If successful, these new drugs can then be further tested and scaled up in partnership with larger pharmaceutical companies.

- Capacity building should not only be focused on manufacturing end-products, but also raw materials/bioreagents. It can currently take up to two years to obtain a plasmid or viral vector; nucleotide

manufacturing also faces limited capacity. By investing in the production of raw materials and bioreagents, the federal government would not only decrease wait times - which could mean saving patient lives - but also reduce U.S. dependence on European and Asian supply chains (also **Q.7**).

- U.S. biomanufacturing capacity should be expanded in a manner that reduces the number of nodes in the supply chain from raw materials to final products. This is especially important in the health space, where product variability increases with an increasing number of chain links (also **Q.7**).

While the health space enjoys robust research funding, there are several areas of biotechnological innovation where U.S. R&D investment is insufficient and discoveries are being made elsewhere, oftentimes in China:

- In plant science, funding falls short of the potential impacts that innovations like genome editing could have on agricultural yields, crop resilience, and food security. The plant and agriculture industry is highly consolidated and vertically integrated, with the Chinese-owned Syngenta one of three main players along with Bayer-Monsanto and Corteva. Most R&D is spent on only a small number of crops, such as soy and maize. Start-ups and smaller companies in the space have a hard time raising capital or obtaining government grants. As has been noted in the literature, increased R&D spending for more resilient agricultural products is imperative to mitigate the uncertainties of an intensifying climate crisis.[1]

- Metabolic engineering, i.e., identifying, developing, and optimizing cellular and microbial processes to produce chemicals, fuels, pharmaceuticals, urgently needs biomanufacturing investment dollars. There is a gap in funding for both individual researchers (in contrast to institutional grants) as well as scale-up of processes to produce titers in the gram-per-liter range. Clearer guidance to scientists on which agency will fund bold, longer-term projects in this and the plant space is also needed. Additionally, microbes remain vastly understudied and, therefore, underutilized. Microbes could unlock the efficient conversion of “waste” as feedstocks by converting organic waste matter, cellulose, plastic, methane, and other inputs into high-quality products, thereby supporting a circular bioeconomy. Here, too, federal investment in research and scaling of processes could have tremendous societal impacts.

- There has been a clear recognition by this Administration that biotechnology can help solve the climate crisis. In the agricultural sector, the federal government has started providing subsidies for carbon sequestration. However, adequate methods of measuring carbon sequestration on a landscape scale are lacking; resources in the development of such tools are needed.

- The federal government could establish an agricultural carbon credit program that incentivizes broad uptake of waste conversion processes and innovations in plant and agricultural sciences. Scientists have the tools and knowledge to develop efficient processes and effective tools, but, in the absence of government support

[1] Cai Y., et al. 2017. Agricultural research spending must increase in light of future uncertainties. Food Policy 70:71-83. https://www.sciencedirect.com/science/article/pii/S0306919216303426

such as subsidies or tax breaks, it will remain cheaper to maintain the status quo than to implement these novel techniques and products.

Short- and long-term goals - Q.1a

We identified several short-term (5-year) and long-term (20-year) goals that would advance the bioeconomy through significant investment in U.S. biotechnology and biomanufacturing.

Short-term goals:

- The federal government has the ability to increase access to cell therapies by investing in greater availability of closed and automated cell manufacturing systems in existing hospital facilities. Closed systems are critical to increasing access to and reducing the cost of autologous cell therapies that can be life-saving. Because these systems are closed, they enable "point-of-care" (POC) manufacturing of cell therapies without the need for elaborate clean rooms that are costly to build and operate and require space that may not be available at existing medical facilities.

  Closed systems would also benefit from targeted innovation funding to incorporate novel methods, such as CRISPR gene editing. Developers are already competing for manufacturing capacity in centralized manufacturing facilities. As more therapeutic modalities come available, limited capacity will restrict how many patients can benefit from discoveries that may be curative. Investments in closed system development and deployment will also translate into better geographic access and free up clean rooms for the manufacture of other cell and gene therapies. The Made-in-Canada CAR-T cell initiative[2] is an example of how government funding can reduce cost and increase access to innovative therapies.

- Federal funding to support the development of alternative cell production and gene delivery methods such as using lipid nanoparticles and in-vivo genomic therapies.

- Development of processes to measure the amount of carbon sequestered, on a landscape scale, through biotechnological interventions.

Long-term goals:

- A key area requiring long-term funding to advance the field is robotics. Biomanufacturing is often highly complex and demands a level of accuracy and precision for which robots are much better suited than humans. Currently, the field of robotics for biomanufacturing remains in its early phase and even for robots that are on the market there are issues with supply chain backlogs for parts.

- One area that has benefited only episodically from government interest and investment is the production of biofuels. After the last investment push (2005-2012), many companies were forced to move their operations into higher-value products like cosmetics. If the U.S. wants to be a leader in the biofuels industry and produce biodiesels and jet fuel from the breakdown products of cellulose, investment is needed at a transformative scale to convert biomass from high-density forests, dry timber of fallen trees, and plants,

[2] https://biocanrx.com/research/made-canada-car-t-platform

such as agave and tall grasses (e.g., switchgrass and Miscanthus), grown on non-arable lands. Agave is particularly attractive as it grows well in arid regions of the Southwest and generates large quantities of cellulose without the need for much water. This stands in contrast to sugar cane, which ties up arable land and is more resource-intensive.

Public Engagement - Q.2

Most research grants include a component around public engagement, outreach and/or education. However, research scientists are being asked to conduct social science programs which typically leads to these important areas being neglected. It is critical that the federal government make available funds for dedicated public engagement and outreach projects which are necessary for public acceptance and societally adapted product development. So far, there are few examples of large societal engagement projects for biotechnology innovations and a robust framework is lacking. To tackle this issue, the Innovative Genomics Institute and the Keystone Policy Center are co-hosting an expert workshop on public engagement best practices for gene editing in agrifood systems in February 2023. Directed investment by the federal government will be key to implementing any recommendations put forth by workshop attendees.

Importantly, existing and future funding should be made more accessible. Since research projects in the social sciences often require less money than in purely STEM fields, grant applications should be less onerous than those for a traditional NIH grant. More individuals interested in working at the nexus of science and public engagement should be given training opportunities.

Workforce Development - Qs. 10 and 11

As the bioeconomy expands, the workforce must, of course, also be further developed to ensure the U.S. can keep pace with biotechnological innovation. Especially in academic biomanufacturing, there is a shortage of skilled labor. This is, in part, due to a lack of awareness about the biomanufacturing industry and associated career paths. There is a need for more formal training and internship programs at various degree levels (certificates, 2-year, 4-year, and graduate degrees) across the country. Many training opportunities are either informal and offered directly in laboratories with manufacturing expertise or are grassroots efforts by individual colleges and universities who have identified the need and/or are working with industry partners to establish a pipeline of skilled workers.

In California, CIRM is working to address this shortage by offering “Bridges Awards" to undergraduate and Master’s level students to acquire laboratory skills in stem cell research with a focus on diversity. Through this program, institutions share curricula, internship opportunities, and other resources to build a diverse biomanufacturing workforce in the state. The federal government has an opportunity through funding and coordination of efforts to pave the way for a more robust training landscape both in biotech hubs but also in areas where manufacturing facilities are or will be operating (e.g., Aldevron’s biomanufacturing plant in Fargo, North Dakota). Importantly, training opportunities should be well compensated to ensure that individuals from low socioeconomic backgrounds can benefit equally as their more privileged peers (also **Q.8**).

Once personnel are trained, a significant issue for academic biomanufacturing efforts is retaining talent due to the significant compensation gap between industry and academia. The federal government could incentivize

individuals to stay in academic centers longer by offering tuition assistance or reimbursement programs to individuals with extensive formal biomanufacturing training (e.g. Master's degree level).

Regulatory Needs

As the nation expands its biomanufacturing capacity and novel biologics and bioproducts emerge, regulations must keep pace. To accomplish this, robust, rigorous, and agile regulatory bodies that are staffed with the appropriate expertise and well-resourced are needed to respond to inquiries in a timely manner. Regulatory agencies like FDA are doing a great job yet are overburdened by the volume of inquiries. To grow the bioeconomy, the federal government should invest the resources to grow its regulatory staff that ensures innovations are safe, effective, and reviewed in a timely fashion.

As alluded to above, Phase I clinical trials are often phase-appropriate, and may, after review and approval by FDA, advance with some raw materials not manufactured under GMPs. This, however, raises the key issue of comparability later in the process when the clinical programs move to Phase III/commercial manufacturing. Developers of novel therapies, especially those in academic settings, may choose to manufacture their product for a Phase I clinical trial with Phase I-GMP-compliant raw materials and in a Phase I-GMP-compliant facility (e.g., an academic manufacturing facility). To comply with increased GMP requirements when advancing to later stage trials, they must transfer their processes to a compliant facility and may need to improve raw material quality, which may lead to incomparability between phases of the clinical study, especially if further process improvements are made. The multiple changes may result in products not moving forward. FDA should refine and better describe the criteria for demonstrating comparability between phases. Where the only change is addition of a new manufacturing site without changes to the process, removal of the comparability hurdle should also be considered. Developers would prefer to develop GMP-compliant processes in support of Phase I, proof-of-concept trials; however, the time and cost burden can be prohibitive. In addition to regulatory clarity, the federal government has an opportunity to substantially reduce the risk of incomparability by robustly supporting the GMP-compliant manufacturing of critical reagents.

FDA may also wish to consider issuing a form of certification to manufacturers that meet compliance standards. The European Medicines Agency, for example, certifies only those manufacturers that are compliant with its requirements. This removes any guesswork for developers and smooths the path to market. The United Kingdom's Human Tissue Authority also licenses manufacturing facilities in academic centers that produce personalized (n-of-1) medicines. A similar model in the U.S. could be adapted to reduce the regulatory burden and facilitate the treatment of patients with unique conditions.

FDA, in reviewing and approving products, gains access to a wide variety of data that would be of great value to all developers in the field. While it is understood that these data are proprietary, they could be collated and de-identified in a way that could make certain data public. This type of data sharing would significantly speed up the drug development process and provide guidance on how a well-established process may be viewed to facilitate more standardized process platforms (also **Q.4**).

Regulatory clarity is also needed for genetically engineered microorganisms (GEMs). So far, GEMs have been regulated based on their ultimate function: by USDA-APHIS for use as animal feed, by FDA-CVM for human

food, and EPA for pesticides or any environmental release of microorganisms. However, these "functions" are rarely well-defined and there is significant overlap across regulatory authority. A microbial additive in cattle feed that can reduce methane production is regulated by the USDA as animal feed, but also by the FDA as an animal drug – both of which have different regulatory standards and steps for approval. There is also ambiguity in the regulations for microbial products that do not neatly fall into any specific category. Under the EPA's Toxic Substances Control Act (TSCA), it is unclear what safety standards are sufficient for a GEM product to be approved for commercial use. The current system of regulations for microbial biotechnology relies too heavily on individual use cases and requires deep involvement of different agencies to sign off on any product. These factors result in long timelines for approval and lost public benefit from valuable innovations.

Conclusion

The Innovative Genomics Institute is excited about the Biden Administration's push to leverage biotechnology to solve pressing societal problems. Our researchers and affiliated experts have identified four key areas of need from an academic perspective:

- R&D: Investment in GMP-compliant manufacturing capacity; point-of-care manufacturing for greater access to novel therapeutics; innovation funding for agrifood systems; support of landscape-scale carbon sequestration measurements.
- Public Engagement: Dedicated funding for public engagement, outreach, and education projects to help develop societally adapted products.
- Workforce: Investment in formal biomanufacturing training programs designed with access for underrepresented trainee in mind and incentives to retain skilled workers in in academic biomanufacturing.
- Regulatory: Clarification at several stages of product manufacturing, testing, and approval.

We look forward to seeing the advances the Administration makes to strengthen the U.S. Bioeconomy.

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