DNA synthesis and biological security

Hans Bügl, John P Danner, Robert J Molinari, John T Mulligan, Han-Oh Park, Bas Reichert, David A Roth, Ralf Wagner, Bruce Budowle, Robert M Scripp, Jenifer A L Smith, Scott J Steele, George Church & Drew Endy

A group of academics, industry executives and security experts propose an oversight framework to address concerns over the security of research involving commercial DNA synthesis.

DNA synthesis allows the direct construction of genetic material starting from information and raw chemicals[1]. Improvements in synthesis technology are accelerating innovation across many areas of research, from the development of renewable energy to the production of fine chemicals, from information processing to environmental monitoring, and from agricultural productivity to breakthroughs in human health and medicine. Like any powerful technology, DNA synthesis has the potential to be purposefully misapplied. Misuse of DNA-synthesis technology could give rise to both known and unforeseeable threats to our biological safety and security. Current government oversight of the DNA-synthesis industry falls short of addressing this unfortunate reality.

Here, we outline a practical plan for developing an effective oversight framework for the DNA-synthesis industry[2]. The resulting framework serves three purposes. First, it promotes biological safety and security. Second, it encourages the further responsible development of synthetic biology technologies and their continued, overwhelmingly constructive application. And third, it is designed to be international in scope. Our plan is informed by past and ongoing discussions of biological security issues associated with DNA-synthesis technology[3–6] and represents the collective views of all founding members of the

Hans Bügl, John P. Danner, Robert J. Molinari, John T. Mulligan, David A. Roth & Ralf Wagner are members of the International Consortium for Polynucleotide Synthesis; Hans Bügl and Ralf Wagner are at GENEART; John P. Danner, George Church & Drew Endy are at Codon Devices; Robert J. Molinari & David A. Roth are at CODA Genomics; John T. Mulligan is at Blue Heron Biotechnology; Han-Oh Park is at Bioneer; Bas Reichert is at BaseClear B.V.; Ralf Wagner is at the University of Regensburg Molecular Virology & Gene Therapy Unit, Institute of Medical Microbiology and Hygiene; Bruce Budowle, Robert M. Scripp, Jenifer A. L. Smith & Scott J. Steele are at the US FBI; George Church is in the Department of Genetics, Harvard Medical School; Drew Endy is in the Department of Biological Engineering, MIT; George Church & Drew Endy are at the multi-institution US National Science Foundation Synthetic Biology Engineering Research Center. e-mail: endy@mit.edu

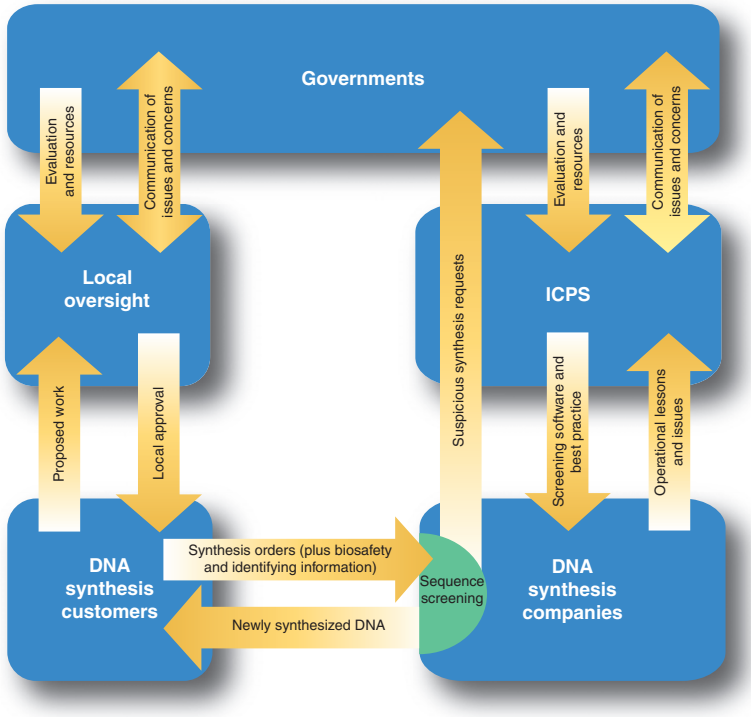

Figure 1 Our framework calls for the immediate and systematic implementation of a tiered DNA synthesis order screening process. To promote and establish accountability, individuals who place orders for DNA synthesis would be required to identify themselves, their home organization and all relevant biosafety information. Next, individual companies would use validated software tools to check synthesis orders against a set of select agents or sequences to help ensure regulatory compliance and flag synthesis orders for further review. Finally, DNA synthesis and synthetic biology companies would work together through the ICPS, and interface with appropriate government agencies (worldwide), to rapidly and continually improve the underlying technologies used to screen orders and identify potentially dangerous sequences, as well as develop a clearly defined process to report behavior that falls outside of agreed-upon guidelines. ICPS, International Consortium for Polynucleotide Synthesis.

International Consortium for Polynucleotide Synthesis (ICPS)[7] as well as the individual opinions of members of the US Federal Bureau of Investigation (FBI), executives of several leading synthetic biology companies and members of academia.

Concern and governance of manipulation of genetic material

Recombinant DNA technologies, including the polymerase chain reaction, allow individuals to construct novel DNA molecules by joining and modifying fragments of preexisting genetic material[8–10]. Although it is not possible to predict the encoded properties of all novel combinations of genetic material, it is possible to imagine dangerous constructs. The researchers who began applying these technologies choose to directly address such possibilities by developing a framework for governance of genetic engineering work[11]. This safety framework has been operationally successful owing in part to the fact that the manipulation of genetic material by these methods is labor intensive, and such work tends to occur in laboratories and organizations that endorse and support an oversight-based safety process.

DNA synthesis, when combined with other advances since the 1970s, such as the development of the Internet and overnight shipping, challenges the existing recombinant-DNA-era safety framework on two fronts. First, synthesis allows the physical decoupling of the design of engineered genetic material from the actual construction and resulting use of the material; DNA can be readily designed in one location, constructed in a second location and delivered to a third. Second, synthesis might provide an effective alternative route to those who would seek to obtain specific pathogens for the purpose of causing harm. Today, such pathogens include the following: first, those for which the natural reservoirs remain unknown or that are otherwise difficult or dangerous to obtain from nature (e.g., Ebola virus); second, those that are physically under lock and key in a very small number of facilities (e.g., smallpox virus); and third, those that no longer exist in nature (e.g., 1918 influenza virus).

The current US approach to biological security depends in part on limiting physical access to such pathogens. Even so, the sequence information that defines the genomes encoding each of these example pathogens is readily available online; DNA synthesis might therefore be used to obtain the genetic material encoding these pathogens. Although additional expertise would be needed to produce infectious agents from the resulting genetic material, such work might not be subject to any review or oversight through our existing biological safety framework (a framework that was not designed to address security issues associated with the intentional misapplication of biological technologies). Thus, practical steps should be taken now to ensure that the existing and future use of DNA-synthesis technology does not debase our current biological safety framework or compromise the development and implementation of an effective strategy for future biological security.

DNA synthesis in practice

Because of operational reliability issues and economies of scale, most DNA synthesis is carried out at commercial organizations or institutional facilities that provide one or more services to the biological and biotech research communities. The core of the DNA-synthesis industry is loosely segregated into two sectors: companies and institutional facilities that provide short fragments of DNA (oligonucleotides <200 nucleotides in length); and firms that provide longer, recombinant fragments of DNA (e.g., genes >200 nucleotides in length).

From a business and supply perspective, oligonucleotide synthesis is a technically facile and relatively mature industry in which providers compete to supply a commodity service to various markets. For example, oligonucleotide costs have fallen over the past decade (at least by a factor of 10 to ~$0.20 per nucleotide) and expected delivery times are currently ~48 hours (from order to delivery). Although small-capacity DNA synthesizers can be found in academic laboratories and are available for purchase via online auction, most researchers choose to obtain oligonucleotides through large-volume providers.

By comparison, gene- and longer-length DNA synthesis is still a technically demanding and relatively immature industry. The industry started in response to high demand for a very small number of gene-length constructs from well-financed industrial customers (e.g., pharmaceutical firms). For example, in 2000, the market price for gene-length DNA synthesis was ~$10 per nucleotide[12]. Early gene-length synthesis companies sought to profit from (and reduce) the cost differential between oligonucleotide- and gene-length DNA synthesis (today's gene-length prices are ~$1.00 per nucleotide)[12]. By late 2005, at least 39 gene synthesis companies were located around the world, including in such locations as Boston, Hong Kong, Moscow, San Francisco, Seattle, Shanghai and Tehran[13].

Needs of industry

Continued improvements in DNA-synthesis technology are critical for reducing the costs and increasing the pace of basic and applied biological research, and enabling the engineering of needed biological technologies. As part of the process of improving DNA-synthesis technology, it is imperative that DNA-synthesis firms develop and implement effective biological safety and security procedures, while retaining the ability to deliver high-quality products at low cost and with very rapid delivery times. The full constructive potential of DNA-synthesis technology will be realized only if a governance framework is developed that is compatible with the needs of industry and customers, and that supports best practice in biological safety and security, including the effective deterrence and investigation of any criminal uses of synthetic DNA.

A governance framework that stymies the open commercial development of synthesis technology will retard research and make the challenge of responsibly developing the technology more difficult. Likewise, a regulatory framework that hampers a single country's or group of countries' commercial market without international consensus will drive consumers to the most facile and cheapest available source, and have a limited impact on enhancing global security. Conversely, a governance framework that works in practice and that can be integrated into commercial synthesis operations at modest cost and with little or no impact on delivery times would directly promote the responsible development of the technology and its constructive application. Because DNA-synthesis technology and its commercialization are undergoing rapid development and improvement, now is the time to begin a process that will result in effective oversight of this area.

Needs of law enforcement

Conventional and novel biological security risks arise when considering synthetic biology and DNA-synthesis technology in particular (see above). Although law enforcement personnel must work closely with public health agencies to prevent, identify and investigate potential biological threats, ultimately, it is the specific responsibility of law enforcement authorities to protect individuals and communities against threats that may arise through the misuse of this promising technology. For example, in the United States, responsibilities have been defined for federal law enforcement agencies such as the FBI in regard to biological agents that could be used to produce biological weapons. These responsibilities include deterrence, prevention, interdiction, criminal investigation and providing forensic evidence for convictions. The FBI is charged with lead agency responsibility for investigating violations that may be terrorist

Table 1 Options for an effective governance framework for DNA synthesis

Impractical options	Future research	Opportunities
Limited access to material, equipment or know-how	Improved software to reduce screening false-positive reports	Develop minimum standards for screening and reporting
Restricted access to select DNA- sequence information	Improved software to handle increasing gene synthesis volumes and higher-volume oligonucleotide synthesis	Develop government points of contact worldwide
Centralized government clearinghouse for screening DNA sequences	Transition from screening based on lists of specific agents to specific DNA and amino acid sequences	Develop standards of record keeping that are acceptable to consumers, industry and government Foster or require industry and consumer best practice as a condition for receiving research funding

in nature, including those defined in Weapons of Mass Destruction–related statutes[14]. For example, any threatened use of a disease-causing organism directed at humans, animals or plants is a crime, regardless of whether the perpetrator actually possesses a disease-causing agent.

Effective law enforcement requires a suite of approaches for deterring, interdicting, responding to and investigating criminal acts. In developing such approaches, it is essential to recognize that no single approach will be 100% effective. Also, given the numerous and paramount constructive uses of DNA-synthesis technology (for example, see ref. 15), we cannot unnecessarily prohibit or restrict the use of DNA synthesis without great risk of compromising short- and long-term economic competitiveness and security, such as improved basic understanding or the development of countermeasures. Thus, as before, it is essential that any oversight framework not have a chilling effect on the ongoing development and use of the technology; the strongest and most effective framework will require the thoughtful integration of responsibilities and capabilities across individuals, commercial organizations, private and nongovernmental organizations and government.

A practical beginning

An effective initial governance framework should meet five goals. First, the framework should promote and later compel responsible behavior on the part of users of DNA-synthesis technology. Second, the framework should be sufficiently simple and robust be adopted as best practice throughout industry. Third, the framework should enable common improvement of needed technologies and promote sharing of operational wisdom throughout industry and government. Fourth, the framework should build on the existing practices that have enabled the safe development and application of recombinant DNA technology over the past three decades. Finally, the framework should foster and support international transparency and cooperation.

In seeking to formulate an effective governance framework, we started by considering existing practices at founding ICPS companies (e.g., customer screening and validation, DNA sequence screening). We then considered how existing practices could be codified and improved in support of widespread adoption. We also considered additional options and mechanisms, some of which we rejected as being impractical or ineffectual (**Table 1**; ref. 2). Operationally, we do support the development and validation of a tiered screening process that clearly identifies the contributions to safety and security due to user responsibilities, corporate practice and corporate technologies (**Fig. 1**).

User responsibilities would include the requirement that individuals who place orders for DNA synthesis identify themselves, their home organization and any relevant biosafety level information. As a result, individual researchers and any local review committees would assume and maintain some accountability for safety and security issues before placing a DNA synthesis order. Next, individual DNA synthesis companies would use ICPS-approved software tools to check synthesis orders against a set of select agents (or select sequences) to help ensure compliance with regulations and, as needed, flag synthesis orders for further review. Finally, synthetic biology companies would work together, and interface with appropriate government agencies, to rapidly and continually improve the underlying technologies used to screen orders and identify potentially dangerous sequences, as well as develop a clearly defined process to report behavior that falls outside of agreed-upon security guidelines.

The key strengths of the process that we describe and endorse here are as follows: first, it directly leverages the existing safety framework governing classical recombinant DNA work to account for recent and ongoing advances in DNA- synthesis technology and issues of biological security; second, it provides a focal point for developing and disseminating improvements in user and corporate best practice; third, it allows the continued commercial improvement and application of DNA-synthesis technology; and fourth, it provides an international platform for industry-government interactions needed to work through remaining issues in an open and cooperative fashion. It is critical to state clearly that we are endorsing a process for developing effective governance of DNA- synthesis technology and commercialization. Although several unresolved issues must be addressed over time to continue to improve our future biological safety and security (**Table 1**; ref. 2), we believe that the plan described here is the best practical path forward.

ACKNOWLEDGMENTS

The article expresses the opinions of the individual authors and does not necessarily reflect US government policy. We thank colleagues serving on the US National Science Advisory Board for Biosecurity, other government agencies and the organizers and participants in a project supported by the Alfred P. Sloan Foundation for sharing information and perspectives that directly inform our Commentary.

COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

1. Baker, D. *et al. Sci. Am.* **294**, 44–51 (2006).
2. Endy, D. *et al. A Practical Perspective on DNA Synthesis and Biological Security*, published online 4 December 2006 <http://pgen.us/PPDSS.htm>
3. Church, G. *A Synthetic Biohazard Non-proliferation Proposal*, published online 18 June 2004; updated 21 May 2005 <http://arep.med.harvard.edu/SBP/Church_Biohazard04c.htm>
4. Public Draft of the Declaration of the Second International Meeting on Synthetic Biology, published online 30 May 2006 <http://dspace.mit.edu/handle/1721.1/32982>
5. Etc. Group. *Extreme Genetic Engineering: An Introduction to Synthetic Biology*, published online January 2007 <http://www.etcgroup.org/upload/publication/602/01/synbioreportweb.pdf>
6. Check, E. *Nature* **436**, 894–895 (2005).
7. <http://polysynth.info/>
8. Cohen, S.N., Chang, A.C., Boyer, H.W. & Helling, R.B. *Proc. Natl. Acad. Sci. USA.* **70**, 3240–3244 (1973).
9. Gefter, M.L., Molineux, I.J., Kornberg, T. & Khorana, H.G. *J. Biol. Chem.* **247**, 3321–3326 (1972).
10. Mullis, K. *et al. Cold Spring Harb. Symp. Quant. Biol.* **51**, 263–273 (1986).
11. Berg, P., Baltimore, D., Brenner, S., Roblin, R.O. & Singer, M.F. *Proc. Natl. Acad. Sci. USA.* **72**, 1981–1984 (1975).
12. Carlson, R. *Biosecur. Bioterror.* **1**, 203–214 (2003).
13. Carlson, R. & Church, G.M. *Wired* **13**, 12–16 (2005).
14. 18 U.S.C. § 2332a
15. Baric, R.S. *et al. Adv. Exp. Med. Biol.* **581**, 553–560 (2006).