U.S. DEPARTMENT OF ENERGY

Synthetic Biology

Report to Congress

July 2013

United States Department of Energy

Washington, DC 20585

Message from the Director, Office of Science

This report was prepared and is being submitted in response to the request in Senate Report 112-75, p. 91-92, and incorporated by reference in the Joint Explanatory Statement of Managers that accompanied Public Law 112-74, Consolidated Appropriations Act, 2012, which provided as follows:

> *The Committee directs the Secretary of Energy, not later than 9 months after enactment of this act, in consultation with other relevant Federal agencies, the academic community, research based nonprofit entities, and the private sector, to submit 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. The plan shall assess the need to create a database for synthetic biology information, the need and process for developing standards for biological parts, components, and systems, and funding requirements for implementing the plan.*

The Secretary assigned responsibility for preparation and submission of this report to the Director of the Office of Science.

The Department is submitting this report to the following Members of the Appropriations Committees and Subcommittees of the Senate and House of Representatives.

- **The Honorable Barbara Mikulski**
  Chairwoman, Senate Committee on Appropriations

- **The Honorable Richard C. Shelby**
  Ranking Member, Senate Committee on Appropriations

- **The Honorable Harold Rogers**
  Chairman, House Committee on Appropriations

- **The Honorable Nita M. Lowey**
  Ranking Member, House Committee on Appropriations

- **The Honorable Dianne Feinstein**
  Chairman, Senate Subcommittee on Energy and Water Development

- **The Honorable Lamar Alexander**
  Ranking Member, Senate Subcommittee on Energy and Water Development

- **The Honorable Rodney P. Frelinghuysen**
  Chairman, House Subcommittee on Energy and Water Development

- **The Honorable Marcy Kaptur**
  Ranking Member, House Subcommittee on Energy and Water Development

If you have any questions or need additional information, please contact me or Mr. Brad Crowell, Acting Assistant Secretary for Congressional and Intergovernmental Affairs, at (202) 586-5450.

Sincerely,

Patricia M. Dehmer
Acting Director

Executive Summary

In the past decade, synthetic biology has emerged as a distinct discipline positioned at the interface of biological science, engineering, and computational bioinformatics. The recent White House National Bioeconomy Blueprint provides a definition for synthetic biology: "Synthetic biology, the design and wholesale construction of new biological parts and systems, and the re-design of existing, natural biological systems for tailored purposes, integrates engineering and computer-assisted design approaches with biological research." Synthetic biology is moving beyond the laboratory and informing the development of new bioengineering approaches in the commercial biotechnology industry. Energy production, biomedicine, agriculture, and a variety of other national priority areas stand to benefit from the continued development of synthetic biology research. However, synthetic biology remains in the early phases of development relative to more mature science disciplines and requires additional basic and applied research and development (R&D) to realize its full potential.

This report provides a brief overview of the current state of synthetic biology, lists R&D needs in both public and private sector research, and identifies research programs at Federal agencies that have current or planned activities relating to synthetic biology. The report also discusses the need for communication and coordination between Federal agencies that support basic and applied synthetic biology research to build synergies, consider new R&D needs, and evaluate issues as they emerge. In particular, close coordination will be needed to properly consider issues such as development of standards in the field, exchange of information via databases and other computational resources, and broader ethical, legal, social, environmental, and safety concerns. In addition to interagency coordination, opportunities also exist to improve communication between Federal research programs, the scientists they support at academic institutions and government laboratories, and private sector companies that are moving synthetic biology research toward commercial development. To realize the full potential of synthetic biology as an engineering and scientific discipline and as a new tool set driving innovation in commercial biotechnology, it will be critical to maintain an atmosphere of open information exchange among relevant agencies and stakeholders in the public and private sectors.

Synthetic Biology

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I. Congressional Language

This report responds to Congressional request in Senate Report 112-75, and incorporated by reference in the Joint Explanatory Statement of Managers report that accompanied Public Law 112-74, Consolidated Appropriations Act, 2012, wherein it is stated:

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II. Introduction

In the past decade, the accelerating pace of discovery in experimental systems biology, high-throughput genome sequencing, and computational bioinformatics have vastly expanded our understanding of the fundamental properties of living organisms and the common principles that govern their functional capabilities. Parallel advances in biotechnology have resulted in more sophisticated metabolic engineering approaches, construction of increasingly large synthetic DNA fragments (in some cases full chromosomes), and capabilities for targeted editing of genome sequences in living cells. The synergistic integration of these fields has resulted in the emergence of a new discipline known as synthetic biology.

The recently released National Bioeconomy Blueprint[1] provides a definition for synthetic biology: "Synthetic biology, the design and wholesale construction of new biological parts and systems, and the re-design of existing, natural biological systems for tailored purposes, integrates engineering and computer-assisted design approaches with biological research." The field has demonstrated several early advancements, developing a variety of tools that now permit the rapid modification of biological systems at the scale of whole genomes, allowing the directed redesign of organisms for specific end uses. Synthetic biology approaches have already been applied to construct new bio-synthetic pathways and increase efficiency of biological product synthesis for pharmaceuticals, biofuels, and commodity chemicals. Synthetic biology also provides a powerful set of tools for fundamental research, allowing sophisticated manipulation of organisms to shed light on the principles governing the organization and evolution of biological systems.

[1] National Bioeconomy Blueprint:
http://www.whitehouse.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf

Federal investments in synthetic biology research and development have expanded since the initial investments made over a decade ago, with several funding agencies providing support for relevant basic and applied research consistent with their respective mission goals. In order to guide future investments in synthetic biology research and development, its transition into a mature discipline, and its translation to a more robust and competitive industrial biotech base in the US; it is prudent to survey current Federal synthetic biology activities and to identify how coordinated Federal funding efforts can best address the major scientific and technical challenges that the field faces. To address these needs, the White House National Science and Technology Council's (NSTC) Committee on Science, Life Sciences Subcommittee established an interagency Synthetic Biology Working Group with representatives from the following executive branch agencies with current or planned synthetic biology research programs or enabling activities:

- Department of Agriculture (USDA)
  - Office of the Chief Scientist (OCS)
  - National Institute of Food and Agriculture (NIFA)
  - Animal and Plant Health Inspection Service (APHIS)
- Department of Commerce (DOC)
  - National Institute of Standards and Technology (NIST)
- Department of Defense (DOD)
  - Defense Advanced Research Project Agency (DARPA)
  - Office of Naval Research (ONR)
- Department of Energy (DOE)
  - Office of Science (SC)
  - Office of Energy Efficiency & Renewable Energy (EERE)
- Department of Health and Human Services (HHS)
  - National Institutes of Health (NIH)
- National Aeronautics and Space Administration (NASA)
  - NASA Ames Research
- National Science Foundation (NSF)
  - Directorate for Engineering
  - Directorate for Biological Sciences

The Synthetic Biology Working Group was co-chaired by representatives from DOD and DOE. Representatives from the Office of Management and Budget (OMB), the Office of Science & Technology Policy (OSTP), and the State Department were also included in the working group as advisory members. The group was specifically tasked to:

1. Provide a definition of synthetic biology with respect to each Federal agency;

2. Describe existing Federally supported research and development in synthetic biology;

3. Identify major research and information resources (including published Federal program workshop reports) on synthetic biology;

4. Develop a plan for the Federal government to address research and development gaps and needs, specifically including the following resources:
   a) Databases;
   b) Standards for tools and component parts; and
   c) Points of potential interagency coordination and industry engagement; and

5. Articulate each Federal agency's role in synthetic biology research and development.

The working group was not tasked to develop a specific funding profile for the plan; agency funding decisions will be made through the annual Budget process according to each agency's budget priorities and Congressional appropriations.

This report presents a survey of current Federal research programs at the various funding agencies and corresponding resources and examines synthetic biology R&D challenges. Members of the working group also sought the perspective of various private, for-profit companies engaged in the commercial development of synthetic biology applications. The report also discusses means for more effective communication and coordination between Federal agencies on synthetic biology R&D to build synergies, leverage investments, share best practices, and minimize the potential for duplication or overlap.

III. Federal R&D Activities in Synthetic Biology

In discussing a broad definition for "synthetic biology", members of the working group agreed to the definition in the National Bioeconomy Blueprint:

> "Synthetic biology, the design and wholesale construction of new biological parts and systems, and the re-design of existing, natural biological systems for tailored purposes, integrates engineering and computer-assisted design approaches with biological research."

This definition is reasonable and is of sufficient breadth to capture the broad set of synthetic biology activities currently being undertaken by the represented agencies both to address fundamental scientific questions and for the directed engineering of novel biosystems. Other more specific definitions of synthetic biology may be appropriate for the purposes of particular agencies or research programs in support of their mission goals, but all are broadly consistent with the definition provided above. Brief descriptions of current synthetic biology focused programs and activities supported by the Federal agencies—namely DOE, NSF, DOD, NIH, and USDA—are listed below. NIST and NASA also have planned or potential programs related to synthetic biology in development.

Although significant progress has been made in the past decade to lay the groundwork for synthetic biology, the field remains in the very early phases of development and requires

substantial basic and applied R&D to realize its full potential as an engineering and scientific discipline and as a viable tool set for commercial biotechnology. To facilitate continued development of the field, Federal agencies with programs supporting biological research and biotechnology will address critical knowledge gaps in order to foster the safe and sustainable development of synthetic biology. During discussion of current and planned Federal R&D activities relevant to the development of synthetic biology, members of the working group identified a shared set of foundational knowledge gaps and technology development challenges that hinder progress in synthetic biology. As appropriate, these challenges have helped inform the R&D planning in this area at each agency. Fundamental challenges for the continued development of synthetic biology fall into three broad categories:

1. Methods and Technologies for Synthetic Biology Engineering:

    - Genome Scale Engineering Tools: Genetic tools allowing the manipulation of nucleic acid sequences at the scale of intact genomes are still in the early phases of development and remain limited in their utility. Areas identified for technological improvement include: the throughput and reliability of tools for targeted editing of the genetic code, recoding of genes for the incorporation of synthetic amino acids in coded proteins, and incorporation of large synthetic DNA constructs.

    - DNA Synthesis and Assembly: One of the major limitations to experimentation in synthetic biology is the synthesis and assembly of large DNA constructs, which remains expensive, slow, and error prone. Engineering new bio-production systems would require new approaches for synthesizing and assembling genetic designs rapidly, cheaply, and accurately.

    - Analytical Tools: Techniques allowing measurement, analysis, and interpretation of the metabolic and regulatory networks that mediate biological functions remain costly and relatively low throughput. Synthetic biology rapidly generates huge numbers of functional variants, so better tools for the characterization of integrated biological pathways would facilitate the discovery of novel functional components, improve the "wiring diagrams" of manipulated organisms, and allow more effective tuning of metabolic pathways to improve efficiency.

2. Development of Biological Platforms for Synthetic Biology:

    - Development of Biological Design Principles: Advances in systems biology research suggest that unifying design principles based on simple, fundamental natural laws are responsible for the complexity in biological systems. Gaining a better understanding of the foundational "design principles" that govern living systems will substantially improve directed synthetic biology by defining the "solution space" available to designers and suggesting new approaches for engineering.

- Genetically Tractable Organisms/Chassis: The development of appropriate genetic tools and systems biology knowledge is a prerequisite to advance organisms to the status of synthetic biology "platforms" or "chassis". Current efforts focus predominantly on well-studied model organisms such as non-pathogenic strains of the bacterium *Escherichia coli* and the yeast *Saccharomyces cerevisiae*; extending synthetic biology tools to a more diverse set of organisms would provide a broader array of functional capabilities and growth characteristics (e.g., photosynthesis, biomass degradation, tolerance to extremes of temperature or pH, ability to synthesize more complex products) that might prove difficult or impossible to engineer into the existing platform organisms.

- Minimal Cell and *in vitro* Systems: In addition to targeted modifications to existing organisms, synthetic biology provides the potential for development of "minimal cell" systems (i.e., highly streamlined platform organisms composed of fully defined components) or entirely cell-free systems would allow a greater degree of design flexibility and provide systems that could be more fully represented in computational modeling frameworks. However, developing these systems still presents considerable technical challenges and in most cases requires significant advances in the understanding of the dynamic interactions of biological components that form integrated biosystems mediating functional processes.

- Tools for Plant Systems: Current synthetic biology efforts have primarily focused on microbes due to their relative simplicity. Current plant model organisms, such as the ubiquitous *Arabidopsis thaliana*, present much greater structural complexity, substantially larger genome size, and other difficulties that complicate genetic engineering. Developing tools for use with plant systems opens up new possibilities for a variety of potential synthetic biology applications that could be more effectively conducted in plants and takes advantage of unique properties (e.g., formation of distinct tissue types, dense photosynthetic arrays, more efficient capture of CO_2) not available in microbial systems.

- Biocontainment Mechanisms: As the field moves forward, it will be critical to incorporate into the design and use of synthetic biology constructs features such as "genetic firewalls" and other mechanisms that mitigate risks associated with misuse or unintended consequences of synthetic biology. Developing strategies for the biocontainment of engineered organisms will need to include reliable assessment of risks associated with synthetic constructs and incorporation of redundant safeguards at successive levels of design, build, test, extend, and manufacture. Of particular interest are adaptive control mechanisms to limit the exchange of genetic information with other organisms, evolution of unpredicted attributes, and persistence in natural environments.

3. Computational Tools and Bioinformatics Resources for Synthetic Biology

- Computational Tools: Synthetic biology requires sophisticated computational tools to provide predictive modeling capabilities and forward design of biological systems. Computer aided design software for biological systems (so called "BioCAD" systems) remain rudimentary and will need to be substantially improved and expanded to accommodate a wider suite of biological parts and platform organisms, allow *in silico* design of synthetic parts and systems, and provide viable pathways towards construction and experimental validation of large numbers of genetic design variants.

- Information Standards and Databases: Increased consideration of appropriate mechanisms for the development of shared minimum information standards and bioinformatic databases for synthetic biology research will be important as the field moves forward. Information standards and databases facilitate the sharing of data that is of known quality, fully transferrable, and properly curated (this topic is addressed in more detail on page 14).

The common need to address these challenges informs the specific programs of synthetic biology R&D being pursued by relevant Federal agencies, which are presented in more detail below. Given that elements of these R&D drivers will need to be addressed by multiple agencies/programs in order to fulfill their specific missions, it will be critical to maintain good communication and coordination between agencies to build synergies, leverage investments, and minimize the potential for duplication or overlap. In addition to these areas of shared emphasis, there are also agency-specific efforts in areas such as materials and bioenergy production, agricultural biotechnology, and human health. Mechanisms to facilitate interagency coordination on synthetic biology R&D are discussed in the Summary and Conclusions section.

Department of Energy (DOE)

DOE supports the development and application of synthetic biology tools to redesign plant, microbial, and hybrid systems for the production of biofuels and high energy impact biobased products. To achieve this goal, DOE Office of Science (DOE-SC) programs support fundamental research to advance understanding of principles that govern bioenergy relevant organisms at the genome scale and enable the development of molecular genomics approaches and computational tools for the design, construction, and validation of improved biological components and systems. DOE's Office of Energy Efficiency and Renewable Energy (DOE-EERE) emphasizes more applied research approaches and supports the development of innovative synthetic biological approaches to the cost-effective fractionation of lignocellulosic biomass into components and/or subsequent conversion into advanced biofuels and bioproducts. DOE's Advance Research Projects Agency for Energy (DOE-ARPA-E) supports synthetic biology approaches in their Electrofuels and Plants Engineered to Replace Oil (PETRO) programs. Further information about DOE synthetic biology activities can be found at:

DOE research programs with synthetic biology related activities:
DOE-SC Genomic Science Program:
http://genomicscience.energy.gov
DOE-EERE Biomass Program:
http://www1.eere.energy.gov/biomass/
DOE-ARPA-E Electrofuels Program:
http://arpa-e.energy.gov/ProgramsProjects/Electrofuels.aspx
DOE-ARPA-E PETRO Program:
http://arpa-e.energy.gov/ProgramsProjects/PETRO.aspx

DOE reports relating to synthetic biology:
DOE-SC Biosystems Design Report:
http://genomicscience.energy.gov/biosystemsdesign/

DOE Funding Opportunity Announcements relating to synthetic biology:
DOE-SC FY2012 Funding Opportunity Announcement "Biosystems Design to Enable Next Generation Biofuels":
http://science.doe.gov/grants/pdf/SC_FOA_0000640.pdf
DOE-EERE FY2012 Funding Opportunity Announcement "Innovative Biosynthetic Pathways to Advanced Biofuels":
https://eere-exchange.energy.gov/#FoaIde0c4ae28-f0fd-4478-977d-2c1130511fe3

National Science Foundation (NSF)

The mission of NSF is to advance discovery, education, and innovation. NSF investments in the emerging field of Synthetic Biology have been predominantly initiated and driven through unsolicited proposals by the research-community. NSF investments in synthetic biology are supported by the Directorate for Engineering, the Directorate for Biological Sciences, the Directorate for Mathematical & Physical Sciences; and the Directorate for Computer & Information Science. These investments are for advancing the knowledgebase of fundamental basic research; developing novel engineered systems; educating a new cadre of students capable of advancing the synthetic biology research agenda and the supporting emerging Synthetic Biology industries. NSF has active projects in its core programs; targeted competitions such as "Ideas Labs"; multidisciplinary group awards supported by the Office of Emerging Frontiers in Research and Innovation (EFRI); in the Engineering Research Centers program; and in Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs.

The largest signature investment by NSF in this area is a multi-institutional center- the Synthetic Biology Engineering Research Center (SynBERC) that was established in 2006 for a potential duration of 10 years, and headquartered at the University of California, Berkeley with University of California, San Francisco (UCSF), Stanford, Massachusetts Institute of Technology

(MIT), and Harvard as core partners. NSF has also made investments relevant to preliminary development of databases, primarily through support by the NSF Engineering and Education Centers program for parts registries such as the Registry of Standard Biological Parts (partsregistry.org) and BioBricks (biobrick.org) as well as parts foundries (BIOFAB www.biofab.org). The NSF Office of Cyber Infrastructure (OCI) has just funded the development of a web of registries through SynBERC that will enable users to search a number of public and private registries through a common portal. In addition, there is support at NSF and DARPA for use of a common programming standard in synthetic biology (SBOL) and support for workshops to continue to discuss/develop standards. Further information on relevant NSF activities can be found at:

<u>NSF research programs with synthetic biology related activities:</u>
Synthetic Biology Engineering Research Center (SynBERC) Program:
http://synberc.org/
Biotechnology, Biochemical, and Biomass Engineering Program:
http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=501024&org=CBET
Molecular & Cellular Biology Program:
http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=503611&org=MCB&from=home
Systems and Synthetic Biology Cluster:
http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=503626&org=MCB&sel_org=MCB&from=fund

<u>NSF workshops and reports relating to synthetic biology:</u>
Synthetic Biology SB4.0 - to SB6.0:
http://sb5.biobricks.org/
Sc2.0 Project International Research Coordination Meeting, Beijing China April 2012:
http://syntheticyeast.org/
NSF-DFG US/German Joint Synthetic Biology Workshop *Exploring the Frontiers in Synthetic Biology*:
http://dfg-nsf12.sys-bio.org/index.php
NASA-NSF Joint Workshop on Synthetic Biology , April 3-4, 2008:
*openwetware.org/images/8/8e/SynBiol_**Workshop**_report.pdf*

Exploring Frontiers in Plant Systems Biology (EFRI), Nov. 2-3 NC State:
http://research.ece.ncsu.edu/plantsysbioeng/
International Conference: Frontiers in Systems and Synthetic Biology in Atlanta, GA, March 20-24, 2013:
http://www.ibsi.gatech.edu/FSSB13/sponsors

<u>NSF funding opportunities relating to synthetic biology:</u> Emerging Frontiers in Research and Innovation (EFRI):
http://www.nsf.gov/eng/efri/fy11awards_MIKS.jsp
Joint NSF/EPSRC “Sandpit” on Synthetic Biology:

http://www.nsf.gov/pubs/2009/nsf09012/nsf09012.jsp?org=NSF

Surpassing Evolution: Transformative Approaches to Enhance the Efficiency of Photosynthesis:
http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=503517&WT.mc_id=USNSF_39

Nitrogen: Improving on Nature:
http://www.bbsrc.ac.uk/funding/opportunities/2012/ideaslab-nitrogen-improving-on-nature.aspx
http://www.bbsrc.ac.uk/news/food-security/2012/120709-pr-uk-us-collaboration-to-rethink-fertilisers.aspx

INSPIRE - SAVI (Science Across Virtual Institutes): Yeast Chromosome (Sc2.0) Synthesis and Analysis (international partnerships between the US, China, Europe, and India):
http://syntheticyeast.org/

INSPRIE - CREATIV - Creative Research Awards for Transformative Interdisciplinary Ventures:
http://www.nsf.gov/pubs/2013/nsf13518/nsf13518.htm?org=NSF

Department of Defense (DoD)

Synthetic Biology is one of six high priority basic research topics for DoD given its potential for transformative impact across a variety of applications from materials to sensors to medicine. DoD's interest in synthetic biology predates the common use of the term Synthetic Biology, with Defense Advanced Research Projects Agency (DARPA) and Office of Naval Research (ONR) programs starting in the late 1990's. Current DoD synthetic biology research efforts are centered on applications such as smart sensing systems, production of high-value materials (particularly products that have difficult or unknown synthetic routes), and DoD specific biomedical applications (e.g. diagnostics and therapeutics). Deliverables will include biologically-based systems with the capability to produce, deliver, detect and respond to compounds or signals. In addition to these areas, DoD is supporting several projects that will provide new, fundamental tools and approaches for the field. Further information on relevant DoD activities can be found at:

DoD research programs with synthetic biology related activities:

ONR Synthetic Biology Program:
http://www.onr.navy.mil/en/Science-Technology/Departments/Code-34/All-Programs/warfighter-protection-applications-342/Synthetic%20Biology.aspx

DoD Funding Opportunity Announcements relating to synthetic biology:

ONR Special Notice on Synthetic Biology Tools for Sensing and Bioprocessing:
http://www.onr.navy.mil/~/media/Files/Funding-Announcements/Special-Notice/2012/12-SN-0027.ashx

Army Research Office/DOD FY13 Multi-disciplinary University Research Initiative, Topic #1, "Artificial Cells for Novel Synthetic Biology Chassis":

http://www.onr.navy.mil/~/media/Files/Funding-Announcements/BAA/2012/12-020.ashx

National Institute of Standards and Technology (NIST)

NIST has been called upon by industry, academia, and other agencies to apply its broad and deep portfolio in biological measurements and standards as critical support for manufacturing applications in engineered synthetic biology. Synthetic biology will be a successful manufacturing technology and a commercial force when it can be engineered in a scalable way. NIST's goal is to play a high impact role in the development of the measurement science and standards applicable to biological systems with complex feedback loops that allow for tremendous biological diversity, evolution, and self-repair. The development of minimum information standards for synthetic biology experiments would facilitate the sharing of data that is high quality, transferrable, and well annotated. NIST can contribute to the development of data, material, and documentary standards to support this emerging discipline.

NIST research programs with synthetic biology related activities:
NIST Biochemical Science Division:
http://www.nist.gov/mml/biochemical/

National Institute of Health (NIH)

NIH support of synthetic biology, like most NIH support for extramural research, is predominately based upon extramural interest through investigator-initiated grants and initiatives. Through such research grants, the NIH has supported the seminal work of several notable pioneers of basic synthetic biology research where the areas of basic biomedical science and synthetic biology overlap. The knowledge gained from synthetic biology research will likely be relevant to the missions of most, if not all, NIH institutes. The NIH does not currently have any targeted funding opportunities towards synthetic biology-centric initiatives, but as illustrated by the selected examples below, various NIH institutes have interests in synthetic biology and areas bridging synthetic biology.

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) provides funding for biomedical imaging and bioengineering research and encourages the integration of engineering with the physical, computational, and life sciences to advance human health. Current institute programs that could be impacted by synthetic biology include biomaterials, drug and gene delivery systems and devices, mathematical modeling, simulation and analysis, medical implants, nanotechnology, sensors, and tissue engineering. NIBIB recognizes the importance of databases or standards efforts related specifically to synthetic biology and will consider expanding its informatics and standards programs to include synthetic biology.

The National Cancer Institute (NCI) supports a broad based portfolio on cancer research encompassing basic, pre-clinical, clinical, and epidemiological research. This includes support for the development of enabling technologies and methods including, where appropriate, synthetic biology approaches to cancer research. NCI emphasizes investigator initiated research but also supports some focused consortia.

None of these current or planned initiatives have a substantial focus on synthetic biology.

The National Institute of General Medical Sciences (NIGMS) primarily supports research that lays the foundation for advances in disease diagnosis, treatment and prevention. Toward these endeavors, synthetic biology has emerged as a new tool with the potential to impact these areas. As such, NIGMS has an interest in much of the basic underlying knowledge that empowers synthetic biology, e.g. developing platforms for testing cellular and metabolic processes and advanced biosynthesis strategies for natural product drug discovery, development and production. NIGMS is currently developing a funding opportunity announcement for high-throughput natural products discovery from genomes.

National Aeronautics and Space Administration (NASA)

NASA has three potential interests in synthetic biology: human missions, astrobiology, and aeronautics. For human missions, a great deal of expense is associated with moving materials into or beyond orbit, and opportunities for resupply are rare. Synthetic biology has the potential to dramatically decrease costs and provide flexibility in manufacturing en route and at the destination. Astrobiology has contributed to - and is increasingly exploiting - synthetic biology through its long history of pioneering work in extremophiles and the origins of life, thus enabling basic scientific discoveries as well as providing tools of use to the broader synthetic biology enterprise. Multiple connections can be made to next generation aeronautics, but most immediately, biofuels and fuel additives provide the strongest link. Likewise, NASA has the potential to contribute to the development of the field because of the need for miniaturization, flexibility and automation, attributes that will allow an expansion of the use of these tools on earth into remote locations for scientific, medical, and military uses.

The value of synthetic biology to human exploration is particularly significant. Humans carry a microbial biome that is a potential target for improving astronaut health through customized probiotics. Astronauts need a substantial life support infrastructure in space. On earth, life recycles air, water and waste; synthetic biology can be used to fine-tune biology to serve the same functions in space. Novel functions for synthetic biology include the generation of electricity from stored chemical energy and as biosensors to monitor life support, literally microbial “canaries”. The flexible production of medicines and vitamins through miniature, “on demand” biomanufacturing allows access to a vast array of drugs including variants that may not have been available at launch. Periodic production of vitamins can compensate for the rapid degradation that occurs during long duration missions. Cleaning and repair of

clothing could be aided through the production of biomaterials as the production of silk by synthetically altered bacteria has already been achieved. Radiation protection through material production or acquisition of novel avoidance or repair mechanisms could be significant.

At planetary destinations a substantial decrease in upmass, and thus cost can be achieved by the use of *in situ* resource utilization (ISRU). The bulk of habitat mass could be produced by agglutinating regolith with bioglues creating "RegoBricks". Synthetically altered photosynthetic microbes can produce organic materials including food, medicines and fuel using primarily inorganic carbon and water found at the destination. The extraction of metals can be achieved through biomining, as can the recycling of spent materials brought from earth.

NASA is interested in the production of novel nanomaterials through synthetic biology. Organisms have the potential to produce novel polymers and metallo-organic compounds that can be built into novel nanostructures. With printing technologies these cells and their products can be built into novel biocomposites using manufacturing technologies such as 3D printing.

Further information on NASA Synthetic Biology Activities can be found at:
NASA Ames Synthetic Biology Initiative
http://syntheticbiology.arc.nasa.gov/

U.S. Department of Agriculture (USDA)

USDA's mission is to provide leadership on food, agriculture, natural resources, and related issues based on sound public policy, the best available science, and efficient management. USDA's strategic plan includes: expanding markets for agricultural products and supporting international economic development, enhancing food safety by taking steps to reduce the prevalence of foodborne hazards from farm to table, improving nutrition and health by providing food assistance and nutrition education and promotion, and managing and protecting America's public and private lands working cooperatively with other levels of government and the private sector. Synthetic biology has the potential to impact all of these areas, and USDA is interested in supporting synthetic applications that might fulfill any of these missions.

USDA is already actively involved in synthetic biology research. USDA's National Institute of Food and Agriculture (NIFA) has awarded more than 27 grants for research involving Synthetic Biology, including at least one project investigating ethical, social and legal implications.

Further information on NASA Synthetic Biology Activities can be found at:
Current Research Information System (CRIS) database (search engine)
http://cris.nifa.usda.gov/

IV. Synthetic Biology: Industry Perspective

A major overarching challenge to the development of synthetic biology for biotechnology applications is the long timeline required for the engineering of biological systems. Addressing the foundational R&D challenges discussed in the previous section and providing a more robust synthetic biology tool set would accelerate the development of useful synthetic biology applications by reducing costs and decreasing timelines associated with genetic design, improving chances of success and allowing high-throughput testing of many design variants.

To discuss synthetic biology R&D being performed under the auspices of Federal agencies and its relevance to commercial development of synthetic biology, members of the synthetic biology working group engaged numerous representatives of private sector companies investing in synthetic biology applications[1]. Those technical challenges to the development of synthetic biology identified by industry leaders align closely with the foundational R&D challenges described in section III. For example, industry respondents found that the relatively high cost and low-throughput of chemically synthesizing large DNA fragments presents a considerable barrier to commercial synthetic biology development and that the development of tools allowing researchers to select parts (genes, promoters, regulatory sequences, intact metabolic pathways, etc.) from databases and reliably synthesize them at reasonable cost would permit more rapid construction and testing of engineered genetic systems. They further found that improved genetic tools for more effective manipulation of genomes and higher throughput analytical technologies allowing rapid measurement of relevant biological variables (e.g., gene/protein expression, metabolic flux, product synthesis) would also accelerate the design cycle considerably.

Industry leaders were in general agreement that current and planned federal investments in foundational synthetic biology R&D are appropriate and will play an important role in enabling the development of commercial synthetic biology applications. Several specific areas were identified in which ongoing Federally-supported synthetic biology R&D efforts contribute important foundational knowledge and basic technology development necessary to facilitate commercial development of platform organisms, process pathways, and related biotechnologies. These include:

- Scale-up of Synthetic Biology Designs: For industrially relevant synthetic biology applications, it will be important to effectively predict the key factors impacting scale-up of processes, to understand the concepts and conditions that lead to better predictions, and to bridge the gap from bench scale proof of principle to pilot scale development and higher. Current Federal efforts at DOE, DOD, NSF, USDA and other agencies address

[1] Industry perspectives were solicited from a broad range of performers (ranging from start-up biotech and biofuel companies to mature pharmaceutical companies) funded by agencies represented on the working group.

foundational R&D challenges, such as the improvement of genome engineering tools and computationally aided design, will provide tools for the private sector to identify these factors at an early phase of development and facilitate more effective scale up.

- Platform Organisms: Federally funded synthetic biology research activities to date have typically focused on well characterized model microbes such as *Escherichia coli*. While model organisms are necessary test beds for development of concepts and prototypes, many are not well suited to further development for industrial applications. Growing Federal efforts at DOE, NSF, and other agencies to build foundational knowledge and synthetic biology techniques for a broader set of bacterial groups (e.g. *Bacillus, Lactococcus*, pseudomonads, streptomycetes), yeast species, filamentous fungi, mammalian cell cultures, and plant systems will be beneficial to the development of commercial synthetic biology applications.

- Biosafety Considerations: Development of synthetic biology to address needs in energy generation, food/biomaterial production, or biomedical applications will involve the use of extensively genetically engineered biological systems, and it will be critical to incorporate biocontainment into design strategies and consider the performance of engineered biological systems under real world conditions. Industry investments can build on Federal programs that…

In addition to these R&D considerations, industry representatives also noted the important role that Federally supported research programs continue to play in contributing to the development of scientists with the skill sets to needed perform synthetic biology research. Synthetic biology is a highly interdisciplinary field, occupying the interface of systems biology, chemical engineering, molecular biology, biophysics, and computational bioinformatics. Scientists capable of flexibly moving between these disciplines are critical to the advancement of the field but remain relatively rare.

A topic of particular interest for the commercial synthetic biology community concerns the establishment of standards for synthetic biology technologies and processes. There are currently a variety of standards being used by different segments of the research community working at various points of continuum between basic and applied synthetic biology research. In the long term the development of standards has the potential to benefit the field in terms of increasing the interoperability of tools, technologies, and component parts, and bringing a more consistent and focused approach to deploying synthetic biology. Despite this agreement about the long term benefit of standards, there is also a broad concern that it is very early in the development of synthetic biology to make effective determinations on standards that would prove beneficial rather than restrictive to overall development of the field. Given the current lack of consensus on key platform organisms and limited understanding of how parts perform in different backgrounds, setting standards at this stage is premature. Similarly, although there is broad agreement that further development of databases relevant to synthetic biology would be potentially useful to the field as a whole, there is not yet a strong consensus

among either public or private sector researchers regarding the appropriate format of such databases or what information they should contain.

At this point, it seems most appropriate for Federal agencies to maintain strong engagement with both the public and private sector synthetic biology research communities and continue to assess the developing needs of the field. This will allow better determinations to be made regarding the most effective role for Federal agencies to play in the development of standards and establishing databases that would be most broadly useful to the synthetic biology community as the specific needs become clearer. Given that the definition of synthetic biology provided in this report incorporates the term "tailored purposes," consideration of future development of standards, databases, and associated tools should involve input from all involved stakeholders to facilitate the advancement of synthetic biology as a scientific discipline with integrally embedded linkages to development of tailored applications.

Federal agencies can play an important role in facilitating the establishment and maintenance of an open and interactive synthetic biology community by leveraging their ongoing technology transfer activities to foster translation of innovation in academic research labs to startup companies and industry (mid- to large-size companies). Startup companies can serve smaller markets, rapidly explore and adapt new technologies, and often tolerate higher risk. Large companies offer experience identifying viable biological candidates, moving them through regulatory review, and developing economic manufacturing processes to bring bioproducts to meet current market opportunities. Facilitating partnerships between these communities would facilitate the development of industrially-relevant organisms and processes. As Federal agencies conduct workshops and other strategic planning activities involving synthetic biology research, including representatives from the private sector will allow industry perspectives to inform discussions. The government may also monitor developing needs for common infrastructure and evaluate where Federal investment may be appropriate. By engaging the private sector in this area, government can balance rapid growth in synthetic biology with accountability for the public good both to leverage early progress the field into new paradigms and products in energy, health, information, and security and to ensure public concerns, including biosafety and biocontainment, are addressed.

V. Summary & Conclusions

The past decade has seen significant progress in the development of synthetic biology as a distinct discipline positioned at the interface of biological science and engineering. Synthetic biology approaches are now beginning to move beyond the laboratory and inform developments in the commercial biotech industry. Energy production, biomedicine, agriculture, and a variety of other national priority areas stand to benefit from the continued development of synthetic biology research. Leading the development of synthetic biology for biotechnological applications may also have implications for US economic competitiveness. However, synthetic biology remains in the very early phases of development relative to more

mature science disciplines and requires substantial basic and applied R&D to realize its full potential.

To maintain development of the field, Federal agencies with programs supporting biological research and biotechnology will continue to invest strategically in the science and technology that advances foundational understanding underlying the field, builds scalable tools and methodologies to facilitate commercial development, and fosters the safe and sustainable development of synthetic biology to address societal needs. A variety of Federal agencies that support basic and applied research in the biological sciences, chemical engineering, and related disciplines have current or planned program activities in synthetic biology. These include DOE, DOD, NSF, NIH, and USDA, and other agencies, such as NASA and NIST, may also support synthetic biology research appropriate to their missions as the field continues to develop. To most effectively address R&D needs, avoid unnecessary overlap, share best practices, and facilitate leveraging of investments, it will be critical to maintain interagency communication and coordination on synthetic biology research activities. Ongoing development of specific agency contributions to a comprehensive Federal synthetic biology effort that address the R&D challenges that were identified in this report will benefit from continued coordination and consultation with the NSTC and OSTP.

Federal working groups organized under the authority of the NSTC Life Sciences Subcommittee (LSSC) can quickly bring together relevant personnel across agencies to gather information on topics of interest and generate formal reports for senior officials. This mechanism was used to form the Synthetic Biology Working Group that generated this report, and this group can be reconstituted in the future as more specific coordination needs are identified. Day to day communication on synthetic biology activities at the various agencies will be maintained via the Synthetic Biology Interest Group, a less formal interagency group involving program staff at NIH, NSF, DOE, DOD, NIST, USDA, and NASA. Topics of interest or potential concern identified by this group can be passed to the Life Sciences Subcommittee to determine if more formal action is required.

Federally supported biological research databases and bioinformatics resources such as the National Center for Biotechnology Information genome databases and existing sets of biological data standards (e.g., MIAME, HUPO) are currently used by the synthetic biology community. At this time, no Federal agency supports databases specifically devoted to synthetic biology data. Although there is general agreement that additional data standards may be needed for synthetic biology data and meta-data, there is a risk in setting strict standards at this relatively early phase of development. Such standards could prove to be overly restrictive and actually impede innovation and progress in the field. The landscape of synthetic biology is still changing rapidly, and at this time it seems most appropriate to continue to monitor these issues and discuss appropriate coordination on development of database resources or standards as the need arises. In addition to the synthetic biology working groups mentioned above, a working group focused on data sharing and standards for biological research is currently being organized under LSSC. It would be appropriate for this group to consider emerging needs of the synthetic biology research community, examine existing data resources and standards that

might be more effectively leveraged to enable development, and identify instances where more specific needs must be considered. Additional emphasis may also be focused on standards for the gene and genome synthesis industry and other providers of synthetic dsDNA products regarding the screening of orders so that they are filled in compliance with current U.S. regulations and to encourage best practices in addressing biosecurity concerns associated with the potential misuse of their products to bypass existing regulatory controls.

Continued progress in synthetic biology has the potential to both accelerate scientific discovery and contribute to economic development in the national bioeconomy. However, as with any new technology, synthetic biology also comes with the potential for misuse or unintended consequences. Legitimate concerns have been raised regarding the potential impacts of the accidental release of genetically modified organisms constructed using synthetic biology approaches and the intentional use of these techniques to engineer organisms with harmful properties. Careful consideration of these issues is critical for scientists engaged in synthetic biology research, companies developing commercial synthetic biology applications, and Federal agencies supporting synthetic biology activities as the field moves forward. Federal agencies have already developed substantial experience in evaluating the biosafety of organisms whose genomes have been modified by recombinant DNA techniques. For example, NIH's *Guidelines for Research Involving Recombinant Molecules*[1] are currently used by many agencies contributing to this report (including DOE and DOD) and has recently been revised to address research involving synthetic nucleic acids. Agencies supporting synthetic biology research should adhere to these guidelines as well as those presented in the National Security Council's *National Strategy for Countering Biological Threats*[2]. A more detailed examination of biosafety and other ethical issues surrounding synthetic biology is beyond the scope of this report, but serious discussion of these issues is occurring at the Federal level and is presented in a recent report from the Presidential Commission for the Study of Bioethical Issues[3].

Federal agencies should play an important role in fostering the development of a synthetic biology community that promotes the open exchange of information and provides opportunities for collaborative efforts between synthetic biology scientists and engineers operating in the public and private sectors. Both sides stand to benefit from increased communication and collaboration, allowing industry to more effectively leverage Federal investments in synthetic biology R&D and providing researchers with better understanding of the knowledge gaps and potential bottlenecks most relevant to the further development of their science. Further fundamental science breakthroughs remain critical for the continued maturation of the field, but sufficient progress has been made to allow for increased

[1] National Institute of Health Guidelines for Research Involving Recombinant Molecules http://oba.od.nih.gov/rdna/nih_guidelines_oba.html

[2] National Strategy for Countering Biological Threats http://www.whitehouse.gov/sites/default/files/National_Strategy_for_Countering_BioThreats.pdf

[3] Presidential Commission for the Study of Bioethical Issues Report: http://www.bioethics.gov/documents/synthetic-biology/PCSBI-Synthetic-Biology-Report-12.16.10.pdf

opportunities in more applied synthetic biology research aimed at enabling commercial development.

VI. Additional Information Resources

The National Bioeconomy Blueprint:
http://www.whitehouse.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf

Presidential Commission for the Study of Bioethical Issues Report:
http://www.bioethics.gov/documents/synthetic-biology/PCSBI-Synthetic-Biology-Report-12.16.10.pdf

Joint European Union-United States Task Force on Biotechnology Research:
http://ec.europa.eu/research/biotechnology/eu-us-task-force/index_en.cfm

The National Select Agent Registry:
http://www.selectagents.gov/SyntheticGenomics.html