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**NATIONAL SCIENCE ADVISORY  
BOARD FOR BIOSECURITY**

# **Working Group on Synthetic Genomics: Progress Report**

Dr. David Relman, Chair  
NSABB Meeting March 30, 2006



# Background

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The Working Group on Synthetic Genomics was launched on November 22, 2005 to:

- examine the potential biosecurity concerns raised by the laboratory synthesis of Select Agents, and the broader field of synthetic biology; and
- recommend possible strategies to address these concerns.

# Current Task

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Consider the adequacy of the current regulatory framework in view of the ability to synthesize  
Select Agent genes and  
genomes

# Issue

- Reverse genetics allows generation of viable virus from their published sequence.
- Traditionally, viruses are “rescued” from recombinant or cloned DNA, which requires access to natural sources of the agent itself.
- The use, possession, and transfer of Select Agents are tightly controlled, but the availability of DNA synthesis technology presents new concerns, with respect to the laboratory synthesis of Select Agent genomes.

# Approach

To address this issue, the Working Group received briefings (Feb 15, 2006) on

- the extant legal framework for controlling Select Agents;
- current technological capabilities for synthesizing nucleic acids; and
- the state of the science, in a few key application areas, for deriving infectious agents from synthetic nucleic acids.

# Summary of Findings

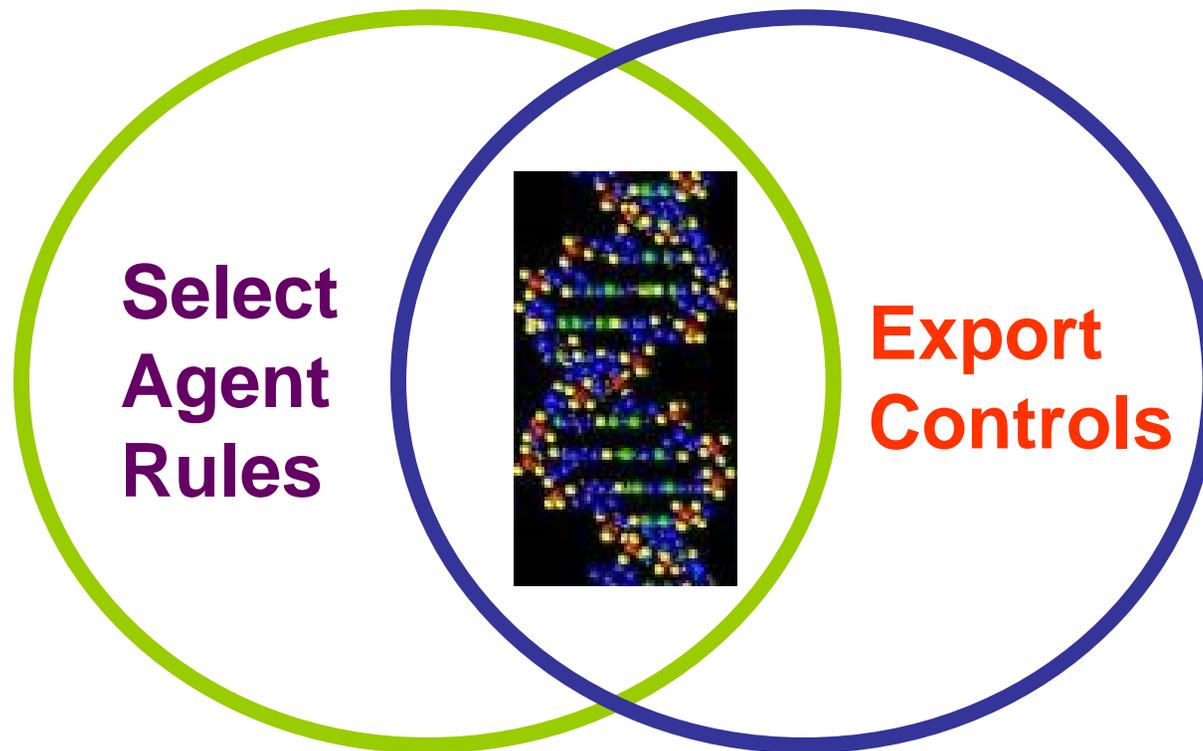
# Legal Framework

- The Select Agent Rules implement the provisions of the USA PATRIOT Act and Public Health Security and Bioterrorism Preparedness and Response Act of 2002.
- These regulations set requirements for possession, use, and transfer of Select Agents and toxins.
  - define regulated agents by organism (name) and their genetic material
- There are additional applicable laws and regulations.



# Key Controls for Select Agent Genetic Material

**Possession, Use and Transfer within U.S.**



**Import into the U.S.**

**Export from the U.S.**

# Synthesis Technology

- Reagents and equipment for synthesizing DNA are readily available, around the globe.
- Synthesizing oligonucleotides up to 120 in length is routine and common; beyond 180 is somewhat of an art.
- Some complete viral genomes can be synthesized at the present time, but not all DNA synthesis companies have this capability.

# DNA Synthesis: Do It Yourself




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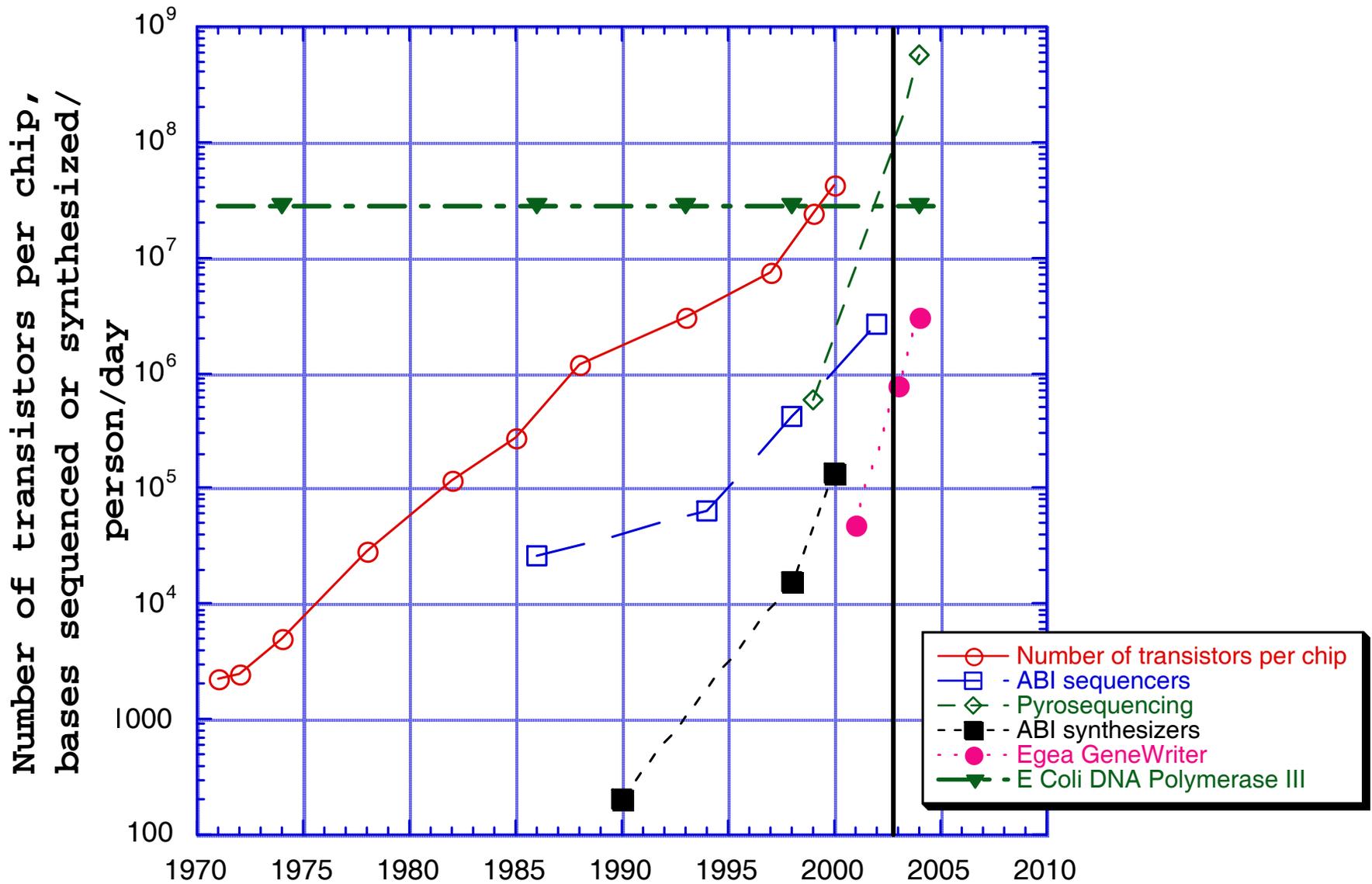
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<input type="checkbox"/>		 <a href="#">ALF Express II DNA Synthesizer Sequencer no reserve</a>		-	\$9.86	<a href="#">Calculate</a>	6d 19h 58m
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<input type="checkbox"/>		<a href="#">AUTOGEN 540 DNA PURIFICATION SYNTHESIZER ISS</a>			\$450.00	Not specified	7d 03h 53m
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<input type="checkbox"/>		<a href="#">Dynatech Laboratory Inc. ML1000 DNA synthesizer</a>			\$799.00	Not specified	11d 13h 05m
<input type="checkbox"/>		<a href="#">QIAGEN AUTOWORK BIO ROBOT 9604 DNA ANALYZER SYNTHESIZER</a>			\$34,999.99	\$249.95	15d 13h 32m
<input type="checkbox"/>		<a href="#">ABI Applied Biosystems 3948 DNA Synthesizer \$5995</a>			\$3,800.00	Not specified	16d 08h 50m
<input type="checkbox"/>		<a href="#">MilliGen / Biosearch 8700 DNA SYNTHESIZER, Lab Bio-Tech</a>			\$495.00	Not specified	18d 15h 03m
<input type="checkbox"/>		<a href="#">DNA oligonucleotide synthesizer PCOS</a>			\$1,999.00	Not specified	26d 09h 37m

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# Comparing the pace of biological technologies and Moore's Law (Robert Carlson, 2003)



# Commercial DNA Synthesis Foundries

Rob Carlson, University of Washington; Gerald Epstein and Anne Yu, CSIS



18 July 05. Method: Rough Google search. Thus not a thorough survey. No academic facilities.

Data Source: Rob Carlson, U of W, Seattle  
[www.synthesis.cc](http://www.synthesis.cc), [rob@synthesis.cc](mailto:rob@synthesis.cc)

## GENE SCREENS

**How 12 companies answered when asked if they screen orders for sequences that bioterrorists could turn into weapons**

<b>BaseClear, Leiden, The Netherlands</b>	<b>Not Routinely</b>
<b>Bio Basic, Markham, Canada</b>	<b>No</b>
<b>Bionexus, Oakland, California</b>	<b>Not Routinely</b>
<b>Bio S&amp;T, Montreal, Canada</b>	<b>No</b>
<b>Blue Heron Biotechnology, Bothell, Washington State</b>	<b>Yes</b>
<b>DNA 2.0, Menlo Park, California</b>	<b>Yes</b>
<b>Entelechon, Regensburg, Germany</b>	<b>Yes</b>
<b>GeneArt, Regensburg, Germany</b>	<b>Yes</b>
<b>Genemed Synthesis, South San Francisco, California</b>	<b>No</b>
<b>GenScript, Piscataway, New Jersey</b>	<b>Usually</b>
<b>Integrated DNA Technologies, Coralville, Iowa</b>	<b>Yes</b>
<b>Picoscript, Houston, Texas</b>	<b>Not Routinely</b>

Adapted from Aldhous, P. "The bioweapon is in the post" *The New Scientist* Issue 2525, 2005.

# State of Science

- It is possible to recover/reconstruct infectious virus from DNA for certain Select Agents (and routine in some laboratories).
  - Successful use of such reverse genetic systems currently requires that one be “skilled in the art”.
- Vaccine researchers have created infectious chimeric viruses using combinations of genomic material from different Select Agents.
  - These novel organisms do not fit into traditional classification schemes
- Scientists have expressed concern that attempts to regulate synthetic genomics may impede scientific progress.

# Preliminary Conclusions

# Genetic/Genomic Material Synthesized *De Novo*

The Select Agent Rules (SAR) regulate:

- **genetic material** that encodes Select Agent toxins, and
- Select Agent **genomic material** that is inherently infectious and capable of producing a Select Agent virus;

regardless of whether this material is obtained via *de novo* synthesis or traditional methods.

## 42 CFR Sections 73.3, 73.4--Final Rule

(c) Genetic Elements, Recombinant Nucleic Acids, and Recombinant Organisms:

(1) Nucleic acids that can produce infectious forms of any of the select agent viruses listed in paragraph (b) of this section.

(2) Recombinant nucleic acids that encode for the functional form(s) of any of the toxins listed in paragraph (b) of this section if the nucleic acids:

(i) Can be expressed *in vivo* or *in vitro*,  
or

(ii) Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.

(3) HHS select agents and toxins listed in paragraph (b) of this section that have been genetically modified.

# Biosecurity Concerns

- The basic concern is that synthetic genomics may enable acquisition of a Select Agent (SA), outside of the SAR.
- This concern emerges from issues pertaining to
  - scientific advances
  - industry practices

# Biosecurity Concerns: Science

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- Individuals versed in, and equipped for routine methods in molecular biology can use readily available starting materials and procedures to express some *SA de novo*.
- This kind of work may not have received adequate attention.
- Synthetic genomics allows the expression of agents that resemble and behave like SA, yet might not be defined as SA based on genome sequence similarity, confounding traditional definitions of agent identity.

# Biosecurity Concerns: Practices

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- Screening of synthesis orders is not a standard practice among vendors of synthetic genes/genomes.
- There is no widely-accepted, optimized methodology for screening ordered sequences.

## 42 CFR Sections 73.3, 73.4--Discussion of Changes (Federal Register 70:13298, 2005)

Commenters asserted that “the government should require that service providers test for Select Agent sequences” before they are made and transferred. The commenters argued that “Although the Select Agent program covers transfer and possession of Select Agents, if DNA synthesis companies do not check the sequences they could inadvertently synthesize and transfer a Select Agent.” We made no changes based on these comments. It is incumbent upon the entities that manufacture substances to know what they are manufacturing and to ensure that they comply with the provisions of the regulations in part 73 and 9 CFR part 121.

# Adequacy of Regulations

Science and technology are rapidly evolving, such that there is a need to

- clarify the legal scope and interpretation of the SAR as they pertain to synthetic genomics;
- deliberate further on the adequacy of the current legal framework controlling select agents; &
- explore a variety of strategies for addressing biosecurity concerns related to synthetic genomics.

# Next Steps

# Points for Further Deliberation

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The WG will consider the need for

- criteria that provide for identification of SA;
- outreach and education to the scientific and business communities, including guidance on their responsibilities under the SAR;
- best practices for DNA synthesis providers; &
- other measures for addressing biosecurity concerns related to synthetic genomics.

# Action Items

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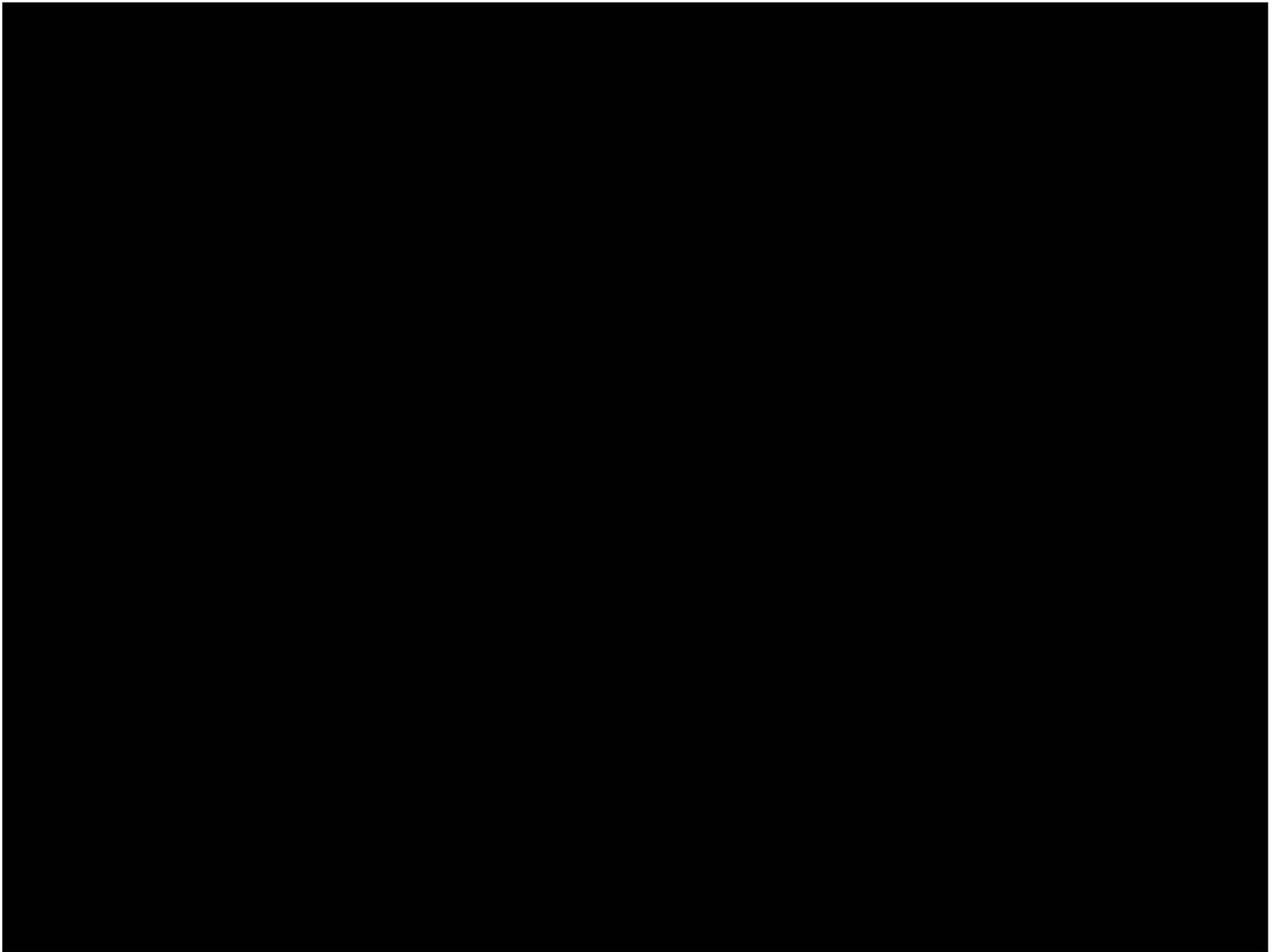
- Collect additional information regarding the biosecurity concerns raised by the synthesis of SA, by engaging
  - additional scientific experts;
  - other groups working on related issues; &
  - relevant international communities.
- Refine preliminary conclusions and develop recommendations to the Board.

# Questions for Board / Points for Discussion

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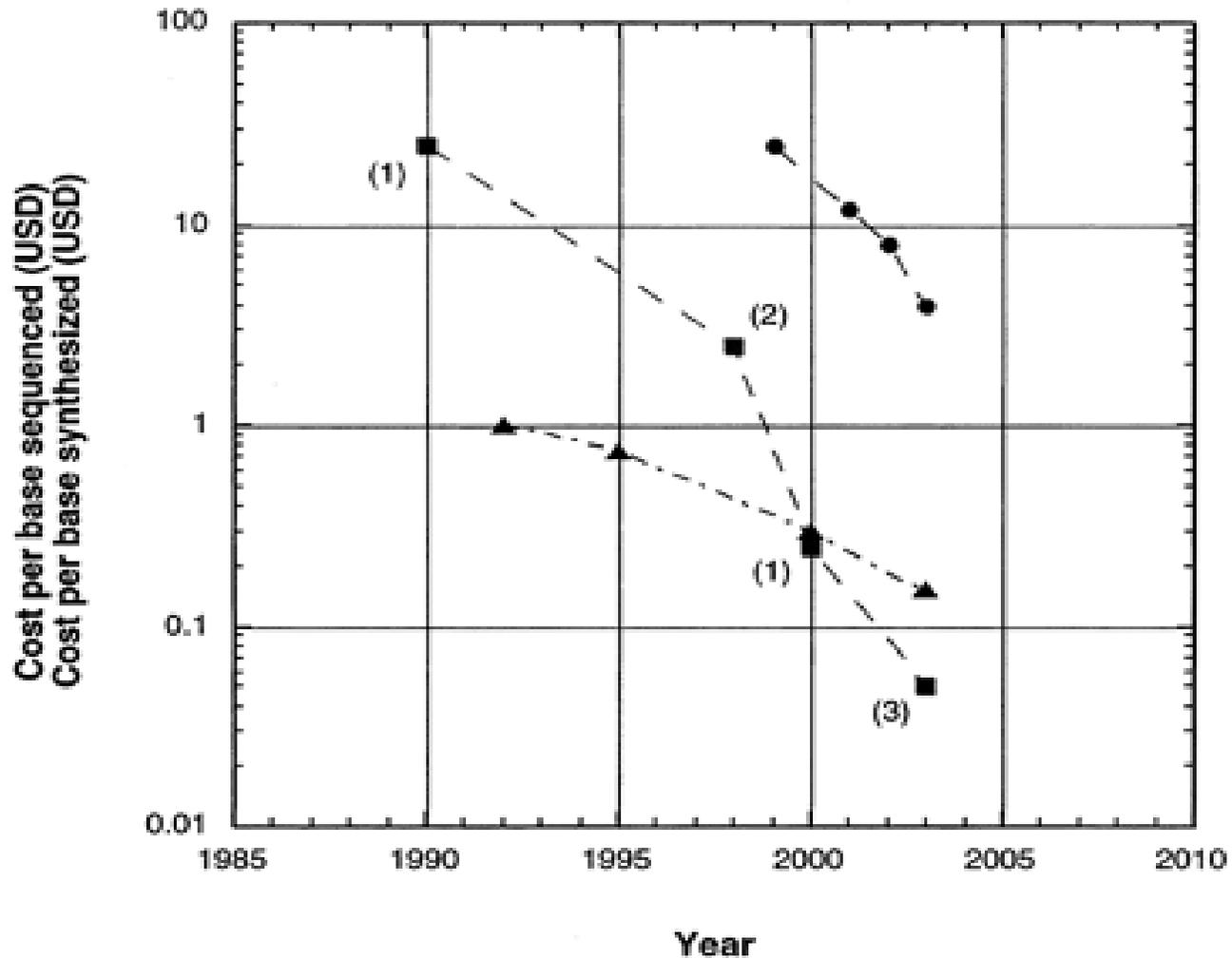
- Given the international nature of this field, what are the most appropriate international parties with whom the WG might engage?
- How do the WG's findings impact the deliberation of other WGs, and vice versa?
- Are there other issues that the Board would like the Working Group to address?



# Optional Slides

- cost per base sequenced
- ▲- cost of short oligo synthesis
- cost of gene synthesis

## Cost Per Base of Sequencing and Synthesis



Carlson, R. "Pace and Proliferation of Biological Technologies",  
*Biosecurity and Bioterrorism* Vol. 1 No. 3, 2003

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● Picoscript, Houston, Texas	Not routinely

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