MEETING OF THE STATES PARTIES TO THE CONVENTION ON THE PROHIBITION OF THE DEVELOPMENT, PRODUCTION AND STOCKPILING OF BACTERIOLOGICAL (BIOLOGICAL) AND TOXIN WEAPONS AND ON THEIR DESTRUCTION

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Consideration of oversight, education, awareness raising, and adoption and/or development of codes of conduct with the aim of preventing misuse in the context of advances in bio-science and bio-technology research with the potential of use for purposes prohibited by the Convention

SYNTHETIC BIOLOGY: A TRANSFORMING TECHNOLOGY

Submitted by the United States of America

1. Synthetic biology refers to the design and construction of biological components and systems that do not already exist in the natural world, as well as the re-design of existing ones imparting novel biological functions. As an interdisciplinary domain that includes biologists, engineers, chemists, and computer modelers, and as an emerging field extending beyond the traditional genetic engineering, synthetic biology is poised to become the next significant transforming technology for the life sciences and beyond.

2. Synthetic biology possesses several features that distinguish it from traditional genetic engineering or recombinant DNA technology, including the fact that there is no requirement for existing genetic material (i.e., whole or partial genomes can be chemically synthesized) and that the advances in automated nucleic acid synthesis enables the much faster acquisition and subsequent testing of newly designed genetic sequences. The first chemical synthesis of a small gene (207 base pairs) in the 1970s[1] jumpstarted the field of synthetic genomics and enabled subsequent achievements in building complex genomes and the creation of synthetic but fully-functional poliovirus[2] and bacteriophage ϕXI74[3], the latter in a matter of weeks.

[1] Agarwal KL, Büchi H, Caruthers MH, Gupta N, Khorana HG, Kleppe K, Kumar A, Ohtsuka E, Rajbhandary UL, Van de Sande JH, Sgaramella V, Weber H, Yamada T. 1970. **Total synthesis of the gene for an alanine transfer ribonucleic acid from yeast**. Nature 227(5253):27–34.
[2] Cello J, Paul AV, Wimmer E. 2002. **Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template**. Science 297:1016-1018.

3. Synthetic biology, including synthetic genomics, holds the potential to facilitate enormous advances in a variety of disciplines. These include rapid, inexpensive, and efficient production of pharmaceuticals, such as vaccines, diagnostics, and therapeutics. Current examples include the production of the anti-malarial drug artemisinin by rewiring the genetic circuitry of "Saccharmomyces cerevisiae" and the branched DNA assay employing novel, synthetic oligonucleotides to detect the viruses HIV-1 and HCV. Other applications of synthetic biology may include the creation of biosystems to detect toxic chemicals and environmental pollutants or the production of biofuels by engineered microbes.

4. A series of annual Synthetic Biology Conferences began in 2004 with Synthetic Biology 1.0 (SB1.0) hosted by the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts, USA. SB1.0 was billed as the first time that the spectrum of individuals working in the area of synthetic biology were brought together, including those involved in the development of associated supportive technologies and those interested in the ethical and societal issues surrounding synthetic biology. SB1.0 was followed in 2006 by SB2.0 held at the University of California – Berkeley, California, USA and in 2007 by SB3.0 held at the Swiss Federal Institute of Technology (ETH) Zurich, Switzerland. SB4.0 is scheduled to take place at the Hong Kong University of Science and Technology in late 2008.

5. One key concept in synthetic biology is the design and development of standard biological parts, design methods, and tools to allow an engineering-like approach to be used in the creation of complex, living systems. The BioBricks Foundation (http://bbf.openwetware.org), founded by engineers and scientists from MIT, Harvard, and the University of California – San Francisco, has the goal of encouraging the development and responsible use of technologies based on standard DNA parts that encode basic biological functions. Building on this is the international Genetically Engineered Machine (iGEM) competition (http://parts.mit.edu/igem07), held annually since 2003. iGEM is an international competition among student teams, which design and assemble engineered "machines" using genetic components and technologies. Their projects include: genetically engineered "Escherichia coli" bacteria with a wintergreen and/or banana scent, biosensors, biological photographic film, and a rudimentary DNA "computer" based on the "Salmonella typhimurium" Hin/hix DNA recombinase system reconstituted as a collection of modular genetic elements in *E. coli*

6. While synthetic genomics has potentially wide beneficial applications toward understanding life processes and developing industrial applications to improve the quality of life, it could also be misused. The same technology could enable unauthorized individuals or would-be terrorists to circumvent existing pathogen control mechanisms and to gain access to sequences and organisms of concern through "de novo" synthesis. Concern for this possibility has attracted the attention of a diverse group of stakeholders, including members of the scientific community, the synthetic nucleic acid industry, and the U.S. Government.

7. Concerns over safety and security in the rapidly advancing field of synthetic biology led in 2006 to the formation of the International Consortium for Polynucleotide Synthesis (ICPS).

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[3] Smith HO, Hutchison III CA, Pfannkoch C, Venter J. 2003. **Generating a synthetic genome by whole genome assembly: ϕX174 bacteriophage from synthetic oligonucleotides**. PNAS 100 (26): 15440-15445.

The ICPS (http://pgen.us/ICPS.htm), a group of leading international synthetic biology companies, was formed to promote safety and security and to foster the development of an appropriate regulatory environment for the synthetic biology industry. In 2007, the ICPS along with several leading synthetic biologists from academia and industry as well as members of the U.S. Government published an article outlining a practical plan for the development of an oversight framework for the synthetic nucleic acid industry[4].

8. Also in 2007, a report entitled "Synthetic Genomics - Options for Governance"[5] was released by co-authors from the J. Craig Venter Institute (Rockville, Maryland, USA), MIT, and the Center for Strategic and International Studies (Washington, DC). The report examines safety and security concerns associated with synthetic genomics, assessing the state of the technology, identifying potential risks and benefits, and postulating a set of policy options that could be implemented by policymakers, researchers, and the synthetic nucleic acid industry to reduce the risks of misuse of this powerful technology, while maximizing its beneficial potential.

9. In 2006, the U.S. National Science Advisory Board for Biosecurity (NSABB) (http://www.biosecurityboard.gov), an advisory committee to the U.S. Government, released a set of recommendations (Addressing Biosecurity Concerns Related to the Synthesis of Select Agents[6]) to the U.S. Government regarding the use of synthetic genomics to synthesize Select Agent genetic sequences. Select Agents are especially dangerous pathogens subject to a national biosecurity system of oversight and regulation, which includes facility registrations, security vetting procedures for researchers, and control of transfers and inventories. The charge of the NSABB that led to the development of this report was to examine the potential biosecurity concerns raised by the synthesis of select agents, to assess the adequacy of the current U.S. domestic regulatory and oversight framework to safeguard against the misuse of synthetic technologies, and to recommend potential strategies to address any biosecurity concerns.

10. The U.S. Government approach to addressing the potential risks surrounding synthetic genomics includes the careful examination and consideration the NSABB report, "Addressing Biosecurity Concerns Related to the Synthesis of Select Agents", along with the findings and recommendations in other key reports on the topic. The development of any oversight mechanism must balance the need to minimize the risk of misuse with the need to ensure that science, innovation, and trade are encouraged. The process for identifying options for any oversight mechanism must involve engaging the synthetic nucleic acid industry, the scientific community, and other stakeholders.

11. Currently, the U.S. Government is developing guidance for the domestic scientific community and industry on the Select Agent Regulations with respect to synthetic nucleic acids, engaging industry and academia to identify, evaluate, and support establishment of a screening infrastructure for use by commercial providers and vetting of legitimate users of synthetic nucleic acids, modifying the U.S. National Institutes of Health "NIH Guidelines for Research

[4] Bügl H, Danner JP, Molinari RJ, Mulligan JT, Park H-O, Reichert B, Roth DA, Wagner R, Budowle B, Scripp RM, Smith JAL, Steele SJ, Church G, Endy D. 2007. DNA synthesis and biological security. Nature Biotechnology 25 (6): 627-629.
[5] Available online at: http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf.
[6] Available online at:: http://www.biosecurityboard.gov/pdf/Final%20NSABB%20Report%20on%20Synthetic%20Genomics.pdf.

Involving Recombinant DNA Molecules"to more explicitly address synthetic nucleic acids, developing recommendations for risk assessment and risk management principles and practices for research involving synthetic nucleic acids, and commissioning a U.S. National Academies of Science study to identify the list of scientific advancements necessary before a predictive oversight system can be postulated, developed, evaluated, and potentially implemented.

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