

Presidential Commission for the Study of Bioethical Issues

September 14, 2010





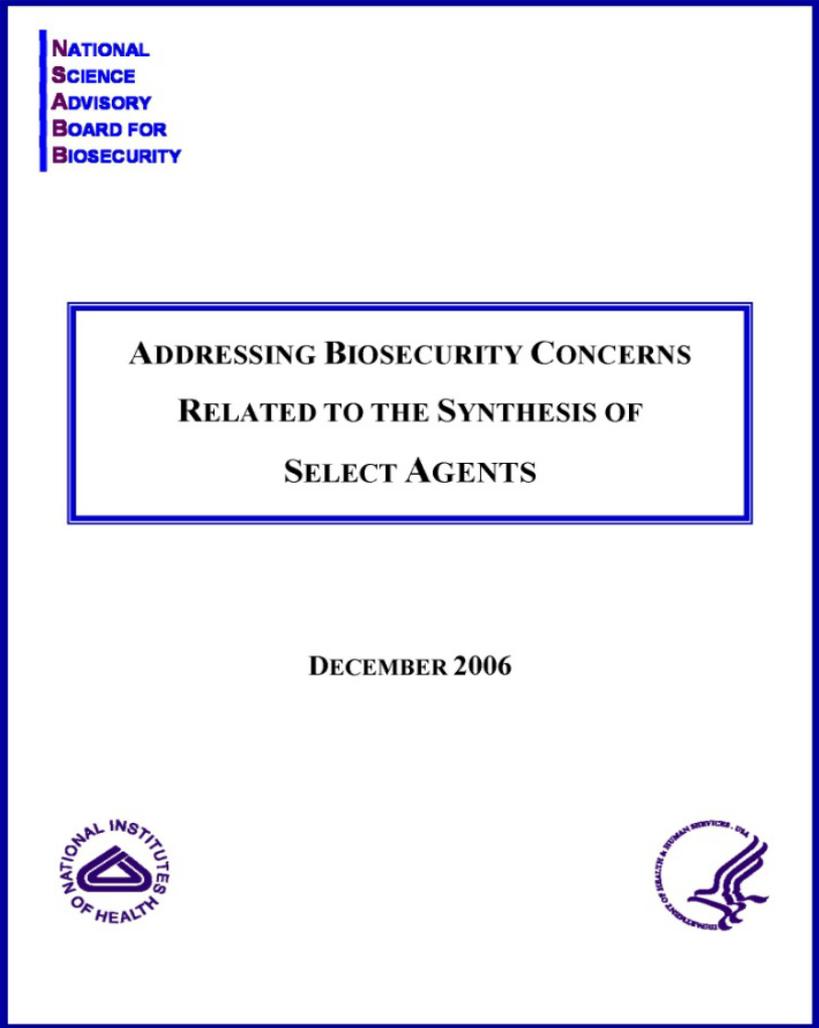
<http://www.genesynthesisconsortium.org>

IGSC Goals and Objectives

- 1) To design and apply a common Protocol to screen both the sequences of synthetic gene orders, and the customers who place them.
- 2) To work together with governments and others concerned to promote the beneficial application of gene synthesis technology, and to safeguard biosecurity.



Industry Collaboration Toward Biosecurity: A Brief History



NSABB Report → Framework Guidance → FBI Reporting Program

- Public Policy Discussion
- Incorporating Guidance into Sequence and Screening Practices
- FBI Reporting Program
 - Visits to IDT and Blue Heron
 - Notification and reporting process now in place

NSABB Report → Framework Guidance → FBI Reporting Program

SYNTHETIC GENOMICS | *Options for Governance*

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October 2007



FOR IMMEDIATE RELEASE

NEW POLICY REPORT OUTLINES OPTIONS FOR GOVERNANCE OF SYNTHETIC GENOMICS

ROCKVILLE, MD, WASHINGTON, DC, and CAMBRIDGE, MA—October 17, 2007— Policy experts from the J. Craig Venter Institute (JCVI), the Center for Strategic & International Studies (CSIS), and the Massachusetts Institute of Technology (MIT) announced today the release of a report, “Synthetic Genomics: Options for Governance,” which outlines areas for interventions and policy options to help mitigate potential risks with this promising area of research. The report, funded by a grant from the Alfred P. Sloan Foundation, resulted from 20 months of in-depth study, review and analysis by the teams above and a core group of 14 experts.

Synthetic genomics is a field of research in which scientists use chemically created pieces of DNA (called oligonucleotides or oligos) to design and assemble chromosomes, parts of chromosomes, genes and gene pathways. Scientists foresee many potential positive applications including new pharmaceuticals and biologically produced, green fuels. However, as with many technologies, there is the potential for misuse and accidents.

The core group set out to analyze the state of the technology in synthetic genomics and to develop a comprehensive set of options for policy makers, researchers, and companies in the field. The report includes options that help to enhance biosecurity, foster laboratory safety, and protect the communities and environment outside of laboratories.

“Designing ways to impede malicious uses of the technology while at the same time not impeding, or even promoting beneficial ones, poses a number of policy challenges for all who wish to use or benefit from synthetic genomics” said Michele Garfinkel, policy analyst at JCVI and lead author of the report. Gerald Epstein, of the CSIS Homeland Security Program and a co-author on the report added, “We have formulated governance options that attempt to reduce security- and safety risks without imposing undue burdens on researchers, industry, or government.”

In addition to Garfinkel and Epstein, the core group was led by Robert M. Friedman of JCVI and Drew Endy of MIT, and convened a series of workshops to hear directly from synthetic genomics researchers, commercial suppliers of synthesized DNA, policy analysts who focus on bioterrorism issues, and those who focus on the legal, ethical, and societal implications of biotechnology. After these workshops, the group developed a preliminary report and offered this for discussion and input at a public meeting held in Washington, DC for policymakers, the media, non-governmental groups and scientists. These interested parties were also invited to submit comments to the authors for potential inclusion into the final report.

The group identified three areas for policy intervention and outlined policy options for each intervention point. Drew Endy noted, “Our report draws upon the perspectives of



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December 3, 2009

**International Gene Synthesis Consortium (IGSC)
Statement on U.S. Government Screening Framework Guidance for
Synthetic Double-Stranded DNA Providers**

Five Member Companies Represent 80 Percent of Worldwide Gene Synthesis Capacity

The IGSC member companies are studying the U.S. government’s draft Screening Framework Guidance for Synthetic Double-Stranded DNA Providers’ with great interest, and we look forward to participating actively in the process of its public consideration. We will provide detailed comment in that forum.

The IGSC welcomes the draft guidance and encourages its final adoption in substance. The guidance is the product of several years’ close consultation between the responsible agencies and the academic, policy, public interest, and gene synthesis communities. That consultation, along with the government’s careful study, has helped to produce practical, useful guidance that all responsible suppliers should apply. We believe that other governments will find it an important model for their own efforts and a strong foundation for international cooperation.

¹ 74 FR 227, 62319 (Nov. 27, 2009). Available at: <http://edocket.access.gpo.gov/2009/E9-28328.htm>

The poster features a dark blue background with white and yellow text. At the top left is the FBI seal, and at the top right is the seal of the FBI Laboratory. The central text reads "FBI Synthetic Biology Conference" and "Building Bridges Around Building Genomes". Below this is a row of three images: a car on a bridge, a DNA double helix, and a city skyline. At the bottom, it states "August 4 - 5, 2009 San Francisco, California" and includes logos for the Department of Health & Human Services, the Department of State, and AAAS.

DEPARTMENT OF JUSTICE
FEDERAL BUREAU OF INVESTIGATION

FBI LABORATORY

FBI Synthetic Biology Conference

“Building Bridges Around Building Genomes”

August 4 - 5, 2009
San Francisco, California

DEPARTMENT OF HEALTH & HUMAN SERVICES

DEPARTMENT OF STATE
UNITED STATES OF AMERICA

AAAS



INTERNATIONAL GENE SYNTHESIS CONSORTIUM (IGSC)

HARMONIZED SCREENING PROTOCOL

Gene Sequence & Customer Screening to Promote Biosecurity

Preamble

This document outlines the standards and practices that IGSC gene synthesis companies apply to prevent the misuse of synthetic genes. By screening the sequences of ordered genes and vetting customers, IGSC companies help to ensure that science and industry realize the many benefits of gene synthesis technology while minimizing risk.

The IGSC companies together represent approximately 80% of commercial gene synthesis capacity world-wide.

1. Gene Sequence Screening

IGSC companies screen synthetic gene orders to identify regulated pathogen sequences and other potentially dangerous sequences.

1. IGSC companies screen the complete DNA sequence of every synthetic gene order against the DNA sequences in a Regulated Pathogen Database, and against all entries found in one or more of the internationally coordinated sequence reference databanks (i.e., NCBI/GenBank, EBI/EMBL, or DDBJ). The IGSC is currently assembling a Regulated Pathogen Database that will include data from all organisms on the Select Agent list, the Australia Group List, and any other national list of regulated pathogens. Until this is deployed, each company is using its own database of pathogen sequences. At a minimum, IGSC companies screen for all pathogen and toxin genes from the US Select Agents and Toxins List and/or from the list specified in paragraphs 1C351-1C354 of European Union Council Regulation 428/2009.
2. IGSC companies translate all six reading frames of each synthetic gene into an amino acid sequence. This sequence is screened against the protein sequences derived from the databases described above.

Harmonized Screening Protocol



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WORLD'S TOP GENE SYNTHESIS COMPANIES ESTABLISH TOUGH BIOSECURITY SCREENING PROTOCOL

*Form International Gene Synthesis Consortium (IGSC)
 to Coordinate Best Practices in Risk Reduction*

Five Member Companies Represent 80 Percent of Worldwide Gene Synthesis Capacity

Washington D. C., November 19, 2009—Five of the world's leading gene synthesis companies today announced agreement that they will apply a common screening protocol to promote biosecurity in the gene synthesis industry. By screening the sequences of synthetic gene orders and the customers who place them, the companies aim to support government efforts to prevent the misuse of gene synthesis technology. Blue Heron Biotechnology, DNA2.0, GENEART, GenScript and Integrated DNA Technologies together represent approximately 80 percent of the global gene synthesis capacity. They have formed the International Gene Synthesis Consortium (IGSC) to coordinate ongoing best practices development and to work together with government and others concerned to promote the beneficial application of gene synthesis technology and to safeguard biosecurity.

"We are proud to announce the formation of the International Gene Synthesis Consortium and equally proud of the commitment to the secure and safe synthesis of DNA it demonstrates," said John Mulligan, Founder and CSO of Blue Heron Biotechnology. "The depth and breadth of expertise in gene synthesis represented by the participating companies, in concert with our dedication to policy based on sound science and thoughtful leadership, will enable us to shape the growth of a safe gene synthesis industry poised to help address the technological needs of the 21st century."

"Safety and security are a chief priority for all of the IGSC companies, as the growth of the gene synthesis industry depends on an impeccable safety record. Each of the founding companies has demonstrated a strong commitment to the safe delivery of synthetic DNA by implementing strong internal biosecurity practices," said Dr. R. Wagner, CEO and CSO of GENEART. "We hope that the IGSC will help to encourage effective collaboration with government and policy organizations and promote internationally consistent approaches to safety and security in gene synthesis."

"Each of the IGSC companies have worked over the past several years to implement internal sequence and customer screening processes, while contributing to the larger conversation amongst government agencies, policy organizations and the broader scientific community about developing an internationally coordinated approach to biosecurity," said Nick Yan, Vice President, Marketing of GenScript USA. "Recognizing that achieving real gains in biosecurity requires harmonization of screening and practices, we have drafted a harmonized screening protocol and decided to form IGSC in an effort to coordinate ongoing work toward shared best practices in the gene synthesis industry."

The IGSC's "Harmonized Screening Protocol for Gene Sequence & Customer Screening to Promote Biosecurity" establishes the five core components that each IGSC member will apply to promote the safe use of synthetic genes:

- **Gene Sequence Screening:** The complete DNA sequence of every synthetic gene order is to be screened against a Regulated Pathogen Database developed by the consortium and one or more of the internationally coordinated sequence reference databanks (i.e., NCBI/GenBank, EBI/EMBL or DDBJ). Amino acid sequences of possible translation products for each synthetic gene ordered also be screened.
- **Gene Customer Screening:** A complete and thorough screening of each synthetic gene synthesis customer will be conducted to establish identity and clear the delivery of genes ordered, in accordance with national guidelines. The screening protocol assigns special considerations to the ordering of Select Agent genes.

- **Record Keeping:** The IGSC companies will keep all screening, customer and order records for at least eight years.
- **Order Refusal & Reporting:** IGSC companies reserve the right to refuse to fill any order and to notify authorities upon identifying potentially problematic orders, coordinating efforts with local and national law enforcement and intelligence agencies.
- **Regulatory Compliance:** IGSC companies comply with all applicable laws and regulations governing the synthesis, possession, transport, export and import of gene synthesis and other products.

"Gene synthesis is the technology driver that will enable research institutions, companies and even individuals or small teams of scientists to develop solutions to the great challenges of our age, such as climate change, world hunger and pandemic disease. Gene synthesis itself provides us with powerful new opportunities to combat the threat of bioterrorism," said Jeremy Minshull, president of DNA2.0. "We won't tolerate attempts to misuse gene synthesis technology to threaten the safety of any community. We scrutinize our orders to ensure that our customers are using our products for their potential benefits."

"The founding companies of the IGSC have been working hand-in-hand with government and with the greater community of scientists and policy advocates to share our expertise in gene synthesis and to help us all devise the most effective biosecurity practices," said Damon Terrill, Senior Vice President & General Counsel for International Legal and Regulatory Affairs for Integrated DNA Technologies. "For over three years, that collaboration has included close consultation with the Federal Bureau of Investigation and the Departments of Homeland Security and State, as well as with governments in Europe, especially. We encourage all companies who conduct gene synthesis to adopt the IGSC's approach to sequence and customer screening, and we invite any company with significant business in gene synthesis to join us in the effort."

About the IGSC

The International Gene Synthesis Consortium (IGSC) represents the gene synthesis industry. For more information please visit www.genesynthesisconsortium.org.

What's Next?

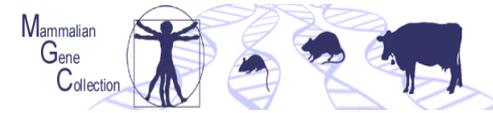
- Improve sequence screening methods and tools
- Incorporation of U.S. Screening Guidance into Protocol
- Participate in policy development and resource discussion
 - Centrally curated sequence database for screening?
 - Grant conditionality?
 - Funding support for screening software?



**Balanced Discussion to
Take Advantage of the
Opportunities and
Minimize Risks**

Projects of Public Interest (selection)

US National Cancer Institute (NCI/NIH): *Mammalian Gene Collection completed*



All human genes available: *optimized for expression in E.coli and mammalian cells*



Wellcome Trust Sanger: *Genes involved in hereditary and infectious diseases*

Big Pharma: *Mutanome, Kinasome, Secretome*



Morphosys: *Platinum library for antibody display*



Bacterial genome synthesis: *Mycoplasma sp., others*

Provision of viral genes in emergency scenario: *H1N1 Influenza*

Contribution to Public Research Clusters (NIH, BMGF, EU):
e.g. SynBio, vaccine development, new pharmaceuticals



Bioinformatics

BioSafety

BioSecurity

„Gene Technology Law“



www



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Country check
Customer check

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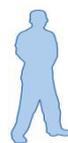
Sales Team
(17)



BLAST
A

Sequence check
Sequence Host
Sequence Function

(9 PhDs)
molecular
biologists



ok?



critical
sequence list
(AG list, CDC)

ok?



FedEx

atlas



Customs regulation
Export control
Documentation
Surprise visit

A: automated
M: manual

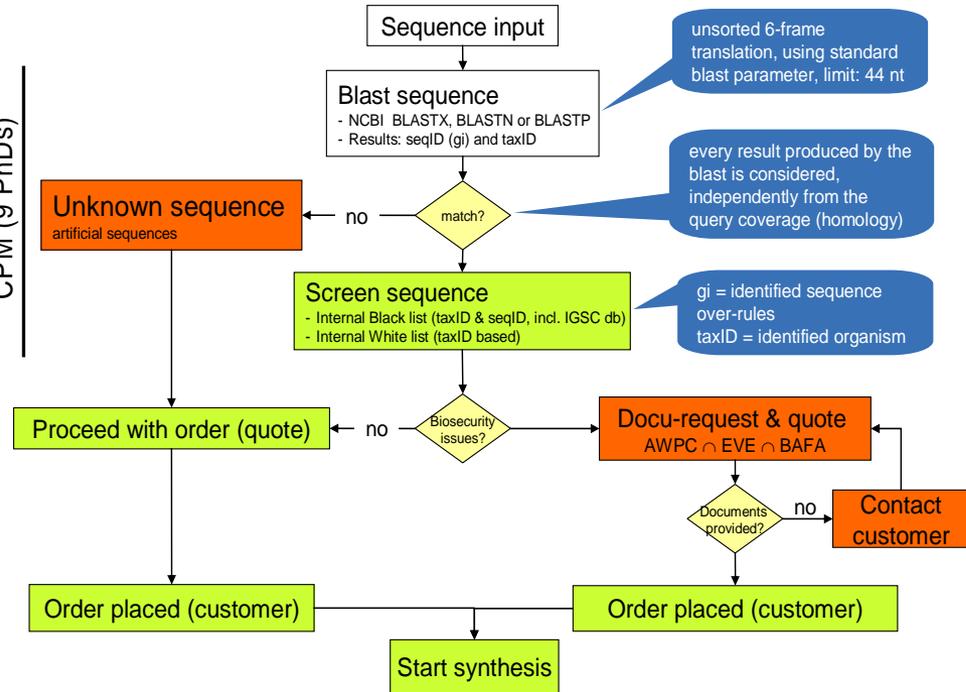
keep customer & sequence data

Sequence Evaluation Process – *in practice*

Work & information flow

User-interface

Rules:



Relevant information

graphical overview alignments

best blacklist hit **best white list hit**

tabular overview alignments
 color coded biosecurity results
 (red: blacklist hit; green: white list hit)

biosecurity evaluation result

No.	UnrefSeq	Accession	Organism	Accession	Hit Len	Ident. %	GI
1	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
2	g 912735489	Escherichia coli	Island DNA polymerase	AF_193300	528	100	912735489
3	g 311235789	Escherichia coli	DNA polymerase	AF_204432	528	100	311235789
4	g 311183263	Escherichia coli	DNA polymerase	AF_204432	528	100	311183263
5	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
6	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
7	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
8	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
9	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
10	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
11	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
12	g 123456789	Shigella boydii	DNA polymerase	AF_110195	528	100	123456789
13	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789
14	g 123456789	Escherichia coli	DNA polymerase	AF_204432	528	100	123456789

high similarity to sequence from white list organism (>90%) → non pathogenic

Need Guidance / Open Questions

Technical advising from Synthetic Biology experts

- Uniform screening practice / ~criteria
- Australian Group List names only organisms, not sequences
- Definition of „*genes associated with pathogenicity*“ leaves room for interpretation
- Definition of “Match” is central for sequence evaluation

A screening database that is continually updated

- Ideally maintained by the U.S. Government / EU and international organizations
- Most complete, updated & classified

Internationally harmonized list of suspicious persons & organizations

- User certification (?)

Need Guidance / Open Questions

- Can deliver botulinus toxin genes within Europe, but can not sent Dengue Env to Novartis Switzerland or NIH US
- What's the consequence of a „hit“ for shipment in Europe
- How can export limitations to institutions such as e.g. delivering genes from EU to NIH be overcome (e.g. for the case of an epidemic)
- **Central role of customer and customer screen**

Ways to Bypass US/EU Based Gene Synthesis Companies

- Can order oligonucleotides @ oligo firms
- Synthesize oligonucleotides on purchased synthesizer (new or used) or on synthesizer that was built according to construction plans available via internet
- Oligos assembled via published technologies
- Synthetic genes ordered from Non-US / Non-EU based companies
- Use conventional genetic engineering
- Isolate harmful species from natural habitats and cultivate
- **Customer screen / identification as important as sequence screening**



**Balanced Discussion to
Take Advantage of the
Opportunities and
Minimize Risks**

Thank You

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