Practical (& Parochial) Perspectives on Synthethic Biology Practice (Policy)

Drew Endy
Stanford Bioengineering
The BioBricks Foundation

Stanford CA
27 July 2011

- Patience is a virtue (frustrating).

  Changing or implementing new policy usually takes a long time. Even the simplest topic to you is likely fascinating and esoteric to >99.9999% others

- Patience is a virtue (frustrating).

Changing or implementing new policy usually takes a long time. Even the simplest topic to you is likely fascinating and esoteric to >99.9999% others

- More people will be involved than you expect.

Policy involves framing, proposing and implementing tools that scale and shape relationships among parties. Many people tend to get involved and pay attention.

- Patience is a virtue (frustrating).

Changing or implementing new policy usually takes a long time. Even the simplest topic to you is likely fascinating and esoteric to >99.9999% others

- More people will be involved than you expect.

Policy involves framing, proposing and implementing tools that scale and shape relationships among parties. Many people tend to get involved and pay attention.

- Both process and product will be unsatisfying.

Limited moves are available for implementing policy (e.g., regulate). All but zero and first-order outcomes v. likely impossible to achieve.

- Patience is a virtue (frustrating).

Changing or implementing new policy usually takes a long time. Even the simplest topic to you is likely fascinating and esoteric to >99.9999% others

- More people will be involved than you expect.

Policy involves framing, proposing and implementing tools that scale and shape relationships among parties. Many people tend to get involved and pay attention.

- Both process and product will be unsatisfying.

Limited moves are available for implementing policy (e.g., regulate). All but zero and first-order outcomes v. likely impossible to achieve.

- External drivers and reality matter.

Government systems tend to react. Trying to get a "problem" solved gets you added to a long queue of problems. How urgent is the problem you are bringing, really? If you ask for government action how will it actually get done? Will it be good for anything?

- Patience is a virtue (frustrating).

Changing or implementing new policy usually takes a long time. Even the simplest topic to you is likely fascinating and esoteric to >99.9999% others

- More people will be involved than you expect.

Policy involves framing, proposing and implementing tools that scale and shape relationships among parties. Many people tend to get involved and pay attention.

- Both process and product will be unsatisfying.

Limited moves are available for implementing policy (e.g., regulate). All but zero and first-order outcomes v. likely impossible to achieve.

- External drivers and reality matter.

Government systems tend to react. Trying to get a "problem" solved gets you added to a long queue of problems. How urgent is the problem you are bringing, really? If you ask for government action how will it actually get done? Will it be good for anything?

- Intrinsic bias towards enabling research.

Advancing science and tech. mostly seen as essential for future competitiveness. Strong warriness about screwing this up.

FEDERAL REGISTER
THE DAILY JOURNAL OF THE UNITED STATES GOVERNMENT

Notice

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

A Notice by the Health and Human Services Department on 10/13/2010

SUMMARY To reduce the risk that individuals with ill intent may exploit the application of nucleic acid synthesis technology to obtain genetic material derived from or encoding Select Agents or Toxins and, as applicable, agents on the Export Administration Regulations' (EAR's) Commerce Control List (CCL), the U.S. Government has developed Guidance that provides a framework for screening synthetic double-stranded DNA (dsDNA). This document, the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* (the Guidance), sets forth recommended baseline 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

Publication Date:
Wednesday, October 13, 2010

Agencies:
Office of the Secretary
Department of Health and Human Services

October 2010

Description: In accordance with Section 1104(b) of Title XI of the Financial Institutions Reform, Recovery, and Enforcement Act of 1989, as amended, notice is hereby given that the Appraisal Subcommittee (ASC) will meet in closed session:

Location: FDIC Building, 1776 F Street, NW., Room 4085, Washington, DC 20429.

Date: October 13, 2010.

Time: Immediately following the ASC open session beginning at 10:30 a.m.

Status: Closed.

Matters to be Considered: September 22, 2010 minutes—Closed Session. Preliminary discussion of State Compliance Reviews.

Dated: October 6, 2010.

James R. Park,

Executive Director.

[FR Doc. 2010–25661 Filed 10–12–10; 8:45 am]

BILLING CODE P

FEDERAL RESERVE SYSTEM

Change in Bank Control Notices; Acquisitions of Shares of a Bank or Bank Holding Company

The notificants listed below have applied under the Change in Bank Control Act (12 U.S.C. 1817(j)) and § 225.41 of the Board's Regulation Y (12 CFR 225.41) to acquire shares of a bank or bank holding company. The factors that are considered in acting on the notices are set forth in paragraph 7 of the Act (12 U.S.C. 1817(j)(7)).

The notices are available for immediate inspection at the Federal Reserve Bank indicated. The notices also will be available for inspection at the offices of the Board of Governors. Interested persons may express their views in writing to the Reserve Bank indicated for that notice or to the offices of the Board of Governors. Comments must be received not later than October 28, 2010.

A. Federal Reserve Bank of Richmond (A. Linwood Gill III, Vice President), 701 East Byrd Street, Richmond, Virginia 23261–4528:

1. William Lee Hale and the William Lee Hale Trust, both of Bland, Virginia, acting in concert to retain control of 20.86% of the voting shares of First Regions Bancshares, Inc., Richlands, Virginia and thereby indirectly acquire voting shares of First Sentinel Bank, Richlands, Virginia.

Board of Governors of the Federal Reserve System, October 7, 2010.

Robert deV. Frierson,

Deputy Secretary of the Board.

[FR Doc. 2010–25679 Filed 10–12–10; 8:45 am]

BILLING CODE 6210–01–P

FEDERAL RETIREMENT THRIFT INVESTMENT BOARD

Sunshine Act; Notice of Meeting

TIME AND DATE: 9 a.m. (Eastern Time) October 18, 2010.

PLACE: 4th Floor Conference Room, 1250 H Street, NW., Washington, DC 20005.

STATUS: Parts will be open to the public and parts will be closed to the public.

MATTERS TO BE CONSIDERED:

Parts Open to the Public

1. Approval of the minutes of the September 20, 2010 Board Member Meeting.
2. Thrift Savings Plan Activity Report by the Executive Director.
   a. Monthly Participant Activity Report
   b. Monthly Investment Performance Review
   c. Legislative Report
3. Mid-Year Financial Audit Report.
4. Quarterly Vendor Financial Report.
5. Annual Budget Discussion.

Parts Closed to the Public

6. Confidential Vendor Information.

CONTACT PERSON FOR MORE INFORMATION: Thomas J. Trabucco, Director, Office of External Affairs, (202) 942–1640.

Dated: October 8, 2010.

Thomas K. Emswiler,

Secretary, Federal Retirement Thrift Investment Board.

[FR Doc. 2010–25854 Filed 10–8–10; 11:15 am]

BILLING CODE 6760–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

AGENCY: Department of Health and Human Services, Office of the Secretary.

ACTION: Notice.

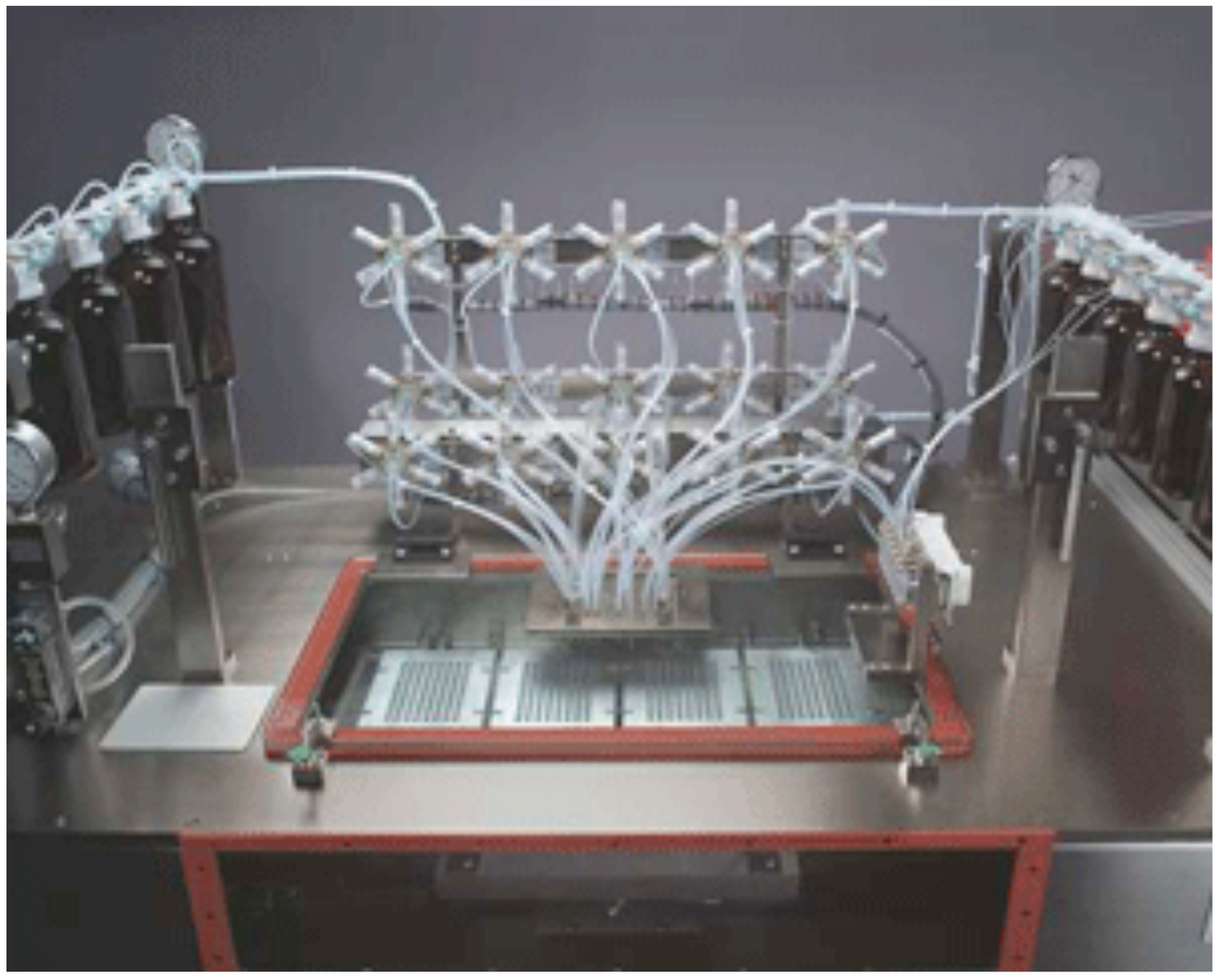
Authority: Public Health Service Act, 42 U.S.C. 241, Section 301; HSPD–10.

SUMMARY: To reduce the risk that individuals with ill intent may exploit the application of nucleic acid synthesis technology to obtain genetic material derived from or encoding Select Agents or Toxins and, as applicable, agents on the Export Administration Regulations' (EAR's) Commerce Control List (CCL), the U.S. Government has developed Guidance that provides a framework for screening synthetic double-stranded DNA (dsDNA). This document, the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* (the Guidance), sets forth recommended baseline 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. Following this Guidance is voluntary, though many specific recommendations serve to remind providers of their obligations under existing regulations. The framework includes customer screening and sequence screening, follow-up screening as necessary, and consultation with U.S. Government contacts, as needed.

A draft version of the Guidance was published as a **Federal Register** Notice (**Federal Register**, Vol. 74, No. 227, November 27, 2009, *Screening Framework Guidance for Synthetic Double-Stranded DNA Providers*) for public consideration and comment for a period of 60 days. Comments were reviewed and the Guidance was amended through a deliberative interagency process. The *Response to Public Comments* document, which precedes the final Guidance in the Supplementary Information section of this Notice, provides a general review of the decisions made to alter the Guidance in response to public comments. The Department of Health and Human Services (HHS) is issuing this document as the lead agency in a broad interagency process to draft the Guidance. The Guidance will be reviewed on a regular basis and revised, as necessary. For further details about the Guidance, to access public comments, and to provide ongoing feedback please refer to *http://www.phe.gov/preparedness/legal/guidance/syndna.*

DATES: The Guidance is effective on October 13, 2010.

FOR FURTHER INFORMATION CONTACT: Jessica Tucker, PhD, Office of Policy and Planning, Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health



~Q1 1999

Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template

Jeronimo Cello, Aniko V. Paul, Eckard Wimmer*

Full-length poliovirus complementary DNA (cDNA) was synthesized by assembling oligonucleotides of plus and minus strand polarity. The synthetic poliovirus cDNA was transcribed by RNA polymerase into viral RNA, which translated and replicated in a cell-free extract, resulting in the de novo synthesis of infectious poliovirus. Experiments in tissue culture using neutralizing antibodies and CD155 receptor–specific antibodies and neurovirulence tests in CD155 transgenic mice confirmed that the synthetic virus had biochemical and pathogenic characteristics of poliovirus. Our results show that it is possible to synthesize an infectious agent by in vitro chemical-biochemical means solely by following instructions from a written sequence.

Research on viruses is driven not only by an urgent need to understand, prevent, and cure viral disease. It is also fueled by a strong curiosity about the minute particles that we can view both as chemicals and as "living" entities. Poliovirus can be crystallized (*1*) and its empirical formula can be calculated (*2*), yet this "chemical" replicates naturally in humans with high efficiency, occasionally causing the paralyzing and lethal poliomyelitis.

Poliovirus, an enterovirus of the *Picornaviridae*, is a small, nonenveloped, icosahedral virus consisting of five different macromolecules: 60 copies each of capsid polypeptides VP1, -2, -3, and -4 and one copy of the positive-sense, single-stranded RNA genome (~7.5 kilobases in length) (Fig. 1A) (*3*). The chemical sequence (*4*, *5*), the genetic map of the genome (*4*), and the three-dimensional crystal structure of the virion (*6*) were determined 2 decades ago. Poliovirus employs one of the simplest genetic systems known for proliferation (*3*, *7*). The virus enters the cell after attaching to the cellular receptor CD155 (*8*, *9*). Immediately after the virus particle uncoats inside the cell, the genomic RNA is translated under the control of the internal ribosomal entry site (IRES) into a single polypeptide, the polyprotein (*10*, *11*). The polyprotein is then processed into functional proteins by two viral proteinases (*3*, *7*). With the aid of viral proteins, most notably the RNA-dependent RNA polymerase $3D^{pol}$ and the genome-linked protein VPg, along with cellular components, the viral RNA is transcribed into minus-strand copies that serve as templates for the synthesis of new viral genomes (plus-strand RNA). Newly synthesized plus-strand RNA can serve as messenger RNA for more protein synthesis, engage further in RNA replication, or be encapsidated by an increasing pool of capsid proteins (*7*, *12*). In suitable tissue culture cells (for example, HeLa cells), the entire replication cycle is complete in only 6 to 8 hours and yields 10^4 to 10^5 progeny virions per cell.

Here we describe the de novo chemical-biochemical synthesis of infectious poliovirus from basic chemical building blocks, independent of viral components previously formed in vivo and with the use of the known sequence as the only instruction for engineering the genome. The succession of macromolecular events in an infected cell was reproduced in a test tube containing a cell-free extract devoid of nuclei, mitochondria, and other cellular organelles and seeded with viral RNA. This result confirms that the genome sequence originally deciphered from virion RNA is correct (*4*, *5*) and demonstrates the feasibility of chemical-biochemical synthesis of an infectious agent in the absence of a natural template.

The strategy of synthesizing the genome of poliovirus type 1 (Mahoney) [PV1(M)] began with the assembly of a full-length cDNA carrying a phage T7 RNA polymerase promoter at the (left) 5′ end (Fig. 1) from three large, overlapping DNA fragments (F1, -2, and -3). Each DNA fragment was obtained by combining overlapping segments of 400 to 600 base pairs (bp). The segments were synthesized by assembling purified oligonucleotides [average length, 69 nucleotides (nt)] of plus and minus polarity with overlapping complementary sequences at their termini, and the segments were then ligated into a plasmid vector (*13*). Five to 15 clones were sequenced to identify either the correct DNA segments or the segments containing small numbers of errors that could be eliminated, either by combining the error-free portions of segments by an internal cleavage site or by standard site-directed mutagenesis (*13*). To ascertain the authenticity of the synthesized viral genome [sPV1(M)] and to distinguish it from the wild-type (*wt*) sequence of PV1(M) [*wt* PV1(M)] (*4*, *5*), we engineered nucleotide substitutions into the sPV1(M) cDNA as genetic markers (*13*).

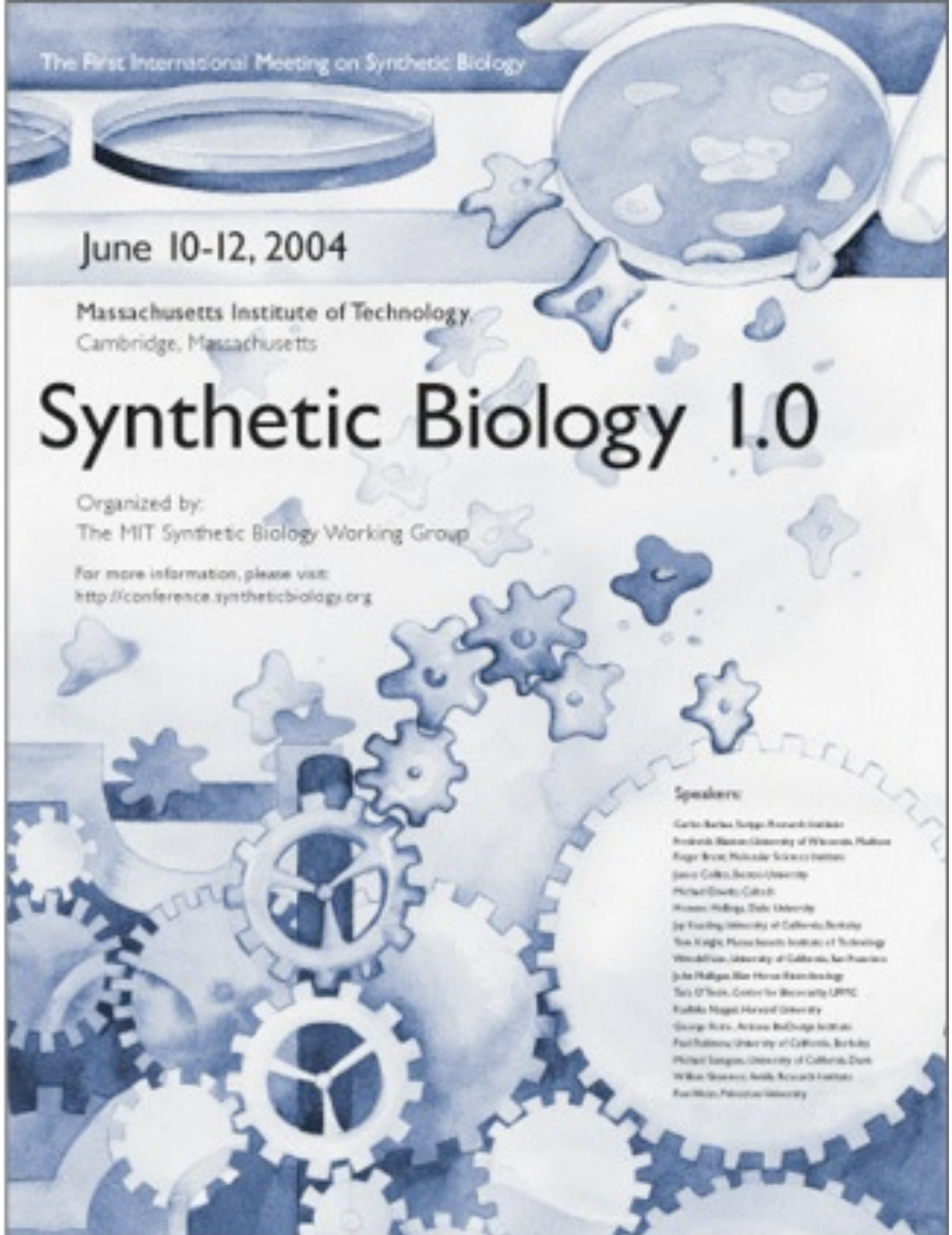
We have shown previously that poliovirus cDNA carrying a phage T7 promoter for the phage RNA polymerase can be transcribed with T7 RNA polymerase into highly infectious RNA (*14*). Accordingly, the sPV1(M) cDNA and *wt* PV1(M) cDNA were transcribed (*13*) and were found to yield transcript RNAs of the same length as virion RNA (*15*). De novo synthesis of poliovirus from transcript RNA of *wt* PV1(M) cDNA in a cell-free extract of uninfected HeLa cells has been previously described by Molla *et al.* (*2*). Therefore, the incubation of transcript RNA from sPV1(M) cDNA in cytoplasmic extracts of uninfected HeLa cells should result in the generation of poliovirus. To examine this possibility, transcript RNA derived from sPV1(M) cDNA was incubated with a cytoplasmic extract of HeLa S3 cells, and the synthesis of virus-specific proteins and infectious viruses were monitored. The products of sPV1(M) cDNA–derived RNA translation and proteolytic processing were the same as those obtained with *wt* PV1(M) RNA (Fig. 2), an observation suggesting that the open reading frame (ORF) of the sPV1(M)-specific RNA is intact. We then tested for the presence of infectious virus particles in the cell-free incubation mixture by adding aliquots of the incubation mixture to monolayers of HeLa cells. After 48 hours, plaques appeared [0.5 to 1×10^5 plaque-forming units (PFU) per μg of transcript RNA in 50 μl of reaction] whose heterogeneous morphology was characteristic of those produced by authentic poliovirus (Fig. 3). All together, these results indicate that the input synthetic RNA was translated and replicated in the cell-free extract and that newly synthesized RNA was encapsidated into newly synthesized coat proteins, resulting in the de novo synthesis of infectious poliovirus.

Experiments were then carried out to confirm that the infectious material isolated from the cell-free extract was indeed sPV1(M), as designated by the oligonucleotide sequence. Restriction enzyme digestion of the reverse transcriptase–polymerase chain reaction (RT-PCR) product of the viral RNA recovered from sPV1(M)-infected HeLa cells revealed the presence of all engineered markers (fig. S1, lanes 1 and 2).

We also tested the effects of the poliovirus

Department of Molecular Genetics and Microbiology, School of Medicine, State University of New York at Stony Brook, Stony Brook, NY 11794–5222, USA.

*To whom correspondence should be addressed. E-mail: ewimmer@ms.cc.sunysb.edu


The First International Meeting on Synthetic Biology
June 10-12, 2004
Massachusetts Institute of Technology
Cambridge, Massachusetts
Synthetic Biology 1.0
Organized by:
The MIT Synthetic Biology Working Group
For more information, please visit:
http://conference.syntheticbiology.org
Speakers:

June 2004

News & Analysis

Experts worry that synthetic biology may spawn biohackers

Chappell Brown

6/29/2004 1:00 PM EDT

HANCOCK, N.H. — Design automation systems tailored to the task of genetic engineering could prove to be double-edged tools. While they represent a central thrust of the emerging synthetic biology movement, they also can lead to the accidental or deliberate creation of pathogenic biological components.

One expert in the field, Harvard University genetics professor George Church, compared the potential misuse of synthetic biological designs with the danger posed by nuclear weapons. But there is one important difference, in his view — it is much harder to build a fusion device than to genetically engineer a pathogen. And the complexity of biological processes also increases the danger of accidents.

"Even if we don't have bioterrorists and teen-age biohackers, we will still create things that do not have the properties that we thought they would," Church said. The problem is that the body has not evolved a general ability to fend off artificial biological agents. "Even if you are genetically resistant and even if you are recently immunized you will have problems with this type of bug."

Church chaired a panel on the problems and opportunities of DNA synthesis at the recent Synthetic Biology 1.0 conference, held at the Massachusetts Institute of Technology earlier this month. A critical question for researchers and entrepreneurs entering the new field is what form technology regulation should take. Church suggested that anyone designing systems with synthetic biological components be required to have a license, which would entail passing basic competency tests.

Licensing might head off the possibility of unintended side effects by maintaining a level of competency among the people in the profession, but would do little to prevent deliberate attempts by terrorists or hackers to create pathogens. The continuing problems the Internet is experiencing with computer viruses that are released secretly give some indication of the problems that synthesized self-replicating systems pose. While the barrier to entry for building a computer or network is very high, once built, it becomes a vehicle for much smaller bits of code that someone with only a low level of expertise can release into the system.

End of June, 2004

October 2004 -> March 2005

NEWS

This Week

PAGE 1543
Neutrino bonanza

1545
Early bipedal hominid

BIODEFENSE

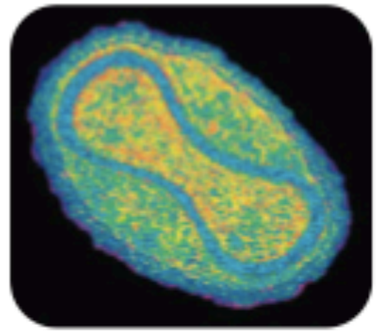
Unnoticed Amendment Bans Synthesis of Smallpox Virus

With hardly anyone noticing, Congress has slapped new restrictions—and hefty penalties—on one type of study involving the most dreaded pathogen on Earth. By adding a last-minute amendment to a massive intelligence reform bill in October, Representative Pete Sessions (R–TX) has made it illegal for most U.S. researchers to synthesize the smallpox virus, variola, from scratch. But some virologists, who are only now becoming aware of the amendment, say the law is ambiguous on what exactly is banned, and it could be interpreted to include some research on closely related poxviruses.

By international agreement, only two labs in the world, one in Russia and one in the United States, can store and study variola. U.S. law also criminalizes possession of the virus—along with many other "select agents"—for purposes other than "bona fide" research. But theoretically, nothing has stopped researchers from trying to assemble the virus except for their own conscience.

The new provision, part of the Intelligence Reform and Terrorism Prevention Act that President George W. Bush signed into law on 17 December 2004, had gone unnoticed even by many bioweapons experts. "It's a fascinating development," says smallpox expert Jonathan Tucker of the Monterey Institute's Center for Nonproliferation Studies in Washington, D.C.

Since smallpox was eradicated, the only known variola stocks sit at the Russian State Research Center of Virology and Biotechnology in Koltsovo, Novosibirsk, and the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. But advances in DNA synthesis have made it possible to create viruses in the lab; synthesizing a full, working variola virus may be possible within 5 years, predicts Eckard Wimmer of Stony Brook University in New York, who first synthesized the tiny poliovirus 3 years ago (*Science*, 9 August 2002, p. 1016).



Made to order? It may soon become possible to synthesize variola, the smallpox virus.

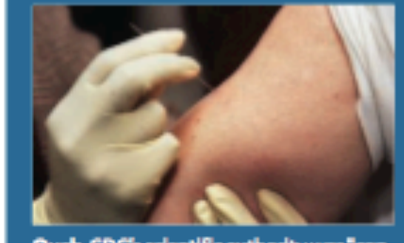
The primary goal of Sessions's amendment—originally introduced as two separate bills, one sponsored by Senator John Cornyn (R–TX)—was to impose much stiffer penalties on the possession of terror weapons, including shoulder-fired missiles, "dirty" bombs, and variola. Until now, for instance, unregistered possession of a select agent carried a maximum penalty of 10 years in prison; under the new law, the minimum is 25 years for variola. Where the law breaks new ground is by also making it illegal to "produce, engineer, [or] synthesize" variola. (Research carried out under the authority of the Secretary of Health and Human Services, who oversees the CDC, is exempt.)

It's extremely rare for the federal government to outlaw specific types of research, ▶

Report Faults Smallpox Vaccination

A review of the ill-fated 2003 U.S. smallpox vaccination campaign charges that the Bush Administration diverged from scientists' advice and moved ahead on a major effort without a clear explanation. The report, issued last week by the Institute of Medicine (IOM), also blames external "constraints" on the Centers for Disease Control and Prevention (CDC) for the program falling short of its goals. CDC Director Julie Gerberding denied the charges.

After the 9/11 attacks and anthrax letters, President George W. Bush in December 2002 announced a plan to vaccinate 500,000 health care workers, and eventually up to 10 million other emergency responders as well as an unspecified number of interested members of the public, against smallpox. But the effort soon foundered, especially after the vaccine caused heart problems in a few people, an unexpected side effect. The program wound down in mid-2003, and ultimately only about 40,000 people were vaccinated.



Ouch. CDC's scientific authority was "constrained" regarding smallpox vaccinations.

The IOM report* notes that "top officials of the executive branch" departed from the recommendations of CDC's vaccination advisory panel, which initially wanted to vaccinate only 20,000 people and later, under political pressure, raised that to 500,000 (*Science*, 20 December 2002, p. 2312). The officials offered "only vague explanation" for vaccinating 10 million more workers and the public, even though the vaccine carried known risks, and there was no evidence of an imminent attack. As a result, workers implementing the program and volunteers expected to line up for vaccinations "remained skeptical," leading to "poor participation," the report says.

The campaign was further hindered because CDC's normally open process of communicating scientific rationale to public health departments "seemed constrained by unknown external influences," the report says. In a strongly worded statement, Gerberding counters that CDC's voice was not "constrained" and that the program "was based on the best scientific advice."

The IOM report refrains from calling the effort a failure. It has apparently improved public health preparedness, as shown by the responses to a subsequent monkeypox outbreak and to severe acute respiratory syndrome, says IOM panel chair and biostatistician Brian Strom of the University of Pennsylvania in Philadelphia. But the panel concluded CDC needs to define and measure smallpox preparedness. Above all, Strom says, while national security concerns have to be balanced against scientific information, CDC "or any other agency needs to speak from the science."

–JOCELYN KAISER

* books.nap.edu/catalog/11240.html

Study to explore risks, benefits of synthetic genomics

June 28, 2005

email comment print share

At a time when biologists are faced with more ethics and security concerns than ever, three organizations--MIT, the J. Craig Venter Institute in Rockville, Md., and the Center for Strategic and International Studies in Washington, D.C.--today announced a new project to examine the societal implications of synthetic genomics, a new field involving the development of viruses and cells using designed and engineered DNA.

The 15-month study will explore the risks and benefits of this emerging technology, as well as possible safeguards to prevent abuse, including bioterrorism. It will be jointly directed by Drew Endy of MIT, Robert M. Friedman of the Venter Institute and Gerald L. Epstein of CSIS.

"The project will serve as a model for policy makers, scientists and engineers who are evaluating potential 'dual-use' research," said Endy, an assistant professor in MIT's Biological Engineering Division and co-founder of the MIT Synthetic Biology Working Group.

"The field of synthetic genomics has the potential for groundbreaking scientific advances, including the development of alternative energy sources, and the production of new vaccines and pharmaceuticals," said J. Craig Venter, founder and president of the Venter Institute. "Synthetic genomics has the potential to enable significant societal

today's news

How the brain assigns objects to categories

New research from MIT neuroscientists suggests how the brain learns which category an object belongs to — for example, fruits or animals.
Image: Christine Daniloff

New findings may explain why children with autism tend to fixate on details instead of

ture.

related

Engineering biology

The first international meeting on synthetic biology, bringing together biologists and computer scientists from around the world, was held at MIT last month. *7/23/2004*

MIT Biological Engineering Division

Center For Strategic & International Studies

J. Craig Venter Institute

contact

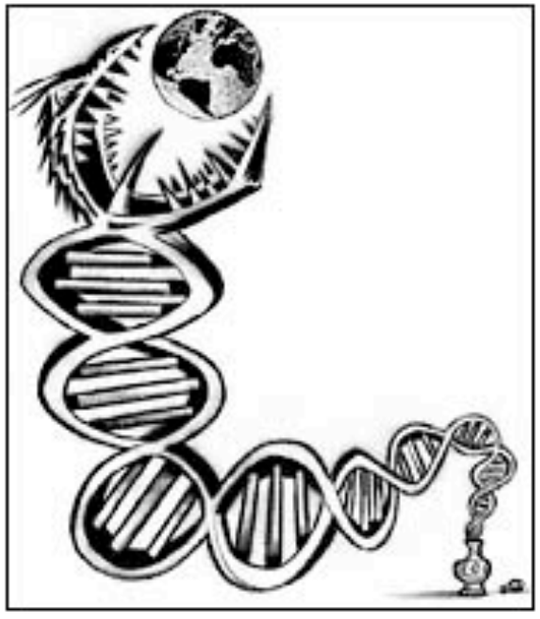
Denise Brehm
MIT News Office
brehm@mit.edu
617-253-2704

OP-ED CONTRIBUTORS

Recipe for Destruction

By RAY KURZWEIL and BILL JOY
Published: October 17, 2005

AFTER a decade of painstaking research, federal and university scientists have reconstructed the 1918 influenza virus that killed 50 million people worldwide. Like the flu viruses now raising alarm bells in Asia, the 1918 virus was a bird flu that jumped directly to humans, the scientists reported. To shed light on how the virus evolved, the United States Department of Health and Human Services published the full genome of the 1918 influenza virus on the Internet in the GenBank database.



This is extremely foolish. The genome is essentially the design of a weapon of mass destruction. No responsible scientist would advocate publishing precise designs for an atomic bomb, and in two ways revealing the sequence for the flu virus is even more dangerous.

First, it would be easier to create and release this highly destructive virus from the genetic data than it would be to build and detonate an atomic bomb given only its design, as you don't need rare raw materials like plutonium or enriched uranium. Synthesizing the virus from scratch would be difficult, but far from impossible. An easier approach would be to modify a conventional flu virus with the eight unique and now published genes of the 1918 killer virus.

1918 Flu and Responsible Science

The influenza pandemic of 1918 is estimated to have caused 50 million deaths worldwide; 675,000 in the United States. The reconstruction of the 1918 virus by the synthesis of all eight subunits and the generation of infectious virus are described on p. 77 of this issue,* and the sequences of the final three gene segments of the virus are described in a concurrent *Nature* paper.† Predictably, but alarmingly, this virus is more lethal to mice than are other influenza strains, suggesting that this property of the 1918 virus has been recovered in the published sequence. The good news is that we now have the sequence of this virus, perhaps permitting the development of new therapies and vaccines to protect against another such pandemic. The concern is that a terrorist group or a careless investigator could convert this new knowledge into another pandemic.

Should the sequence of the 1918 virus have been published, given its potential use by terrorists? The dual-use nature of biological information has been debated widely since September 11, 2001. In 2003, a committee of the U.S. National Academies chaired by Gerald Fink considered this issue, weighing the benefits against the risks of restricting the publication of such biological information. They outlined the tradeoff between erring on the side of prudence, thus potentially hindering the progress of critical science, and erring on the side of disclosure, thus potentially aiding terrorists. The U.S. National Science Advisory Board for Biosecurity (NSABB) was established to advise governmental agencies and the scientific community on policies relative to public disclosure. This board has begun to deliberate, but the questions are complex, as typified by these papers on the 1918 virus. It is reassuring that the NSABB was asked to consider these papers before publication and concluded that the scientific benefit of the future use of this information far outweighs the potential risk of misuse. People may be reassured that the system is working, because agencies representing the public, the scientific community, and the publishing journals were involved in the decision.

I firmly believe that allowing the publication of this information was the correct decision in terms of both national security and public health. It is impossible to forecast how scientific observations might stimulate others to create new treatments or procedures to control future pandemics. For example, in the *Nature* article, sequence comparisons suggest that the 1918 virus was generated not by incremental changes in the polymerase genes, but by the movement of these genes, in total, from an avian source into a human influenza virus. The availability of these sequences will permit identification of their avian origin and should show why this particular set of genes was selected. Similarly, the results in the *Science* article suggest that the cleavage of a protein on the surface of the 1918 virus, a step critical for virulent infection, may occur by a previously unknown mechanism—a hint that could lead to new drugs for inhibiting this step and thus preventing future pandemic eruptions.

Influenza is highly infectious, and a new strain could spread around the world in a matter of months, if not weeks. The public needs confidence that the 1918 virus will not escape from research labs. All of the described experiments were done in a Biosafety Level 3 laboratory, a high-containment environment recommended by the U.S. Centers for Disease Control and Prevention and the National Institutes of Health on an interim basis, whose use should become a permanent requirement for such experiments. Current evidence suggests that some available drugs and possible future vaccines could suppress infections by the 1918 virus. Given the prospect of another natural influenza pandemic, the recent decision by the U.S. administration to stockpile antivirals for influenza treatment seems wise. Finally, although a sequence of the 1918 virus has been determined and is highly virulent in mice, this may not be the specific form of the virus that caused the pandemic of 1918. An article in the same issue of *Nature*‡ reports the existence of sequence variation in a natural population of influenza virus; yet we have only one sequence for the 1918 pandemic strain, and the reconstructed virus described in the *Science* article was built into the backbone of a laboratory strain. Because a pandemic infection is dependent on many unknown properties, there is no certainty that the reconstructed 1918 virus is capable of causing a pandemic.

Phillip A. Sharp

Phillip A. Sharp is Institute Professor at the Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA.

October 2005

From Understanding to Action: Community-Based Options for Improving Safety and Security in Synthetic Biology

Stephen M. Maurer, Keith V. Lucas & Starr Terrell
Goldman School of Public Policy
University of California at Berkeley

Draft 1.1 April 15, 2006

April 2006

Executive Summary

The vast majority of today's biosafety and biosecurity concerns predate synthethic biology and would be substantially the same even if this new field did not exist. Nevertheless synthetic biologists have an obligation to make sure that their work does not amplify earlier risks or create new ones. That discussion has been ongoing in various formal and informal venues since 2000. Today, synthetic biologists share a deep understanding of the biosafety/biosecurity problem and – in some cases – emerging consensus about what can and should be done to manage it. Many options can be implemented through community self-governance without outside intervention.

Understanding alone is not sufficient. The challenge now is action. Synthetic Biology 2.0 provides a natural forum for community self-governance. Because time is limited, however, members must come prepared. This document provides a self-contained review of previous discussions (Section I), discusses design principles for possible interventions (Section II), identifies instances where synthetic biology could potentially change earlier biosecurity/biosafety risks (Section III), and summarizes possible interventions that the community should consider at Synthetic Biology 2.0 (Section IV). Possible actions include:

> ***A.1 Insist That All Commercial Gene Synthesis Houses Adopt Current Best Practice Screening Procedures.*** While most gene synthesis companies screen orders for dangerous sequences, a few do not. This gives both community members and outsiders access to feedstocks for both wild-type and genetically-engineered bioweapons. Community members should stop doing business with any gene synthesis company that fails to implement current best-practice screening methods by January 1, 2007.
>
> ***A.2 Create and Endorse New Watch-Lists To Improve Industry Screening Programs.*** Improved watch-lists and software tools can make industry screening more accurate and efficient. Members should prepare the necessary lists and tools in time for Synthetic Biology 3.0.
>
> ***B.1. Create a Confidential Hotline For Biosafety and Biosecurity Issues.*** All experimenters contemplating "experiments of concern" should obtain independent expert advice before proceeding. The community should make such advice freely available to all experimenters, including non-members (*e.g.* hackers) who cannot otherwise obtain such advice from formal university, company, or NIH safety committees.
>
> ***B.2. Affirm Members' Ethical Obligation to Investigate and Report Dangerous Behavior.*** Members have an obligation to investigate and, if necessary, report dangerous behavior. Members should affirm this obligation by formal resolution at Synthetic Biology 2.0.
>
> ***C. Create a Community-Wide Clearinghouse for Identifying and Tracking Potential Biosafety/Biosecurity Issues.*** Members who notice potential biosecurity issues have an obligation to share them with the broader community. A central clearinghouse will help the community to identify, track, and if necessary respond to the biosafety/biosecurity implications of a changing technology.
>
> ***D. Endorse Biosecurity/Biosafety R&D Priorities.*** New technologies can potentially reduce current biosafety/biosecurity risks even further. Members should identify, endorse, and urge funding agencies to invest in priority technologies such as safe chasses and bar codes.

This document is part of a sustained effort by The Berkeley SynBio Policy Group to help members learn about security issues and facilitate community self-governance at Synthetic Biology 2.0. In coming weeks, we will host Town Hall Meetings at Berkeley (April 11) and MIT (April 21) to further discuss what the community can do to improve

Synthetic Biology 2.0

The Second International Meeting on Synthetic Biology

May 20-22, 2006

at the

University of California, Berkeley

Berkeley, CA

Official Conference Website

Taken from the Official Conference Website

The Second International Conference on Synthetic Biology (SB2.0) will take place on May 20-22, 2006, at the University of California, Berkeley. The conference will bring together a diverse group of participants from a variety of disciplines, including some of the world's leaders in biological engineering, biochemistry, quantitative biology, biophysics, molecular and cellular biology, bioethics, policy and governance, and the biotech industry. A collaborative effort among Berkeley Lab, MIT, UC Berkeley, and UCSF, the conference will promote and guide the further, constructive development of the field.

SB2.0 will begin with two days of plenary talks and discussions focused on five research areas: energy, chemistry, health, materials, and foundational technologies. The third day of the conference will be dedicated to presentation, discussion, and deliberation of the four key societal issues associated with synthetic biology: biosecurity & risk, public understanding & perception, ownership, sharing & innovation, and community organization. All conferees will be expected to participate in these conversations.

May 2006

Open Letter from Civil Society

In response to the proposed voluntary code that is being discussed at Synthetic Biology 2.0, Thirty-five civil society organizations have issued a joint letter calling on the synthetic biologists to withdraw from this self-governance approach. The letter emphasizes that:

- Society - especially social movements and marginalized peoples - must be fully engaged in designing and directing societal dialogue on every aspect of synthetic biology research and products. Because of the extraordinary power and scope of synthetic biology technologies, this discussion must take place globally, nationally and locally
- Scientific self-governance doesn't work and is anti-democratic. It is not for scientists to have the determinant voice in regulating their research or their products
- The development of synthetic biology technologies must be evaluated for their broader socio-economic, cultural, health and environmental implications not simply for their misuse in the hands of 'evildoers.'

The organizations that have signed the open letter work in over sixty countries and include scientists, engineers, environmentalists, farmers, social justice advocates, trade unionists and biowarfare experts:

List of Organizations Signing the Open Letter

Acción Ecológica (Ecuador) - *www.accionecologica.org*
California for GE Free Agriculture - *www.calgefree.org*
Centro Ecológico (Brazil)
Clean Production Action - *www.cleanproduction.org*
Cornerhouse UK - *www.thecornerhouse.org.uk*
Corporate Europe Observatory - *www.corporateeurope.org*
Corporate Watch (UK) - *www.corporatewatch.org*
EcoNexus - *www.econexus.info*
Ecoropa
Edmonds Institute - *www.edmonds-institute.org*
ETC Group - *www.etcgroup.org*
Farmers Link - *www.farmerslink.org.uk*
Friends of the Earth International - *www.foe.org*
Foundation on Future Farming (Germany) - *www.zs-l.de*
Foundation Science Citoyennes (France) - *www.sciencescitoyennes.org*

A Roadmap to the Assembly of Synthetic DNA from Raw Materials

Yogesh S. Sanghvi

Rasayan Inc., Encinitas, California

Cite as:

Sanghvi Y. 2005. A Roadmap to the Assembly of Synthetic DNA from Raw Materials. In: *Working Papers for Synthetic Genomics: Risks and Benefits for Science and Society*, pp. 17-33. Garfinkel MS, Endy D, Epstein GL, Friedman RM, editors. 2007.

The views and opinions expressed are those of the author of the paper.

< April 2007

A Roadmap to the Assembly of Synthetic DNA from Raw Materials

Yogesh S. Sanghvi

Rasayan Inc., Encinitas, California

Cite as:

Sanghvi Y. 2005. A Roadmap to t
In: *Working Papers for Synthetic*
pp. 17-33. Garfinkel MS, Endy D,

Introduction

Until recently, the synthesis of DNA has been a tedious, time consuming, expensive and experimentally challenging task. But advances in automated instrumentation and improved chemistry have now made it possible to make any moderate-length sequence of DNA in any quantity. The ease of automated chemical synthesis of DNA has triggered a whole new industry of low-cost DNA suppliers around the globe. The convenience of ordering DNA sequence by mail has opened new avenues in research both in academia and in the healthcare products developed by pharmaceutical companies. At the same time, these advances have made it theoretically possible to synthesize DNA that could be used to do harm. This article aims to describe the first stages of DNA synthesis, from readily available raw materials to medium-sized segments with a desired sequence (oligonucleotides), and examines whether there are points at which such activities could be, for example, monitored or controlled. Some academic and commercial applications of DNA synthesis require the construction of very small quantities of the desired sequence; others involve synthesis at the gram scale or larger. I provide comments on possible intervention points for both types of application. Terms shown in bold are defined in the glossary.

< April 2007

A Roadmap to the Assembly of Synthetic DNA from Raw Materials

Yogesh S. Sanghvi

Rasayan Inc., Encinitas, California

Cite as:

Sanghvi Y. 2005. A Roadmap to t
In: *Working Papers for Synthetic*
pp. 17-33. Garfinkel MS, Endy D,

Introduction

Until recently, the synthesis of DNA has been a tedious, time consuming, expensive and experimentally challenging task. But advances in automated instrumentation and improved chemistry have now made it possible to make any moderate-length sequence of DNA in any quantity. The ease of automated chemical synthesis of DNA has triggered a whole new industry of low-cost DNA suppliers around the globe. The convenience of ordering DNA sequence by mail has opened new avenues in research both in academia and in the healthcare products developed by pharmaceutical companies. At the same time, these advances have made it theoretically possible to synthesize DNA that could be used to do harm. This article aims to describe the first stages of DNA synthesis, from readily available raw materials to medium-sized segments with a desired sequence (oligonucleotides), and examines whether there are points at which such activities could be, for example, monitored or controlled. Some academic and commercial applications of DNA synthesis require the constructi
others involve synthesis at the gram
intervention points for both types of
glossary.

Conclusion

It would not be an easy matter to restrict the supply of the reagents needed for DNA synthesis to such an extent as to prevent a motivated individual from making oligonucleotides at a small scale. As noted above, the least implausible option for tracking and restriction would seem to be solid support beads. However, since these are widely used by the legitimate DNA synthesis industry, the restrictions must also include protocols for monitoring reagent use within a company and reporting their disposition. Several of the companies making and using these reagents reside outside the USA, complicating the task of imposing effective tracking policies.

< April 2007

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

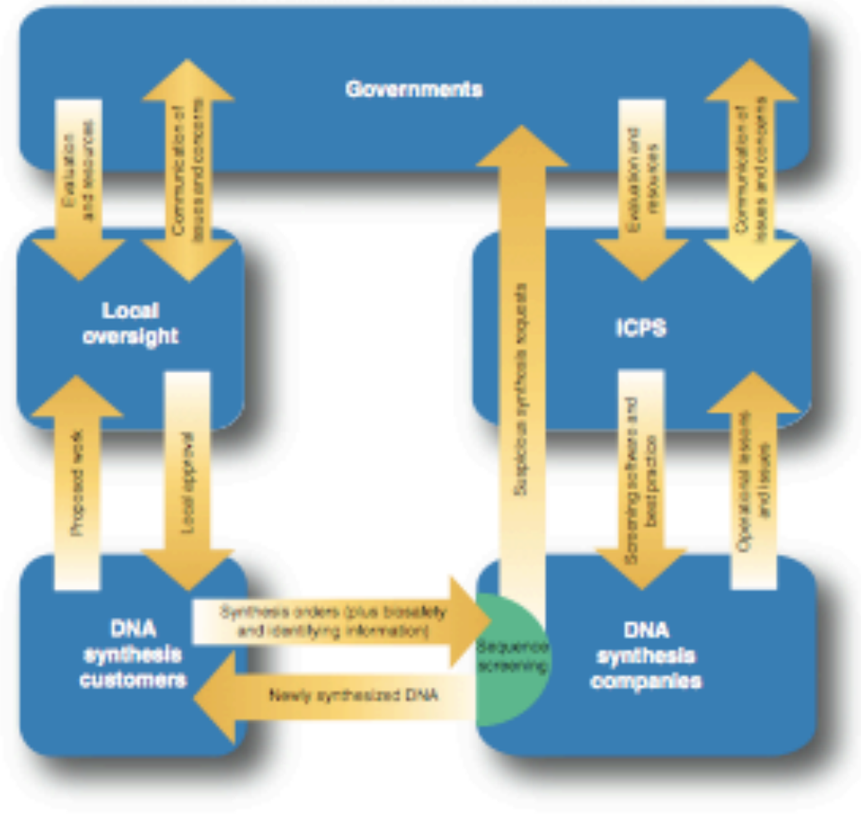
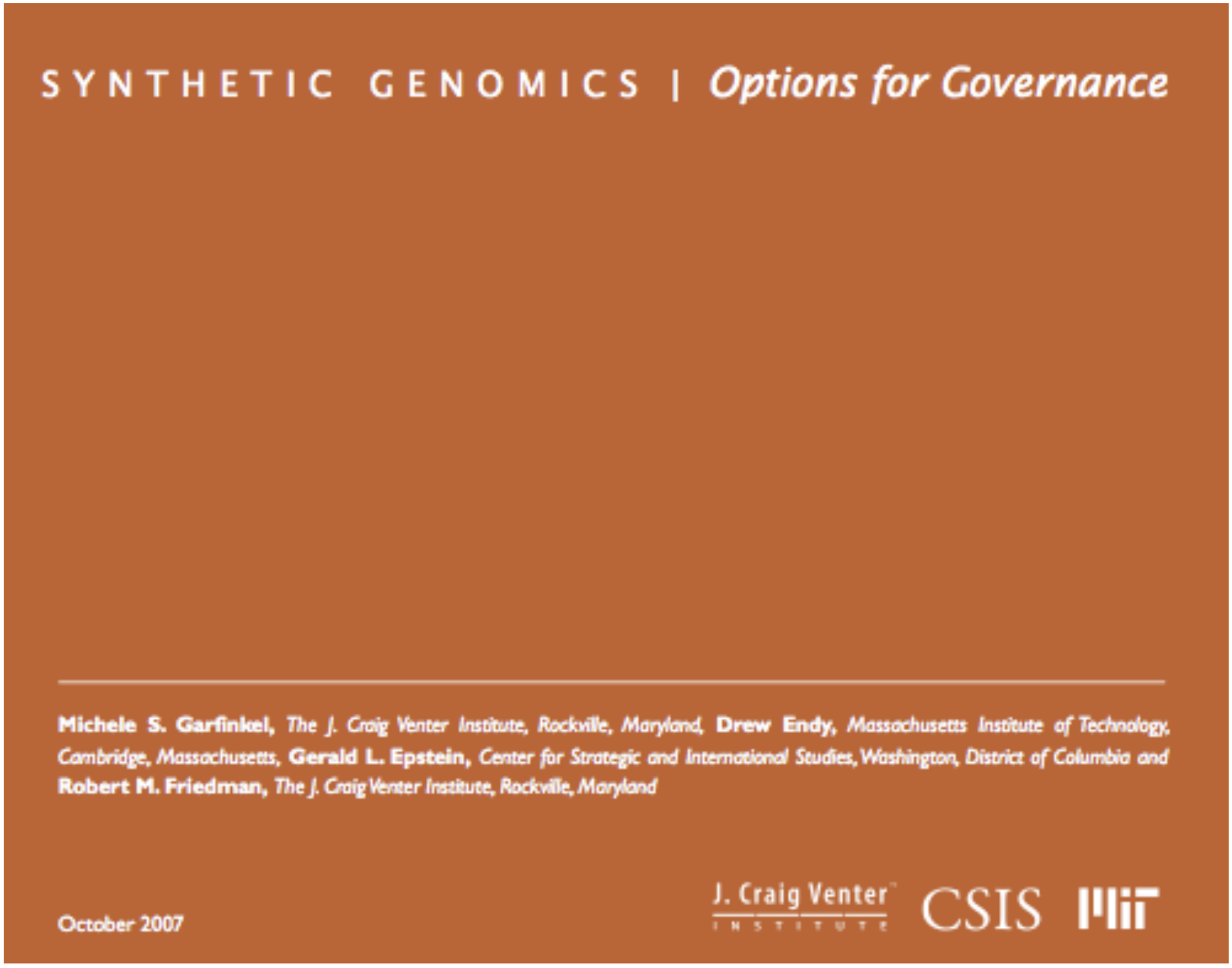


Figure 1 Our framework calls for the immediate and systematic implementation of a tiered DNA synthesis order screening process. To promote and establish accountability, individuals who place orders for DNA synthesis would be required to identify themselves, their home organization and all relevant biosafety 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.

June 2007



October 2007

Summary Table of Options

Key to Scoring:

- ● Most effective for this goal. Most effective performance on this consideration.
- ◉ Relatively effective.
- ◎ Moderately effective.
- ○ Somewhat effective.
- ○ Minimally effective.

Does the Option:	Gene Firms				Oligo Manufacturers				DNA Synthesizers			Users and Organizations					
	IA-1. Gene firms must screen orders	IA-2. Biosafety officers must certify people who place orders	IA-3. Hybrid: Firms must screen and biosafety officer must verify people	IA-4. Firms must store information about orders	IB-1. Oligonucleotide manufacturers must screen orders	IB-2. Biosafety officer must verify people who place orders	IB-3. Hybrid: Firms must screen and biosafety officer must verify people	IB-4. Firms must store information about orders	II-1. Owners of DNA synthesizers must register their machines	II-2. Owners of DNA synthesizers must be licensed	II-3. Licensing of equipment, plus license required to buy reagents and services	III-1. Education about risks and best practices in university curricula	III-2. Compile a manual for "Biosafety in Synthetic Biology Laboratories"	III-3. Establish a clearinghouse for best practices	III-4. Broaden IBC review responsibilities	III-5. Broaden IBC review; plus oversight by National Advisory	III-6. Broaden IBC review; plus enhanced enforcement
Enhance Biosecurity																	
by preventing incidents?	◉	◎	●	○	◎	◎	◉	○	○	○	◎	○	–	–	○	◉	○
by helping to respond?	–	–	–	◎	–	–	–	◎	○	○	○	○	–	–	–	–	–
Foster Laboratory Safety																	
by preventing incidents?	○	–	○	–	○	–	○	–	–	–	–	◉	●	◎	○	◉	◉
by helping to respond?	–	–	–	–	–	–	–	–	–	–	–	◉	–	–	–	○	–
Protect the Environment																	
by preventing incidents?	○	–	○	–	–	–	–	–	–	–	–	◉	●	◎	○	◉	◉
by helping to respond?	–	–	–	◎	–	–	–	○	–	–	–	○	◉	◉	○	–	–
Other Considerations:																	
Minimize costs and burdens to government and industry?	◎	◎	○	●	○	◎	○	●	●	◉	◎	◉	○	◎	○	◎	○
Perform to potential without additional research?	◎	●	◉	◎	○	●	◎	◎	●	●	◉	◉	○	○	○	◎	◉
Not impede research?	◉	◉	◎	●	○	○	○	●	◉	◎	○	●	◉	●	○	◎	○
Promote constructive applications?	–	–	–	–	–	–	–	–	–	–	–	●	○	◎	○	–	–

Background Information on ICCVAM, NICEATM, and SACATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that use or generate toxicological information. ICCVAM conducts technical evaluations of new, revised, and alternative methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological test methods that more accurately assess the safety and hazards of chemicals and products and that refine, reduce, and replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3, available at *http://iccvam.niehs.nih.gov/docs/about_docs/PL106545.pdf*) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM and provides scientific and operational support for ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of Federal agencies. Additional information about ICCVAM and NICEATM is available on the NICEATM–ICCVAM Web site: *http://iccvam.niehs.nih.gov*.

SACATM was established January 9, 2002 and is composed of scientists from the public and private sectors (67 FR 11358). SACATM provides advice to the Director of the NIEHS, ICCVAM, and NICEATM regarding the statutorily mandated duties of ICCVAM and activities of NICEATM. Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at *http://ntp.niehs.nih.gov/go/167*.

Dated: November 16, 2009.

John R. Bucher,

Associate Director, National Toxicology Program.

[FR Doc. E9–28278 Filed 11–25–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Screening Framework Guidance for Synthetic Double-Stranded DNA Providers

AGENCY: Department of Health and Human Services, Office of the Secretary.

ACTION: Notice.

SUMMARY: To reduce the risk that individuals with ill intent may exploit the commercial application of nucleic acid synthesis technology to access genetic material derived from or encoding Select Agents or Toxins, the U.S. Government has developed recommendations for a framework for synthetic nucleic acid screening. This document is intended to provide guidance to producers of synthetic genomic products regarding the screening of orders so that these orders are filled in compliance with current U.S. regulations and to encourage best practices in addressing potential biosecurity concerns. Following this guidance is voluntary, though many specific recommendations serve to remind providers of their obligations under existing regulations. The target audience for this guidance is the gene and genome synthesis industry, because the technical hurdles for *de novo* synthesis of Select Agents and Toxins from double-stranded DNA are much lower than for *de novo* synthesis of these agents from single-stranded oligonucleotides. This guidance proposes a screening framework for commercial providers of synthetic double-stranded DNA 200 base pairs (bps) or greater in length to address concerns associated with the potential for misuse of their products. The framework includes customer screening and sequence screening, follow-up screening as necessary, and consultation with U.S. Government contacts, as needed.

This guidance is submitted for public consideration and comment for a period of 60 days. The Office of the Assistant Secretary of Preparedness and Response (ASPR) within the Department of Health and Human Services (HHS) is submitting this document for public consideration as the lead agency in a broad interagency process to draft the guidance.

DATES: The public is encouraged to submit written comments on this proposed action. Comments may be submitted to HHS/ASPR in electronic or paper form at the HHS/ASPR e-mail address, mailing address, and fax number shown below under the heading **FOR FURTHER INFORMATION CONTACT.** All comments should be submitted by January 26, 2010. All written comments received in response to this notice will be available for review by request.

FOR FURTHER INFORMATION CONTACT: Jessica Tucker, Ph.D., Office of Medicine, Science, and Public Health, Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services, 330 C Street, SW., Room 5008B, Washington, DC 20201; phone: 202–260–0632; fax: 202–205–8494; e-mail address: *asprfrcorrespondence@hhs.gov*.

SUPPLEMENTARY INFORMATION:

Authority: Public Health Service Act, 42 U.S.C. 241, Section 301; HSPD–10.

Screening Framework Guidance for Synthetic Double-Stranded DNA Providers

I. Summary

Synthetic biology, the developing interdisciplinary field that focuses on both the design and fabrication of novel biological components and systems as well as the re-design and fabrication of existing biological systems, is poised to become the next significant transforming technology for the life sciences and beyond. Synthetic biology is not constrained by the requirement of using existing genetic material. Thus, technologies that permit the directed synthesis of polynucleotides have great potential to be used to generate organisms, both currently existing and novel, including pathogens that could threaten public health, agriculture, plants, animals, the environment, or material. To reduce the risk that individuals with ill intent may exploit the commercial application of nucleic acid synthesis technology to access genetic material derived from or encoding Select Agents or Toxins, the U.S. Government has developed recommendations for a framework for synthetic nucleic acid screening. This document is intended to provide guidance to producers of synthetic genomic products regarding the screening of orders so that these orders are filled in compliance with current U.S. regulations and to encourage best practices in addressing potential biosecurity concerns.

Following this guidance is voluntary, though many specific recommendations serve to remind providers of their obligations under existing regulations. The target audience for this guidance is the gene and genome synthesis industry, because the technical hurdles for *de novo* synthesis of Select Agents and Toxins from double-stranded DNA are much lower than for *de novo* synthesis of these agents from single-stranded oligonucleotides. This guidance proposes a screening framework for commercial providers of synthetic double-stranded DNA 200 base pairs (bps) or greater in length to address concerns associated with the potential for misuse of their products. The framework includes customer screening and sequence screening, follow-up screening as necessary, and consultation with U.S. Government contacts, as

FEDERAL REGISTER
THE DAILY JOURNAL OF THE UNITED STATES GOVERNMENT

Notice

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

A Notice by the Health and Human Services Department on 10/13/2010

SUMMARY To reduce the risk that individuals with ill intent may exploit the application of nucleic acid synthesis technology to obtain genetic material derived from or encoding Select Agents or Toxins and, as applicable, agents on the Export Administration Regulations' (EAR's) Commerce Control List (CCL), the U.S. Government has developed Guidance that provides a framework for screening synthetic double-stranded DNA (dsDNA). This document, the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* (the Guidance), sets forth recommended baseline 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

Publication Date:
Wednesday, October 13, 2010

Agencies:
Office of the Secretary
Department of Health and Human Services

October 2010

Published online 18 October 2010 | *Nature* **467**, 898 (2010) |
doi:10.1038/467898a

News

Gene-synthesis rules favour convenience

But synthetic DNA standards offer little protection, critics say.

Heidi Ledford

Before the US government released its long-awaited guidelines for purveyors of synthetic DNA last week, some scientists were concerned that the standards, meant to foil would-be bioterrorists, would also hamper legitimate researchers. Instead, the limited scope of the voluntary guidelines has thrown into stark relief the difficulty of keeping tabs on the fast-growing business of gene synthesis.

The US Department of Health and Human Services (DHHS) in Washington DC spent more than three years crafting the guidelines, which advise biotech companies to screen customers and their orders for possible threats to human health or agriculture. DNA sequences that match those unique to organisms on the government's Select Agents and Toxins list, potentially representing a public-health risk, will be reported to the DHHS. The screening will not impinge on legitimate research, or burden industry to such an extent that companies might leave the country, says Michael Imperiale, a microbiologist at the University of Michigan, Ann Arbor, and a member of the National Science Advisory Board for Biosecurity.

Published online 18 October 2010 | *Nature* **467**, 898 (2010) |
doi:10.1038/467898a

News

Gene-synthesis rules favour convenience

But synthetic DNA standards offer little protection, critics say.

Heidi Ledford

Before the US government released its long-awaited guidelines for purveyors of synthetic DNA last week, some scientists were concerned that the standards, meant to foil would-be bioterrorists, would also hamper legitimate researchers. Instead, the limited scope of the voluntary guidelines has thrown into sta
keeping tabs on the fast-growing busine

The US Department of Health and Huma
Washington DC spent more than three y
which advise biotech companies to scre
for possible threats to human health or
that match those unique to organisms o
Agents and Toxins list, potentially repre
will be reported to the DHHS. The scree
legitimate research, or burden industry
companies might leave the country, say
microbiologist at the University of Michi
of the National Science Advisory Board f

> "The US government is urging a lower security standard on the world."

But in achieving that level of comfort, the DHHS has drastically restricted the guidelines' reach. The rules apply only to double-stranded DNA, for example, and not to single-stranded fragments — a decision that has puzzled even proponents of the guidelines. "It seems like an arbitrary distinction," says George Church, a geneticist at Harvard Medical School in Boston, Massachusetts. Although the techniques for stitching together double-stranded DNA fragments are better established, Church and his colleagues recently published a method for re-engineering bacterial genomes using single-stranded DNA fragments only 90 bases long (H. H. Wang *et al. Nature* **460,** 894–898; 2009).

Small single-stranded DNA fragments are widely used in molecular biology, and the DHHS says that it would be too burdensome for industry to screen such a high volume of orders. Church, who says the guidelines are a good first step, disagrees. "I don't see why these guidelines wouldn't work for single-stranded DNA," he says.

Published online 18 October 2010 | *Nature* **467**, 898 (2010) |
doi:10.1038/467898a

News

Gene-synthesis rules favour convenience

But synthetic DNA standards offer little protection, critics say.

Heidi Ledford

Before the US government released its long-awaited guidelines for purveyors of synthetic DNA last week, some scientists were concerned that the standards, meant to foil would-be bioterrorists, would also hamper legitimate researchers. Instead, the limited scope of the voluntary guidelines has thrown into sta
keeping tabs on the fast-growing busine

> **"The US government is urging a lower security standard on the world."**

The US Department of Health and Huma
Washington DC spent more than three y
which advise biotech companies to scre
for possible threats to human health or
that match those unique to organisms o
Agents and Toxins list, potentially repre
will be reported to the DHHS. The scree
legitimate research, or burden industry
companies might leave the country, say
microbiologist at the University of Michi
of the National Science Advisory Board f

But in achieving that level of comfort, the DHHS has drastically restricted the guidelines' reach. The rules apply only to double-stranded DNA, for example, and not to single-stranded fragments — a decision that has puzzled even proponents of the guidelines. "It seems like an arbitrary disti
Church, a geneticist at Harvard Medical Sc
Massachusetts. Although the techniques fo
stranded DNA fragments are better establi
colleagues recently published a method fo
genomes using single-stranded DNA fragm
(H. H. Wang *et al. Nature* **460,** 894–898;

Small single-stranded DNA fragments are
biology, and the DHHS says that it would b
industry to screen such a high volume of c
guidelines are a good first step, disagrees.
guidelines wouldn't work for single-strand

Stephen Maurer, a public-policy researcher at the University of California, Berkeley, adds that the guidelines call for an initial automated screen of sequences by computer, a less stringent survey than getting employees to analyse each order as it comes in, as many companies already do. "You have a strange situation in which the US government is urging a lower security standard on the world," he says. But human screens could lead to inconsistencies between companies, says Theresa Lawrence, a health scientist at the US Public Health Service, whose office coordinated the final guidelines. "We want to ensure a consistent baseline that can be uniformly applied across industry," she says.

Some argue that any focus on synthetic DNA and its providers does little to improve security, because it assumes that specific DNA sequences are difficult to obtain. "That framework is appropriate for plutonium, but not for some lousy gene encoded by some lousy pox virus," says Roger Brent, a molecular biologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington. "I can make that by getting a clone from a colleague, or isolating it from nature. I don't need double-stranded DNA to do it." ■

October 2010

What is our strategy for biology security as we sustain incremental improvements in getting better at engineering biology?

- Patience is a virtue (frustrating).

Changing or implementing new policy usually takes a long time. Even the simplest topic to you is likely fascinating and esoteric to >99.9999% others

- More people will be involved than you expect.

Policy involves framing, proposing and implementing tools that scale and shape relationships among parties. Many people tend to get involved and pay attention.

- Both process and product will be unsatisfying.

Limited moves are available for implementing policy (e.g., regulate). All but zero and first-order outcomes v. likely impossible to achieve.

- External drivers and reality matter.

Government systems tend to react. Trying to get a "problem" solved gets you added to a long queue of problems. How urgent is the problem you are bringing, really? If you ask for government action how will it actually get done? Will it be good for anything?

- Intrinsic bias towards enabling research.

Advancing science and tech. mostly seen as essential for future competitiveness. Strong warriness about screwing this up.