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A brief overview of synthetic biology research programs and roadmap studies in the United States

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A B S T R A C T

The United States is a leading nation in the development of synthetic biology, an emerging engineering discipline to create, control and reprogram biological systems. With strategic investment from its government agencies, the U.S. has established numerous research centers and programs in synthetic biology, enabling significant advances in foundational tool development and practical applications ranging from bioenergy, biomanufacturing, to biomedicine. To maintain its leadership in synthetic biology, U.S, has conducted several roadmap studies to provide strategic visions and action recommendations. Here we will provide a brief overview of the major research programs and roadmap studies of synthetic biology in the U.S.

Contents

1. Introduction

Synthetic biology promises to provide sustainable solutions to many grand challenges of the modern society via innovations in agriculture, chemicals, pharmaceuticals, energy, and bioremediation [1–3,4,5]. Given its interdisciplinary nature, however, a consensus definition of synthetic biology has yet been reached. But at its core, the field of synthetic biology centers on “design, construction, and characterization of improved or novel biological systems using engineering design principles” [6]. Although synthetic biology is becoming a global research enterprise, the U.S. is the leading nation in the world [7]. In 2000, two U.S. research groups reported the creation of genetic oscillators and toggle switches that function in an analogous manner to electrical circuits [8,9], which marks the birth of the synthetic biology field. Since then, the U.S. government has been the biggest investor in this emerging discipline, providing approximately $500 million to $1 billion research funding since 2005 [10,11], with a yearly spending estimated at $140 million [12]. Many U.S. research centers focusing

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on synthetic biology have been established, including but not limited to Synthetic Biology Engineering Research Center (Synberc), the Centers for Synthetic Biology at MIT and University of California at San Francisco (UCSF), and the J. Craig Venter Institute. Moreover, U.S. industry has also been investing heavily in the medical and biotechnological applications of synthetic biology with an expected market value of $10.8 billion by 2016 [13]. Exemplary companies are from multinationals such as DuPont, BP, ExxonMobil, to start-ups such as Synthetic Genomics, Amyris, Intrexon, Ginkgo Bioworks, and Zymergen.

In this review, we will briefly summarize the research landscape of synthetic biology in the U.S., focusing on major funding agencies and research initiatives (Fig. 1 and Table 1). In particular, the organizational structure and major accomplishments of Synberc, the first major U.S. synthetic biology research center, will be discussed in details. U.S. roadmap studies will also be discussed, highlighting strategic plans to fully realize the potential of synthetic biology and to maintain the U.S.'s leadership in this field.

2. Major U.S. research agencies that fund synthetic biology

The funding from the U.S. government for synthetic biology is spread among different agencies, lacking a coordinated government funding mechanism [14]. Some of the most important federal funders include the National Science Foundation (NSF), Department of Energy (DOE), Department of Health & Human Services (HHS, including National Institutes of Health (NIH)), Department of Defense (DOD, including Defense Advanced Research Projects Agency (DARPA)), the Navy, the Air Force, Department of Agriculture (USDA), and National Aeronautics & Space Administration (NASA) [10,11]. Dependent on the specific missions, different federal agencies have their own focuses in synthetic biology [15]. For example, NSF aims to advance fundamental basic research, develop novel engineered systems, educate a new cadre of students, and support an emerging synthetic biology industry. DOE focuses on the development and application of synthetic biology tools to redesign plant, microbial and hybrid systems to manufacture biofuels and bio-based products. NIH is interested in fundamental and translational research areas where biomedical science and synthetic biology overlap. DOD considers synthetic biology as one of six high priority basic research topics because of its potentially transformative impact in defense applications, including smart sensing, novel materials, and medicine. For NASA, three focuses are material resupply en route and at the destination for human missions, astrobiology, and next-generation aeronautics including the use of biofuel and fuel additives. Moreover, synthetic biology may also impact many USDA's strategic plans, such as expanding agricultural markets, food safety, and nutrition and health. Here we will highlight four U.S. government agencies as major sponsors of synthetic biology research, including NSF, DOE, DOD, and NIH (Table 1).

NSF's Engineering Research Center (NRC) Program funded Synberc in 2006, one of the earliest major research grants in synthetic biology from the U.S. government. Synberc is a multi-institutional research center (see the next session for details), and its key members include faculty from University of California at Berkeley (leading institution), Harvard, MIT, UCSF, and Stanford, as well as a few industrial companies. Over 10 years, NSF has committed $39 million to support Synberc [14,16], whose missions are to (1) develop the foundational understanding and technologies to build biological components and assemble them into integrated systems to accomplish many particular tasks; (2) train a new cadre of engineers who will specialize in engineering biology; and (3) engage the public about the opportunities and challenges of engineering biology (https://www.synberc.org/about). In 2008, a second NSF ERC Center, Center for Biorenewable Chemicals (CBiRC) was established at the Iowa State University, whose mission is to "develop the fundamental knowledge and technology and the academic and industrial partnerships needed to provide a foundation for industrial chemical production to be transformed from a petroleum-based industry to a renewable resource-based industry" (http://www.cbirc.iastate.edu/overview/mission/). Furthermore, NSF has been actively promoting international collaborations in synthetic biology. In 2008, the NSF Division of Molecular and Cellular Biosciences (MCB) co-organized an "Ideas Lab" or "Sandpit" program in synthetic biology with the United Kingdom Physical Science Research Council (EPSRC). In 2011, the second U.K.-U.S. Ideas lab with a focus on improving photosynthesis was held with a combined investment of $18 million. In 2014, NSF collaborated with the U.K. Biotechnology and Biological Sciences Research Council (BBSRC) to start a Pilot program in synthetic biology. To reduce the barriers to work internationally, a simplified and flexible

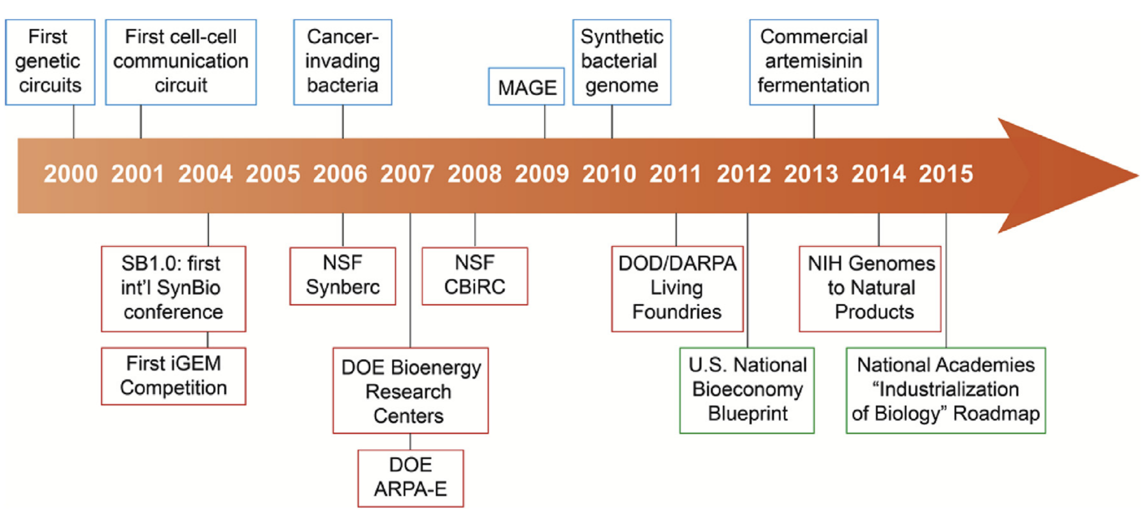

Fig. 1. A brief timeline of synthetic biology in the U.S. Blue box: major research achievements; Red box: major research centers and programs; Green box: major roadmap studies. MAGE: multiplex automated genome engineering; SB1.0: Synthetic Biology 1.0; iGEM: International Genetically Engineered Machine; Synberc: Synthetic Biology Engineering Research Center; CBiRC: The Center for Biorenewable Chemicals; ARPA-E: Advanced Research Projects Agency-Energy; DARPA: Defense Advanced Research Project Agency.

Table 1
Major synthetic biology centers/initiatives in the U.S.

Agency	Program name	Lead institution	Program duration	Funding (million dollar)
NSF	Synthetic Biology Engineering Research Center (SynBERC)	UC Berkeley	2006–2016	39
DOE	DOE Bioenergy Science Center	Oak Ridge National Lab	2007–2018	250
DOE	DOE Great Lakes Bioenergy Research Center	U Wisconsin/Michigan State University	2007–2018	250
DOE	DOE Joint BioEnergy Institute	Lawrence Berkeley National Lab	2007–2018	250
NIH	Center for Systems and Synthetic Biology	UC San Francisco	2011–2016	15
NIH	MIT Center for Integrative Synthetic Biology	MIT	2013–2017	12
NIH	Genomes-to-Natural Products program	Rockefeller University/Stanford	2014–2019	20
DOD-DARPA	Living Foundries: ATCG	MIT/U Texas/Caltech/J Craig Venter Institute	2011–2014	35
DOD-DARPA	Living Foundries: 1000 Molecules	UC Berkeley/MIT/Harvard/UIUC/U Colorado/ Zymergen/Amyris	2013-now	110

review process was adopted, whereas a single review process by only one of the partner agencies is necessary for the successfully proposals to be funded by both NSF and BBSRC. In addition to the collaborations between the U.S. and U.K., NSF initiated a bilateral funding program, *Metabolism: for a Low Carbon Society*, with the Japan Science and Technology (JST) with $12 million grants in 2011. Other than the research centers and special programs, NSF also provides smaller grants that have come out of unsolicited proposals, adding up to $55 million funding in synthetic biology annually [14].

DOE has been estimated to invest the most research funding in synthetic biology among U.S. government agencies (over $700 million), primarily in the area of bioenergy [14]. Four major synthetic biology programs are supported by DOE, including Joint Genome Institute, Genomic Sciences Program, Bioenergy Research Centers, and Advanced Research Projects Agency-Energy (ARPA-E). In particular, DOE's Bioenergy Research Centers program has committed $750 million to support three centers for ten years since 2007, with the aim to “better understand the biological mechanisms underlying biofuel production so that those mechanisms can be redesigned, improved, and used to develop novel, efficient, bioenergy strategies that can be replicated on a mass scale” [14]. The three centers are BioEnergy Science Center (BESC, Oak Ridge, Tennessee), Great Lakes Bioenergy Research Center (GLBRC, Madison, Wisconsin), and Joint BioEnergy Institute (JBEI, Emeryville, California). These centers emphasize on different research areas of bioenergy, with BESC focusing on poplar and switchgrass crops and their biomass formation, structure and recalcitrance, GLBRC focusing on plant fiber breakdown to maximize production of starches and oils, and JBEI focusing on microbial synthesis of advanced biofuels. On the other hand, for ARPA-E, its creation was recommended by a report from U.S. National Academies as a response to the request from the U.S. congress to “identify the most urgent challenges the U.S. faces in maintaining leadership in key areas of science and technology.” ARPA-E was authorized by The America COMPETES Act in 2007, and is modeled after the DOD's DARPA, whose mission is to prevent unforeseen attack from negatively impacting U.S. national security and to ensure strategic military advantage for the U.S. military through technological superiority. ARPA-E funds “high-risk, high-impact” research programs to develop transformational energy technologies, and exemplary projects that are related to synthetic biology include “Synthetic Gene Circuits to Enhance Production of Transgenic Bioenergy Crops”, “Synthetic Methylotrophy to Liquid Fuel”, “Anaerobic Bioconversion of Methane to Methanol”, and “Synthetic Biology, Protein Engineering, and Semi-Biological Photocatalysis to Convert Methane to n-Butanol” [10].

In DOD, synthetic biology is identified as one of the six high-interest basic science areas [15]. Although most DOD research is classified, public reports indicate there are 18 synthetic biology projects within Naval Biosciences and Biocentric Technology Program [11]. The DOD's Office of Naval Research (ONR) has invested about $5 million per year in synthetic biology research “to develop engineered organisms to produce, deliver, detect, and/or respond to target compounds or signals, and that can communicate with non-living devices, in support of future naval capabilities.” Representative projects that are awarded include “Powerful Combinatorial Sensors to Program Microbes” and “Multiplexed Pathway and Organism Engineering” [11]. Furthermore, DARPR has initiated two Living Foundries programs—Living Foundries: Advanced Tools and Capabilities for Generalizable Platforms (ATCG) and Living Foundries: 1000 Molecules (Table 1) [14]. The goal of the Living Foundries initiative is “to create a revolutionary, biologically based manufacturing platform to provide access to new materials, capabilities and manufacturing paradigms” [14]. With a budget of about $35 million from 2012 to 2014, the Living Foundries: ATCG program aims to accelerate the biological design-build-test-learn cycle by at least 10 fold in both time and cost via the development of next-generation tools. Building upon the technological advancements under ATCG, the Living Foundries: 1000 Molecules program seeks to create a scalable and integrated infrastructure for rapid design and prototyping of engineered biological systems. With a $110 million budget, the 1000 Molecules program expects a milestone demonstration to generate 1000 novel chemical molecules of relevance to the DOD, such as chemical building blocks towards radical new materials [14]. To achieve this specific goal and more broadly, to leverage biology as a technology platform to pursue transformative applications across chemicals, materials, sensing capabilities and therapeutics, the 1000 Molecules program seeks the development of “a fully integrated, rapid design and prototyping infrastructure that spans design tools, scalable, automated, and parallelized design fabrication, and high-throughput design evaluation and validation” [17]. The overall objective is to automate and scale-up the design-build-test-learn cycles to streamline biological engineering. Six teams, including University of California at Berkeley, MIT, Harvard, University of Colorado, University of Illinois at Urbana-Champaign (UIUC), and a start-up company Zymergen, were selected for Task Area 1 phase funding (Table 1). MIT and Zymergen, as well as another company Amyris, were selected for Task Area 2 phase funding with around $35 million per team (Table 1).

NIH, an organization of HHS, supports extramural research of synthetic biology with biomedical and healthcare applications via investigator-initiated grants, which was estimated to be more than $50 million during 2005–2010 [10]. As NIH operates as 27 separate institutes with individual research agenda, most NIH grants in synthetic biology are small ones awarded to individual researchers, but NIH also funded a few large center-level grants including the UCSF Center for Systems & Synthetic Biology, MIT Center for Integrative Synthetic Biology, the Johns Hopkins University School of

Medicine Center for Systems Biology of Retrotransposition, and the Stanford Center for Systems Biology (Table 1) [14]. In particular, the UCSF center focuses on the principles and architectural features involved in common cellular processing behaviors and use this information to engineer synthetic circuits that can trigger desirable cellular responses to external cues, making them potentially useful in biotechnology and biomedicine. The MIT center explores using synthetic, RNA-based circuits to sense and destroy cancerous cells; programming the differentiation of stem cells to generate insulin-producing beta-islet cells for diabetes; and engineering approaches to target antibiotic-resistant bacteria. Moreover, NIH has recently awarded $20 million between 2014 and 2019 to Rockefeller University and Stanford University under the Genomes-to-Natural Products program (Table 1), aiming to apply “well-integrated genomics, synthetic biology, and bioinformatics expertise to develop innovative, high-throughput, and broadly applicable genome-based methods for natural products discovery that overcome technical barriers and fill knowledge gaps for translation of genetic information into chemical information” (http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-14-002.html).

On a separate note, the involvement of government agencies in commercial development of synthetic biology is primarily indirect [15]. For example, federal investments in synthetic biology research contribute foundational knowledge and technological development to facilitate commercial applications in platform organisms, process pathways and related biotechnologies [15]. Moreover, through government funded synthetic biology research, a new generation of scientists are trained at the interface of systems biology, chemical engineering, molecular biology, and bioinformatics, and the skill sets are critical in applied synthetic biology R&D but rarely acquired in traditional research programs [15]. There are also instances where the federal agencies directly fund the private sectors in synthetic biology applications. The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs provide grants to domestic small businesses in commercialization of innovations derived from federally funded research (https://www.sbir.gov/). Synthetic biology-related SBIR/STTR solicitations from NSF, DOD, and NASA seek proposals in the area of metabolic engineering, large DNA constructs, microbiome, space exploration, *etc*. Furthermore, start-up synthetic biology companies are also awarded federal funding in their early stage [14]. For instance, Solazyme received a $21 million grant from DOE to develop algae-based biofuels. Modular Genetics was awarded a $200 K NSF Rapid Response grant for bioremediation in the 2010 Deepwater Horizon oil spill in the Gulf of Mexico. Amyris, Zymergen, and Twist Bioscience received $35, 35 and 5 million from DOD, respectively, through the DARPR Living Foundries: 1000 molecules program.

In sum, significant financial support across many U.S. agencies is steadily growing for synthetic biology and the major research programs have laid the groundwork for synthetic biology, including fundamental understanding and tools to design, build and test biological systems at all scales, a new cadre of scientists and engineers specialized in synthetic biology, and a fast-growing industry for a wide-range of applications. As multiple U.S. government agencies are investing in synthetic biology, it is increasingly recognized that good interagency communication and coordination is critical to build synergies, leverage investments, and minimize duplication or overlap, but currently the U.S. still lacks a national infrastructure to coordinate research funding in this area [14,15]. Although the U.S. White House Office of Science and Technology Policy (OSTP) is increasingly trying to identify collaboration opportunities across different government agencies in synthetic biology and related disciplines (systems biology, bioprocessing, and biomanufacturing), in the near future it is unlikely to witness a coordinated national effort on the scale of the U.S. National Nanotechnology Initiative [14].

3. Synberc

Since its establishment in 2006, Synberc has helped to shape the global research agenda for synthetic biology, by developing foundational technologies, convening academic and industrial researchers, and training many of the leading investigators in this field. Synberc is considered an effective model to explore and align biotechnology activities with public needs via dialogue, research and education [14,16]. In particular, recognizing synthetic biology would require a collective rather than individual effort, Synberc was established as a “virtual” center to establish a common research and education infrastructure. Synberc uses a distributed organizational structure in its leadership team, including a Center Director (Jay Keasling), a Deputy Director (Wendell Lim), Directors specialized in various areas (administrative, industrial collaboration, education and training, and bioethics), and support staff. Each research direction is also led by a scientific leader chosen across the partner institutions. Synberc has a headquarter at UC Berkeley, and three core facilities in Synthetic Microbial Characterization, Computational Design, and Registry of Standard Biological Parts. The participating institutions also formed two core centers in San Francisco and Boston areas based on geographic locations. Financially, in addition to the NSF center grant, which accounts for 87% of the total funding, Synberc also assists participating investigators to procure additional funding from federal programs, state opportunities, targeted private foundations and industry. In retrospect, the “virtual” center mechanism is considered essential to develop the synthetic biology community, as well as to establish intellectual foundation and commercialization for the field [14,16], by bringing researchers from allied fields in sustained conversation, forming a nucleus of interdisciplinary leaders for major proof-of-concept programs, and enabling the foundation for industry-academia collaboration. These achievements may be simply beyond the capability of any individual laboratory alone.

Synberc pursues three major programmatic areas: Research, Education, and Practices (The Synthetic Biology Security, Policy and Ethics Program) [14,16]. The Research program aims to build and assemble standardized biological components into an integrated system to accomplish a particular task [14]. This goal is achieved through three “thrust” areas, including Parts and Part Composition, Device and Device Composition, and Chassis Design, Construction and Characterization. The main principles behind these research areas are standardization, models and methods, composability, evolution and open access. Two Testbed applications, a bacterium capable of moving to and attacking a chemical or biological entity, as well as a microbial drug factory to produce a large range of natural and un-natural products, are used as vehicles to drive development of the research thrusts [14]. These research activities have provided fundamental advances in synthetic biology, such as “highly multiplexed genome engineering, rational design tools, computer programs, standardized parts and registries, biofabs, and engineered cell traits” [14], which collectively have substantially reduced time and cost of biological engineering with increased predictability. As of April 2015, Synberc has produced 364 papers in peer-reviewed journals, 88 patent applications (9 patents awarded, 5 licenses issued), 71 graduated PhDs, 8 start-up companies, and $88.6 million direct associated project funding (personal communication). Moreover, many large-scale synthetic biology centers are started around Synberc, such as the ones in MIT, UCSF, and UC Berkeley. For Education, Synberc offers a series of programs targeting different audiences, including graduate and undergraduate students, the general public, policymakers, and K-12 students.

These programs have led to 36 new university-level courses, as well as outreach events cumulatively covering more than 53,000 students, teachers and others. Notably, Synberc is one of the main supporters for iGEM (International Genetically Engineered Machine Competition), which is now a global synthetic biology education program for undergraduate students. For the Practices program, it examines and addresses safety, security, responsible conduct of research, intellectual property, and ethical, legal, and social implications of synthetic biology [14]. In addition to the above three areas, Synberc is required by NSF to develop a strong relationship with industry. In its Industrial Advisory Board (IAB), Synberc includes 29 established and start-up companies with a wide range of focused markets, such as industrial biotechnology, health care and nutrition, software and service, and agriculture. The IAB provides regular feedback to Synberc on its research programs and directions, and participates in the development of white papers with the community. Some IAB members also sponsor Synberc activities and support student involvement through internship [14].

The NSF Engineering Research Centers (ERC) program, through which Synberc is funded and established, publishes program evaluations and case studies of program impact for its awarded centers (http://erc-assoc.org/). These reports assess the ERC programs from the following aspects: strategic planning, undergraduate and graduate education, institutional and cultural change on the home institutions, post-graduation status, interaction with industry, and economic impact. So far, Synberc is only mentioned in one public report, "ERC-Generated Commercialized Products, Processes, and Startups", which has listed Amyris and LS9, two Synberc spinoff companies, as commercialization successes for semi-synthetic artemisinic acid production and rapid genomic engineering for biofuel production, respectively. In addition, on the ERC website, the achievements of the ERC centers are classified into Research Advances, Technology Translation and Innovation, and Education and Outreach, whereby the impactful accomplishments of Synberc are also listed (http://erc-assoc.org/achievements/by_center?id=13).

It is the policy of NSF to cease funding for ERC programs at the end of the ten-year cooperative agreement with the expectation that these centers may become self-sustaining [18], especially considering the strong emphasis on industrial collaboration and technology transfer in the ERC programs. In 2016, as the 10-year support from NSF is discontinued, Synberc has been transformed into the Engineering Biology Research Consortium (EBRC) as an independent non-profit organization (http://ebrc.org). The vision of this new organization is "to be the leading organization in the US bringing together the synthetic biology community to provide the future vision for synthetic biology, catalyze leading-edge research and education programs, and promote dialogue about synthetic biology among policy-makers and other members of the public." (https://www.synberc.org/ebrc). As EBRC was newly launched, there is not much public information available for its operational details, except for a few FAQs that briefly explain EBRC's research missions, Board of Directors, membership, and funding plans (http://ebrc.org/about/faq/).

4. U.S. roadmap studies for synthetic biology

Recognizing the strategic importance of synthetic biology, many U.S. public agencies have published roadmap studies to provide visions and recommendations to address the key challenges and deliver important applications of synthetic biology. Given the specific missions of various agencies, these roadmap reports have different focuses such as bioeconomy, bioenergy, biomanufacturing, biosecurity, and social implications.

In 2012, the National Bioeconomy Blueprint was released by the U.S. White House Office of Science & Technology Policy (OSTP) to "lay out strategic objectives that address the key elements to help realize the full potential of the U.S. bioeconomy and to highlight early achievements toward those objectives." Although not addressed specifically to synthetic biology, the five strategic objectives outlined in the report are highly relevant—increasing R&D, facilitating commercialization, streamlining regulation, increasing education, and broadening scientific knowledge [19]. Moreover, a subsequent report, *Putting the Bioeconomy Blueprint to Work*, outlined several immediate action steps that depend on advancement in synthetic biology [20], such as building support for biofuel production facilities to create jobs and expand the use of alternative energy, training the power of induced pluripotent cell technology on blood-related and neurological diseases, growing the economy and rural jobs by supporting biomass production, collaborating to reduce the need for nitrogen fertilizer inputs, and improving national security through biological research.

In July 2013, DOE prepared a *Report to Congress: Synthetic Biology* in response to the request from the U.S. congress for "a comprehensive synthetic biology plan for federally supported research and development activities that will support the energy and environmental missions of the Department and enable a competitive synthetic biology industry in the United States." In this report, the current state, future R&D needs, and federal research programs of synthetic biology in the U.S. were summarized [15]. Enhanced coordination between federal agencies to establish a comprehensive effort in synthetic biology on a national level was recommended. Moreover, this report identified the need for open information exchange among public and private stakeholders, recommending the development of standards for information, tools and component parts and databases specific to synthetic biology. Three key challenges for synthetic biology research were identified:

1. **Methods and Technologies**: Genome Scale Engineering Tools, DNA Synthesis and Assembly, Analytical Tools
2. **Platform Development**: Biological Design Principles, Genetically Tractable Organisms/Chassis, Minimal Cell and in vitro Systems, Tools for Plant Systems, Biocontainment Mechanisms
3. **Computational Tools and Bioinformatics Resources**: Computational Tools, Information Standards and Databases

As NSF's 10-year financial commitment for Synberc ends in 2016, Synberc started a sustainability initiative in 2013 to develop a strategic action plan with the aim "to extend the efforts begun by Synberc and advance the field of synthetic biology in the U.S." [14,16]. In addition to identify an operational plan toward a self-sustaining future for Synberc, this initiative also seeks to provide a shared infrastructure for the U.S. synthetic biology research community in an environment of uncertain funding sources [14,16]. The final report recommended the evolution of Synberc into a new type of research center ("NewOrg") with a mission to "develop, promote and sustain biologically engineered solutions for a sustainable global future with a focus on energy, agriculture, the environment, and health." In 2016, EBRC was launched as the successor organization to Synberc. Although comprehensive information about EBRC has yet been released publicly, EBRC's vision, missions, goals and plans have been outlined at the Synberc's website (www.synberc.org/ebrc). Moreover, the sustainability initiative report also proposed to perform a U.S. Synthetic Biology Strategic Roadmap to address the following aspects [16]:

1. **Research**. a. Development of a Research Agenda with both short- and long-term goals and a shared vision for achieving outcomes consistent with public values and priorities. b. Renewed, sustained investment in foundational tools and

research. This includes building parts and devices, ever-better methods in the design-build-test cycle, and developing a context-independent framework for integrating biological components. c. Definition of large, multi-institutional research projects with clear connections to commercial applications.
2. **Public Infrastructure and Scaling**. This includes professional-scale registries, repositories, foundries, an advanced research center, novel practices for making IP available to practitioners at fair and reasonable terms (including free use via the public domain), and standards in the context of an open resource facility available to the entire synthetic biology community to work together in a pre-competitive environment.
3. **Policy Development and Regulation** to address potential security, safety, environmental and economic effects of synthetic biology, establish regulatory jurisdiction, reduce regulatory uncertainty, and address ethical, legal and social concerns surrounding the research.
4. **Industry/Academic Collaborations** to align strategic research aims, spur economic development, promote commercialization of academic research, and encourage new start-up ventures.
5. **Education and Leadership Development** – creating tomorrow's practitioners, educators, legislators, and regulators, and a workforce that is diverse in socioeconomic background, discipline, and thought.
6. **Public Engagement** to educate, inform, learn, and engage in a robust debate about how to create science that is toward in the greatest public interest, and carried out in a transparent and democratic manner.
7. **Connecting with the Global Community** to ensure efficient, equitable adoption of synthetic biology technologies and distribution of products throughout the world, and to participate in international discussion about the regulation and distribution of the science.

In January 2015, DOD published a report titled *Technical Assessment: Synthetic Biology*. It was released by DOD's Office of Technical Intelligence (OTI), whose mission is to provide "holistic, defense-relevant insights into emerging and potentially disruptive technology to enable U.S. and mitigate adversary technological surprises." Four major defense applications of synthetic biology—commodity and specialty materials, sensing, medical and human performance modification, and biological and chemical defense—were identified, and practical R&D steps were recommended to advance these applications [21]. In addition, human capital development was highlighted to train DOD personnel with deep knowledge of synthetic biology.

In March 2015, the U.S. National Academies of Sciences, Engineering and Medicine released the report *Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacturing of Chemicals*. Recognizing industrial biotechnology as an important and growing part of the U.S. economy ($350 billion or 2% of U.S. GDP in 2012), this report aims to develop a technical roadmap of scientific and engineering advances to fully realize the vision of a future that "biological synthesis and engineering and chemical synthesis and engineering are on par with one another for chemical manufacturing" [22]. Six technical areas are outlined, and synthetic biology is identified at the center of technological development for all areas including:

1. **Feedstocks and Pre-Processing:** enhancing the availability and reliability of economic and environmentally sustainable feedstocks of diverse sources
2. **Fermentation and Processing**: Improving mass and heat transfer, continuous product removal; more extensive use of co-cultures, co-products, and co-substrates; Developing predictive computational tools based on small-scale experimental models that realistically predict performance at scale
3. **Design Toolchain**: An integrated, predictive, forward design framework across all scales of the biomanufacturing process.
4. **Organism: Pathways**: fast development of enzymes with desirable catalytic activity and specific activity
5. **Organism: Chassis:** Enabling technologies to enhance genetic manipulation; Expanding the collection of domesticated microbial and cell-free platforms; Cultivating robust strains with stable performances
6. **Test and Measurement:** Rapidly, routinely, and reproducibly measuring pathway function and cellular physiology with decreased cost and increased throughput.

In addition to the research aspects, the importance of social, ethical and legal implications of synthetic biology has been recognized but not systematically addressed in most of the above roadmap studies. For related issues, in 2010, the U.S. president Barack Obama appointed Presidential Commission to study bioethical issues to "review the developing field of synthetic biology and identify appropriate ethical boundaries to maximize public benefits and minimize risks." The Commission published a report, *New Directions: The Ethics of Synthetic Biology & Emerging Technologies*, which identified five criteria for assessing the social implications of synthetic biology: public beneficence, responsible stewardship, intellectual freedom and responsibility, democratic deliberation, and justice and fairness [23]. For the legal and regulatory aspects of synthetic biology, the J. Craig Venter Institute released a report in 2014, *Synthetic Biology and the U.S. Biotechnology Regulatory Systems: Challenges and Options*, to address "how well the current U.S. regulatory system for genetically engineered products is equipped to handle the near-term introduction of organisms engineered using synthetic biology." Key challenges and policy options were analyzed, focusing on the engineered organisms that are used or grown directly in the environment, outside a contained facility [24].

Common to all these U.S. roadmap reports, the strategic significance of synthetic biology and increasing competitions from other countries are well recognized. Although specific technical recommendations are provided given the different scopes of these studies, taking systematic approaches across different disciplines and public/private sections is a recurring theme to fully realize the potential of synthetic biology. Due to lack of an overarching funding or governance plan from the U.S. government [12], it remains unclear to what extent these roadmap studies has impacted the funding landscape of synthetic biology. Within individual agencies (DOD and DOE, in particular), however, a general match is observed between the funding agenda and technical recommendations in the roadmaps published by the corresponding agencies.

5. Conclusion

The U.S. has been pioneering synthetic biology research for more than 15 years since the inception of this field. As a nation that has so far invested the largest public research funding in synthetic biology, the U.S. continues to increase the investment rapidly, especially in the form of large-scale integrated programs (Table 1), in the hope to maintain its leadership and foster transformative breakthroughs. Although a national initiative is not expected in the near future [14], U.S. roadmap studies in synthetic biology have been performed to recommend R&D strategies to tackle key challenges and enable innovative applications. It is anticipated that with the sustainable strategic investment from the U.S. government agencies, synthetic biology will continue to thrive in both basic and applied research in the U.S.

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