NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

Working Group on Synthetic Genomics: Progress Report

David Relman, M.D., Chair

NSABB Meeting July 13, 2006

Working Group Roster

Voting Members	Federal Representatives
Judge Susan Ehrlich Claire Fraser-Liggett, Ph.D. John Gordon, GEN. USAF (Retired) Michael Imperiale. Ph.D. Adel Mahmoud M.D., Ph.D. David Relman, M.D. Harvey Rubin, M.D., Ph.D. Thomas Shenk, Ph.D.	Jason E. Boehm (OSTP) Kenneth A. Cole (DOD) Jerome Donlon (HHS) Maria Giovanni (NIH) Susan D. Haseltine (DOI) Mark Hemphill (CDC) Maryanna Henkart (NSF) Stuart L. Nightingale (HHS) Tanuja Rastogi (DOS) Caird E. Rexroad (USDA) Scott Steele (DOJ) David G. Thomassen (DOE) Vincent Vilker (DOC) Ronald A. Walters (Intel. Com.)

Charge

Phase 1: Examine the potential biosecurity concerns raised by synthesis of Select Agents (SA)

- **Assess the adequacy of the current regulatory and oversight framework**
- **Recommend potential strategies to address any biosecurity concerns**

Phase 2: Identify, assess, and recommend strategies to address potential dual use concerns that may arise from work being performed in the nascent field of synthetic biology.

Current Status

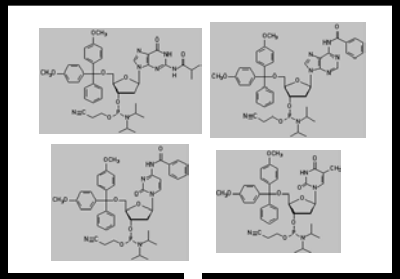
The Working Group (WG) is nearing completion of Phase 1 of its charge. To date, the WG has:

- **Assessed current, key controls for Select Agent genetic material;**
- **Identified potential biosecurity concerns; and**
- **Considered possible strategies for addressing these concerns.**

Scope of Deliberations

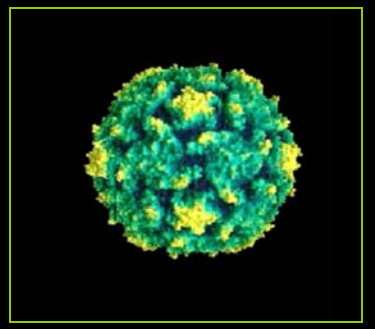
Current Oversight Framework

Starting Material



Synthesized DNA

Recovered Virus



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Sequence Data

Technological Capability

State of Science

Presentations & Panel Discussion

Panelists & Key Issues

Issue	Presenter
Scope of Select Agent Rules: genetic materials regulated	Mark Hemphill CDC
Current technological capability to synthesize DNA	John Mulligan, Ph.D. Blue Heron Biotechnology
State of the science for the recovery/reconstruction of Select Agent viruses from synthetic DNA	Ralph Baric, Ph.D. UNC Chapel Hill

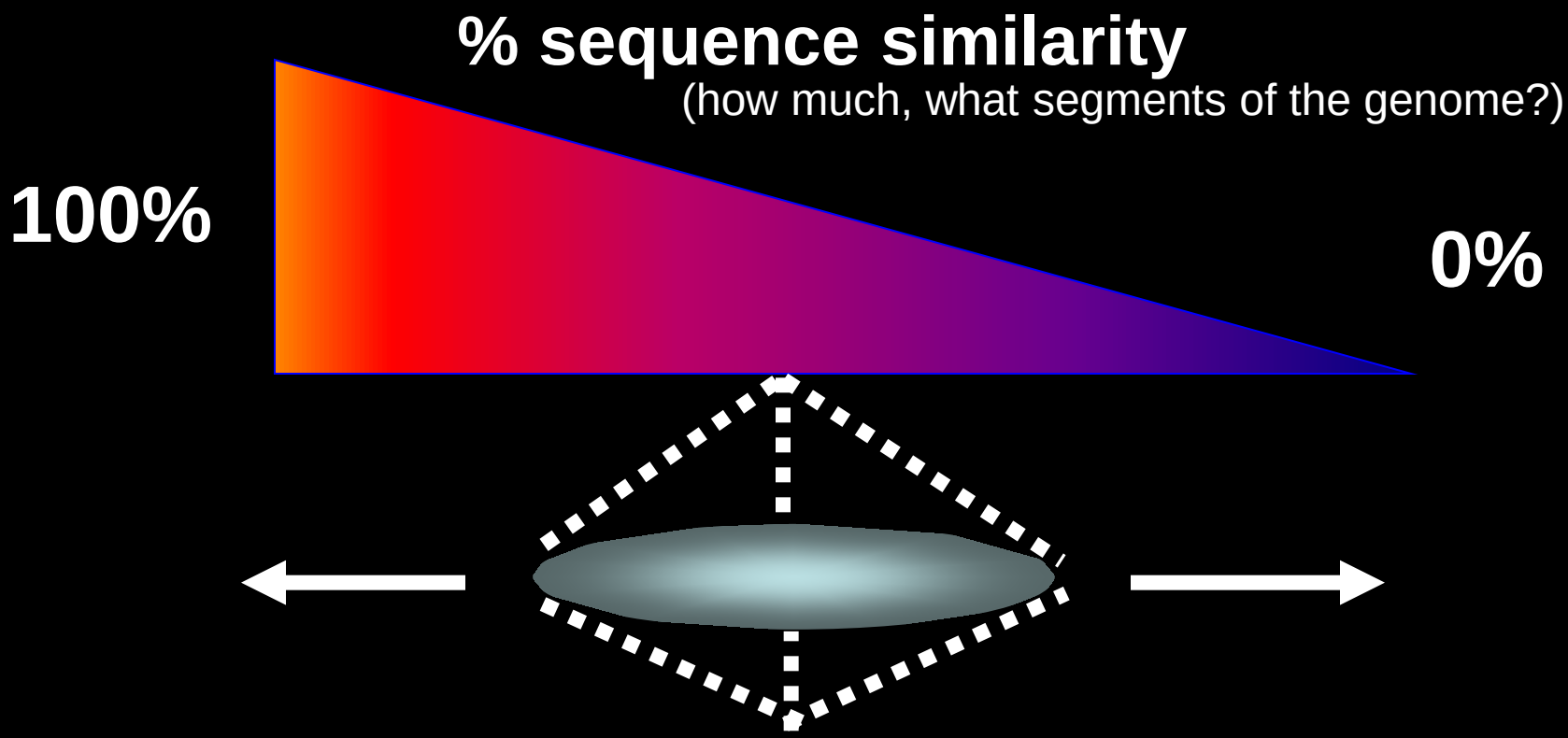
Findings, Concerns, Issues

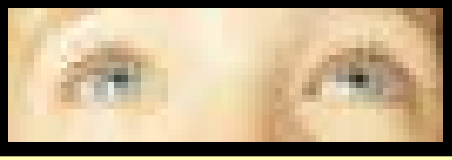
Relevant Oversight Mechanisms

The WG identified the following components of the oversight framework for Select Agents (SA) to be relevant to the control of synthetic SA nucleic acids:

- **Select Agent Rules (SAR)**
- **Export Controls (Commerce Control List)**
- **18 USC 175c (Variola amendment)**
  - **[18 USC 175 (Prohibitions with respect to biological weapons)]**

Challenges in Defining a Select Agent on the Basis of its Genetic Sequence





Attributes of Select Agents

Biosecurity Concerns

- **Synthetic genomics enables the synthesis and production of a SA by nontraditional means, perhaps bypassing HHS/USDA review**
- **It is possible to develop and produce agents that resemble, and have the attributes of specific Select Agent(s), without being clearly identifiable as SA based on their sequence**

Biosecurity Concerns (Con't)

These concerns arise from scientific advances and current industry practices, and highlight several associated issues and challenges:

- **Ease of acquisition of synthetic SA nucleic acids**
- **Need for additional regulatory clarity in specific areas**
- **Difficulty in developing a suitable regulatory framework**
- **Need for consensus among scientists regarding preferred approach and methods for screening sequences and identifying/defining SA**
- **Ability to construct new pathogens; need to re-consider effectiveness of current approach, possible alternatives**

Issue: Ease of Acquisition of Synthetic SA Nucleic Acids

- **Individuals versed in, and equipped for routine methods in molecular biology can use readily available starting material and procedures to derive some SA *de novo***
- **Screening orders is not a standard practice among vendors**

Issue: Need for Additional Regulatory Clarity in Specific Areas

- **The preamble of the SAR notes that it is incumbent on entities that manufacture "substances" to "know what they are manufacturing" and to ensure that they comply with the SAR**
- **However, the regulations do not currently contain provisions that explicitly require genome service providers to screen the sequences of ordered synthetic DNA**
- **Therefore, orders for regulated Select Agent nucleic acids may evade detection**

Issue : Difficulty in Developing a Suitable Regulatory Framework

The SAR do not provide precise definitions for nucleic acid covered under the Rules. But developing precise definitions will be challenging given that…

- **there are many possible genetic alterations to the sequence of an SA that would still lead to expression of an agent with similar properties**
- **pathogens can be engineered *de novo* with features of known SA, that may not be easily identified as SA (e.g., it is now possible to build pathogens using combined genetic material of multiple SAs)**
- **our ability to predict function and behavior of an agent from its genetic sequence is inadequate**

Issue: Need for Scientific Consensus

- **Although some DNA synthesis providers screen orders against known sequences, including those of pathogens (such as SA), there is no optimized, standardized, or agreed-upon method for screening**

Issue : Construction of New Pathogens

Synthetic Genomics:

- **Allows expression of agents that resemble, and have the attributes of specific Select Agent(s), without being clearly identifiable as SA based on their sequence**
- **Provides or enhances the capability for producing novel agents that pose risks equal to, or greater than those of naturally-occurring SA.**

Principal Conclusions

The language and requirements of existing controls for Select Agents will become increasingly ambiguous because of developments in the field of Synthetic Genomics. Therefore, relevant agencies should:

- **Consider options for refining existing oversight mechanisms**
- **Re-evaluate reliance upon a finite list of agents as the foundation for the oversight framework**

Possible Recommendations

Possible Recommendation: Provide/Promote Outreach & Education

Biosecurity Concern: Ease of acquisition of SA nucleic acids; Need for scientific consensus

Findings: The SAR regulate the use, possession, and transfer of certain SA nucleic acids; however, the methodology for screening sequences relevant to the SAR is complex and currently there are no highly effective standardized procedure(s) for accomplishing this objective.

USG should provide outreach and education for users/providers of synthetically-derived nucleic acids and contribute to the development of best practices--such as standard procedures for ordering, screening, transferring, or using synthetic genomes of SA

Possible Recommendation: Foster International Collaboration

Biosecurity Concern: Ease of Acquisition of SA nucleic acids
Findings**:** Synthetic genomics technology is globally distributed and used by scientists worldwide. Yet, not all countries recognize the dissemination of Synthetic Genomics research and technology as an issue of global biosecurity concern, which could limit the effectiveness of domestically-led strategies.
USG should consider potential international implications of any proposed changes to the current oversight framework and should foster an international dialogue on these issues.

Possible Recommendation: Provide Additional Guidance

Biosecurity Concern: Need for additional regulatory clarity in specific areas
Finding**:** Responsible agencies, affected scientists, and commercial providers differ in their interpretation of key laws, regulations, and policies.
The U.S. Government (USG) should provide additional guidance to users/providers of synthetically-derived nucleic acids on the interpretation of the SARs

Possible Recommendation: Reconcile the SA List and CCL

Biosecurity Concern: Need for additional regulatory clarity in specific areas
Finding**:** The effectiveness of an oversight system relies upon the coordination of activities across agencies sharing the oversight responsibility.
Department of Commerce should continue efforts to reconcile the Select Agent List and the Commerce Control List (CCL)

Possible Recommendation: Re-examine Language of 18 U.S.C. 175c

Biosecurity Concern: Need for additional regulatory clarity in specific areas
Finding**:** The language of the Code allows for multiple interpretations of what is actually covered, and the sequence homology stipulation is arbitrary.
Lawmakers should consider re-examining the language of 18 U.S.C. 175c

Possible Recommendation: Work with Experts to Develop Guidance on SAR

Biosecurity Concern: Difficulty in developing a suitable regulatory framework
Findings**:** The rapid rate of scientific and technological advancements outpaces the development of list-based regulations, whereas policies and best practices can more readily accommodate new breakthroughs.
The relevant government agencies should establish (and work with) a group of experts from the gene synthesis industry and research communities to clarify further the purview of the SAR, in particular, sections 73.3c/73.4c, and develop guidance regarding genetic elements, recombinant nucleic acids and recombinant organisms

Possible Recommendation: Consider a New Framework

Biosecurity Concern: Construction of new pathogens, need for scientific consensus, and difficulty in developing suitable regulatory framework
Findings**:** It is now feasible to produce synthetic genomes that encode novel and taxonomically unclassified agents with properties equivalent to, or "worse" than, current SA
U.S. government agencies should re-evaluate their reliance on an oversight framework that is predicated on a finite list of agents.

Next Steps

- **Continue to engage groups, within and outside of the US government, developing relevant policy options**
- **Finalize recommendations**
- **Write report including recommendations for the Board to review at the next NSABB meeting (October, 2006)**

Questions for Board/ Points for Discussion

- **Are there additional options for recommendations that the Board suggests the Working Group address?**
- **Given the international nature of this field, who are the most appropriate international parties with whom the WG might engage?**