Public report on NSTC INTERAGENCY SYNTHETIC BIOLOGY WORKSHOP

This document is a summary of a workshop with stakeholder engagement and does not reflect the opinion of the U.S. Government.

Synthetic and engineering biology are disciplines that are advancing fundamental understanding of complex natural living systems and enabling novel functions and capabilities in support of a growing bioeconomy. Recent technology roadmaps, for example the Engineering Biology Roadmap produced by EBRC[1], identified a number of gaps and opportunities that would greatly accelerate engineering biology. Better coordinated efforts across U.S. government agencies and with academia and industry partners as well as more strategic investment in synthetic biology should accelerate science and technology innovation and translation. To better coordinate U.S. federal investment and efforts, a workshop was convened by the NSTC Interagency Synthetic Biology Working Group and held on October 16-18, 2019. U.S. Government agencies represented on the Interagency Synthetic Biology Working Group are listed in **Table 1**.

The workshop consisted of a public portion that aimed to gather perspectives and ideas pertaining to what is needed to advance synthetic biology and a government-only portion to identify areas of interagency coordination and collaboration. The two-day, public portion of the workshop included approximately 100 leading experts from academia, industry, and government. The format included a series of forward-looking talks followed by discussion of challenges and solutions for specific case studies organized around four application areas: bioenergy and agriculture, cellular factories, medicine, and biomanufacturing (see **Annex A** for agenda). The workshop included presentations and discussions that considered the role of synthetic and engineering biology in the global bioeconomy as well as public acceptance of this emerging technology.

The third day was a government-only meeting held at Eisenhower Executive Office Building. One product of the workshop was the development of a list of specific topical areas in which further investment could benefit US competitiveness in the field of synthetic and engineering biology (see **Table 2**). This list is a synthesis of the input from all stakeholders who participated in the workshop but is not meant to represent funding priorities of the U.S. Government. The narrative that follows provides a snapshot of the discussions among experts over the course of the public workshop.

The workshop began with an overview of the U.S. Bioeconomy by Dr. Mary Maxon, Lawrence Berkeley National Laboratory, describing the current state of US Bioeconomy. She presented its outlook, particularly with respect to its value, the impact of US policy, its relationship to the research enterprise, as well as the broader context within the global bioeconomy. Notably, the US Bioeconomy, with an estimated value of over $350B per year, is fueled by emerging biotechnology and synthetic biology. Professor James Collins, Massachusetts Institute of Technology, followed by providing a broad overview of the field from its early days of synthetic toggle switches to today, using examples of paper-based synthetic biology for diagnostics, synthetic microbiomes for treating cholera, and the power of synthetic biology to engage the next generation via programs like iGEM (high school and undergraduate students) and BioBits (middle school students). Other speakers included Professor Doug Densmore, Boston University, and Dr. Asa Oudes, Benchling, who highlighted the importance of computational and

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[1] https://Roadmap.ebrc.org

automation tools, data sharing, data repositories and standards, and support for this critical infrastructure. Dr. John Glass, JCVI, and Professor Drew Endy, Stanford University, added their unique perspectives on the needs of the field. Dr. Glass spoke to the need for a full understanding of genomes in a given organism to enable more predictive design. Professor Endy emphasized the needs in measurement, modeling and assembly that could power the next wave in innovation. Professor Barbara Harthorn, University of California Santa Barbara, engaged the workshop participants in an exercise to highlight and discuss public perceptions and misperceptions, as well as the role of public acceptance in the future of the field.

Findings from use case examination:

Bioenergy and Agriculture: Exploration of synthetic and engineering biology for the agriculture and bioenergy sectors started with a TED-style talk by Professor June Medford, Colorado State University, on the potential to use plant synthetic biology to deliver water desalination. She highlighted both the power and the challenges associated with applying the tools of synthetic biology in plants, as well as illustrating the potential opportunities in the field that are ready for more focused investments. In case studies, participants discussed applications that would lead to the enhancement of photosynthesis efficiency, easier degradation of lignin, and apomixis or more efficient clonal reproduction as a complement to traditional breeding approaches. The discussions further highlighted the limited development of synthetic biology tools in plant systems compared to capabilities for simpler (prokaryotic) organisms. Challenges included high throughput phenotyping tools, genome stability, clear paths to regulatory approval, lack of model systems, and the need for advanced phenotyping including ‘omics. Participants highlighted the differences in plant genomics and the role of ploidy on the efficiency of genome editing as well as challenges in plant tissue-specific targeting. Beyond basic research challenges, more infrastructure stood out as a clear need to support the field including data resources as well as platforms for pilot testing of new manufacturing technologies. In addition, there was a need for more training specific to plant biology and plant synthetic biology.

Cellular Factories: The discussion of synthetic biology to enable the use of cells as factories to compute, sense, respond and produce chemicals began with a TED-style talk by Professor Kristala Prather, Massachusetts Institute of Technology, that highlighted opportunities in the field. She challenged the community to incorporate more of the periodic table in synthetic biology designs and to find ways to leverage both chemical and biological routes to new molecules, as they worked to advance cellular factories. She drew parallels between the devices we need in cellular factories and chemical processing plants, including sensors, actuators, logic and process control and highlighted the potential to increase robustness through the adoption of these processes. Participants discussed opportunities and challenges in the biological synthesis of (macro)molecules in case studies that focused on cell free systems, synthetic cells, and microbial consortia. The advantages and limitations of each platform were discussed. There was discussion of the challenges associated with limited development of tools in organisms beyond a few well-developed models (for example, *E. coli*), scalability of the different platforms, and the relatively abundant “dark genome” (genes of unknown function). Also highlighted were challenges associated with the manufacture and assembly of three-dimensional materials. Included in this session was a discussion of the importance of standards both for the development of platforms such as cell free and synthetic cell systems, as well as for manufacturing. Biosafety and public acceptance of various cellular factory platforms were also addressed as important factors impacting the future of the field.

Medicine: Examination of the potential for synthetic and engineering biology to impact the field of medicine began with a talk by Professor Bruce Levine, University of Pennsylvania, who presented fascinating results of the first Chimeric Antigen Receptor (CAR) T cell trials for the treatment of human cancers and subsequent efforts to bring them to market as well as how synthetic and engineering biology tools are now revolutionizing the design and development of better therapeutics. The subsequent discussion included the importance of understanding CAR-T cell targeting for successful outcomes, as well as the challenges associated with the heterogeneity in patients and with personalized therapies. Discussions of public acceptance included issues of equitable access, escalating costs of therapies, cost of failure and failure to act. Case studies examined applications that ranged from synthetic microbiomes that sense and stimulate the host, artificial organs, and bio-electric devices. Participant discussions covered a wide range of topics from using synthetic and engineering biology tools to develop better sensors for detection of disease, issues with treatment delivery, the need for cyberinfrastructure resources, models for the ownership and sharing of data, the need to address regulatory issues early in development, and the importance of collaboration with physicians. Workshop participants highlighted challenges with cell sourcing for therapies, control of cell fate and differentiation, understanding and control of cell signaling, and issues with manufacturing cellular therapeutics at scale. Participants generally agreed that the public was more willing to accept risks associated with synthetic and engineering biology-based therapies in the medical field for life-threatening disease treatment. However, issues of social justice, that is who had access to expensive life-saving therapies, were also highlighted.

Biomanufacturing: Two leaders from industry, Dr. Patrick Boyle, Ginkgo Bioworks, and Michael Koepke, LanzaTech, led off the discussion of the opportunities for synthetic and engineering biology to advance biomanufacturing. They emphasized the tremendous impact of the reduced cost and speed of DNA synthesis, and the development of design and automation tools on the speed of research and development in the field. Both Boyle and Koepke talked about the importance of platform technologies, standards, and scalability, issues of feedstocks and supply chain, as well as markets. They pointed to the lack of expertise in the US workforce in scale up as well as downstream processing for biomanufacturing and emphasized the lack of critical infrastructure for pilot scale and contract manufacturing in the US that could potentially limit US industry competitiveness. Case studies addressed supply chain gaps and possibility to scale up cell-free manufacturing. Participants discussed the need for developing new manufacturing technologies, including continuous manufacturing, advantages of distributed versus centralized manufacturing via synthetic biology platforms, and the use of microfluidic platforms for personalized on-demand manufacturing. Other needs highlighted included development of standards, process models, and facilities for rapid prototyping. Obstacles to advancement included global competition, an uncertain regulatory environment, lack of a trained workforce, lack of support for data and physical infrastructure including secure, domestic DNA synthesis facilities, and lack of capital to de-risk commercialization.

During the discussion of each case study, participants were asked specifically to address technical feasibility, and in doing so to identify needs in basic science, enabling technologies, workforce and infrastructure. In **Table 2**, a synthesis of some of the identified needs across all sectors, as determined by the stakeholder discussions, is presented. The investments described in the table do not represent a commitment of funding from any agency or U.S. Government funding priorities.

Table 1. List of agencies represented on Interagency Synthetic Biology Working Group

1. CDC-NIOSH
2. DARPA
3. DOD – Air Force (AFRL and AFOSR)
4. DOD – Army (ARL, MRDC, and ARO)
5. DOD – Navy (NRL, ONR)
6. DOD – OUSD
7. DOE
8. NASA
9. NIH
10. NIST
11. NSF
12. USDA-NIFA
13. USGS

Table 2. Synthesis of needs in basic science, enabling technologies, infrastructure, workforce and other areas to advance impact of synthetic biology across all sectors based on feedback received at the workshop. The investments do not represent a commitment of funding from any agency or U.S. Government funding priorities.

Basic Science
Genotypes to phenotypes/ including uncovering dark genome.
Spatial and temporal control of synthetic biology; tissue specificity, as well as cell-compartment specificity; emergent behavior of multicellular systems and hybrid biological/material systems
New measurement technologies to quantify complex *living* systems and processes, multi-modal measurement in real-time, in living single cells and multicellular systems to improve structural/functional understanding
Data acquisition, AI tools, and computational models to improve understanding of systems and engineering biology; better computational modeling (tied to Genotypes to phenotypes, A1)
Enabling Technologies
Expanded set of well-characterized chassis for cellular engineering: microbial, plants, other eukaryotes beyond yeast; transformation technologies beyond model systems; enable a broader range of product/material synthesis to sense/respond/function in different environments. Ability to engineer these as monocultures or consortia (e.g., Extremophile microbes, plants/plant cells, host-associated communities).
New tools, platforms, and data/knowledge to standardize parts and circuit construction and predictively engineer biological systems, high-throughput phenotyping; Expand capabilities for rapid high-throughput screening with non-model, as well as conventional chassis: “X-on a chip”, organs, plants, cell-free, chemical/material/polymer products, hybrid cellular/material systems
DNA synthesis: Secure, domestic, rapid, and reliable -at the scale of multi-gene plasmids, eventually at genome scale, assembly/synthesis of large pieces of DNA; DNA delivery: rapid, reliable, functional insertion of DNA into a broad range of organisms
New manufacturing technologies: distributed manufacturing, smart bioreactors, agile scale up and out
Workforce
Interdisciplinary training - training for engineering biologists, to include more exposure to statistics, data science (bioinformatics/AI), material science, process engineering, safety professionals, *etc.* undergrad->postdoc
Citizen Science and mechanisms to attract more young people to synthetic biology (K-12, undergraduate)
Interdisciplinary training for graduate students and postdocs at National Labs and industry; More collaborations with the industry
More collaborations with the industry
Infrastructure
Accessible data repositories, data storage and computing power
Public-private partnerships to advance regulatory science and standards development
Access to core facilities for rapid prototyping, scale up, manufacturing, *etc.*; promote industry, academia, government collaboration
Other considerations
More funding and continuing discussions to understand and promote public understanding of new technologies, understand public perception, mitigate potential risks, help provide data/science for policy input, *etc.*
Privacy concerns with potential data generated from SynBio
Contribute to public engagement and informed policy and regulatory framework
Website to communicate with the public USG SynBio efforts
Coordinate with other NSTC IWGs (Biorepository, Data, *etc.)*
Promote collaboration among U.S. government scientists

Annex A. Public workshop agenda

Interagency Workshop on Synthetic Biology
Examining Needs to Realize Future Potential
October 16-17, 2019
North Bethesda Marriott

Wednesday, October 16, 2019

8:00 AM	Registration/Breakfast	*Foyer - Salon Room F*
8:30 AM	Introduction, Overview, and Goals *Sheng Lin-Gibson, NIST, Jessica Tucker, NIH, Theresa Good, NSF*	*Salon Room F*
8:50 AM	Role of Synthetic Biology in a Global Bioeconomy *Mary Maxon, LBNL*	*Salon Room F*
9:10 AM	EBRC Roadmap – an opportunity to chart a course for future collaboration *Doug Friedman/Emily Aurand, EBRC*	*Salon Room F*
9:30 AM	Opportunities in synthetic biology – reflections on the past and a vision for the future *Jim Collins, MIT*	*Salon Room F*
10:00 AM	Break	*Foyer - Salon Room F*
10:15 AM	Transforming Bioenergy and Agriculture with Synthetic Biology *June Medford, Colorado State*	*Salon Room F*
10:40 AM	Break out groups to examine case studies in **bioenergy/agriculture** sector Group Leaders: *Cynthia Collins, Patrick Shih, Nathan Hillson, Nigel Mouncey, Jennifer Kuzma* • Presentation of the case study • Break out group discussion of questions (same questions for each case) ○ What is the timeline for feasibility? 5 years, 10 years, 20 years ○ Is it technically feasible? If not, what are the major technical hurdles to be overcome? Are there additional basic science, enabling technologies, infrastructure needs? ○ What are the key opportunities for collaboration that could jump start/ accelerate this use case? ○ What are the barriers to public acceptance and commercialization?	*Great Falls (Collins)* *Middlebrook (Shih)* *Timberlawn (Hillson)* *Seneca (Mouncey)* *Strathmore (Kuzma)*
12:00 PM	Working Lunch	
12:45 PM	Breakout group report out & discussion Discussion Leader: *Sean Cutler, UC Riverside*	*Salon Room F*
1:45 PM	Transforming Cellular Factories with Synthetic Biology *Kristala Prather, MIT*	*Salon Room F*

2:10 PM	Breakout groups to examine case studies in **cellular factories** sector Group Leaders: *Mike Jewett, Kristala Prather, Eric Klavins, Kate Adamala, Neal Devaraj*	*Great Falls (Jewett)* *Middlebrook (Prather)* *Timberlawn (Klavins)* *Seneca (Adamala)* *Strathmore (Devaraj)*
3:30 PM	Break	*Foyer – Salon Room F*
3:45 PM	Break out group report out & discussion Discussion Leader: *John Glass, JCVI*	*Salon Room F*
4:30 PM	Public Acceptance of Synthetic Biology *Barbara Harthorn, University of California Santa Barbara*	*Salon Room F*
4:50 PM	Unmet computational needs *Chris Myers, University of Utah (Contributions from Doug Densmore and Eric Klavins)*	*Salon Room F*
5:10 PM	Unmet basic science needs *John Glass, JCVI*	*Salon Room F*
5:30 PM	Synthesis of Day 1 – common themes & opportunities *Theresa Good, NSF & Jessica Tucker, NIH*	*Salon Room F*

Thursday, October 17, 2019

8:00 AM	Registration/Breakfast	*Foyer - Salon Room F*
8:15 AM	Recap, Goals for Day 2 *Alias Smith, NSF*	*Salon Room F*
8:20 AM	Transforming Medicine with Synthetic Biology *Bruce Levine, University of Pennsylvania*	*Salon Room F*
8:45 AM	Break out groups to examine case studies in **medicine** sector Group Leaders: *Lydia Contreras, Chris Myers, Laura Segatori, Ahmad Khalil, Doug Densmore*	*Great Falls (Contreras)* *Middlebrook (Myers)* *Timberlawn (Segatori)* *Seneca (Khalil)* *Strathmore (Densmore)*
10:00 AM	Break	*Foyer - Salon Room F*
10:15 AM	Breakout group report out & discussion Discussion Leader: *Ron Weiss, MIT*	*Salon Room F*
11:10 AM	Unmet needs – a company perspective *Asa Oudes, Benchling*	*Salon Room F*
11:30 AM	Transforming Biomanufacturing with Synthetic Biology *Patrick Boyle, Ginkgo Bioworks and Michael Koepke, LanzaTech*	*Salon Room F*
11:55 AM	Breakout groups to examine case studies in **biomanufacturing** sector Group Leaders: *Michael Dosier, Derek Abbott, Rebecca Nugent, Ari Friedland, Kelvin Lee*	*Great Falls (Dosier)* *Middlebrook (Abbott)* *Timberlawn (Nugent)* *Seneca (Friedland)* *Strathmore (Lee)*
12:00 PM	Working Lunch	
2:00 PM	Breakout group report out & discussion Discussion Leader: *Michael Koepke, LanzaTech*	*Salon Room F*
2:45 PM	Imagining a future enabled by synthetic biology *Drew Endy, Stanford*	*Salon Room F*
3:15 PM	General Discussion – where are the gaps and opportunities that will enable us to realize the future potential in the field *Sheng Lin-Gibson, NIST*	*Salon Room F*
4:00 PM	Adjourn Day 2	