NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

Working Group on Synthetic Genomics: Progress Report

Dr. David Relman, Chair

NSABB Meeting March 30, 2006

Background

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

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 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.

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NEWS

This Week

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).

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.)

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

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

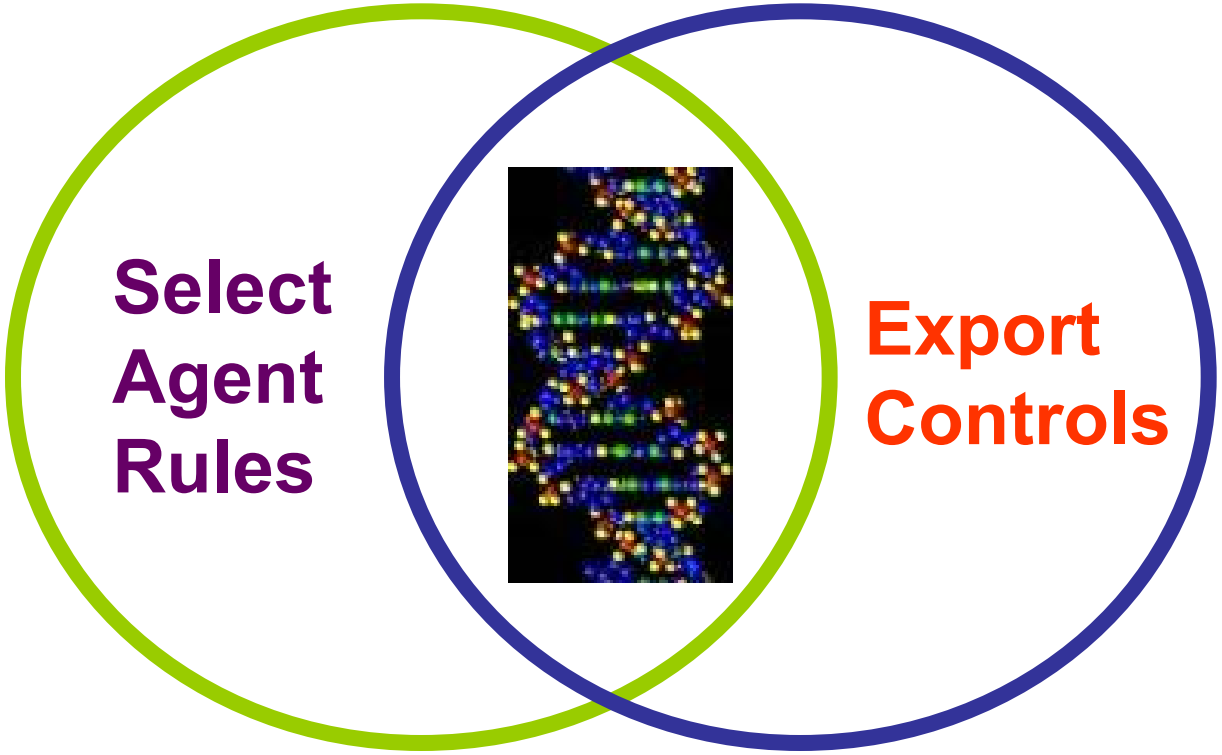
* books.nap.edu/catalog/11240.html

CREDIT: (TOP TO BOTTOM) SCIENCE VOYAGEURS; UNLIMITED; JAMES CATHAY/CDC

- Makes it unlawful to knowingly produce, synthesize, engineer variola virus
- Definition for variola virus includes "any derivative of the variola major virus that contains more than 85% of the gene sequence of the variola major virus or the variola minor virus"

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.
- Complete certain viral genomes can be synthesized at the present time, but not all DNA synthesis companies have this capability.

DNA Synthesis: Do It Yourself

http://www.bioautomation.com/MerMade-384.htm

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	MilliGen / Biosearch 8700 DNA SYNTHESIZER, Lab Bio-Tech	P	Buy It Now or Best Offer	$495.00	Not specified	18d 15h 03m
	DNA oligonucleotide synthesizer PCOS	P	Buy It Now or Best Offer	$1,999.00	Not specified	26d 09h 37m

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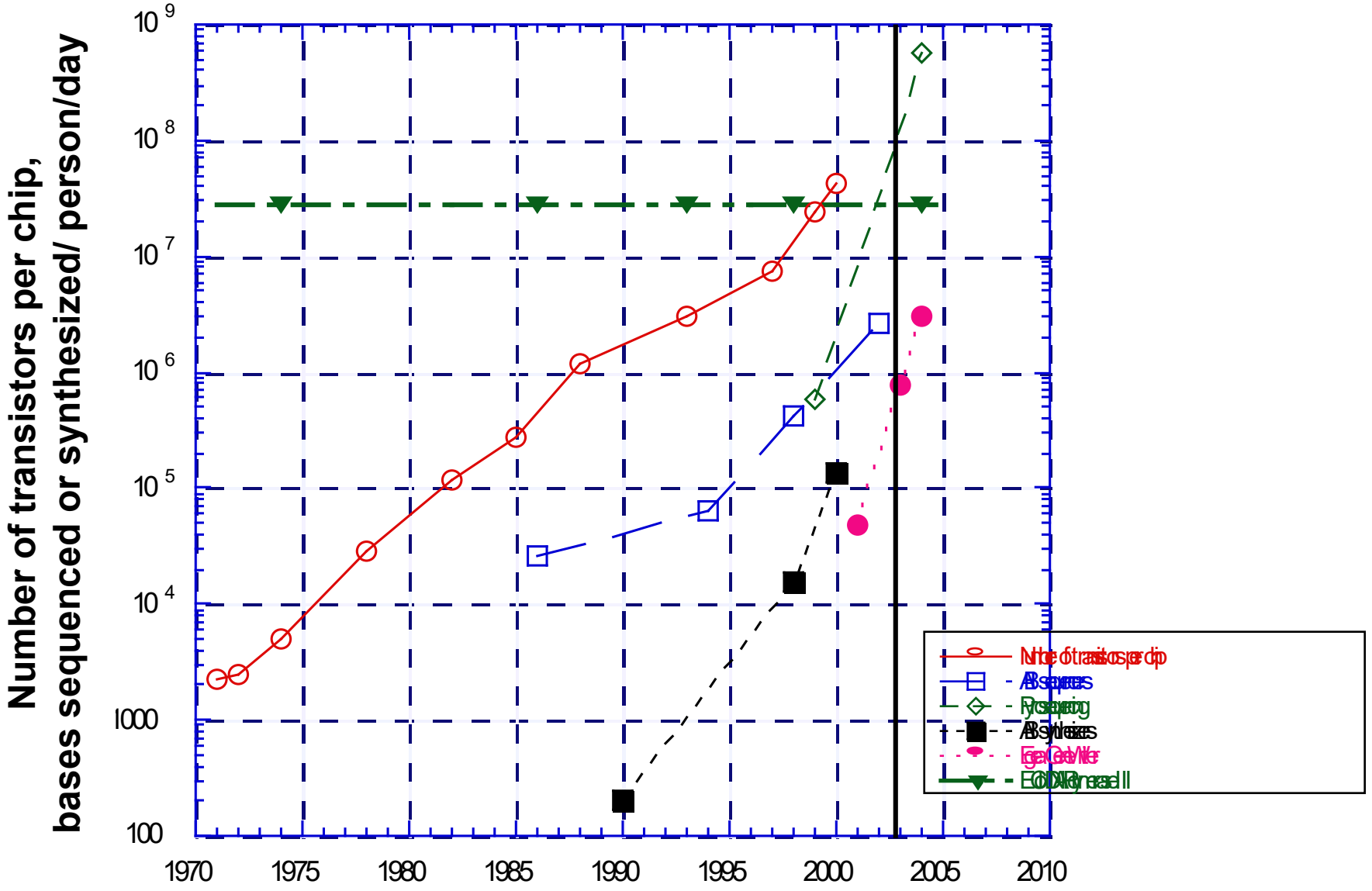
Comparing the pace of biological technologies and Moore's Law (Robert Carlson, 2003)



Biosecurity and Bioterrorism: Biodefense, Strategy, Practice and Science Vol. 1 No. 3, 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, rob@synthesis.cc

GENE SCREENS

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

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

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 various Select Agents.
  - These novel organisms do not fit into traditional classification schemes
- Scientist 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.

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

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: Science

- Individuals versed in, and equipped for, routine molecular biology can use readily available starting materials and procedures to express some SA *de novo.*
- There is a potential lack of adequate attention given to this activity.
- 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

- Screening orders is not a standard practice among vendors of synthetic genes/genomes.
- There is no 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 genomes;
- deliberate further on the adequacy of the current legal framework controlling select agents; and
- explore a variety of strategies for addressing biosecurity concerns related to synthetic genomics.

Next Steps

Points for Further Deliberation

The WG will consider the need for

- criteria for the 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.

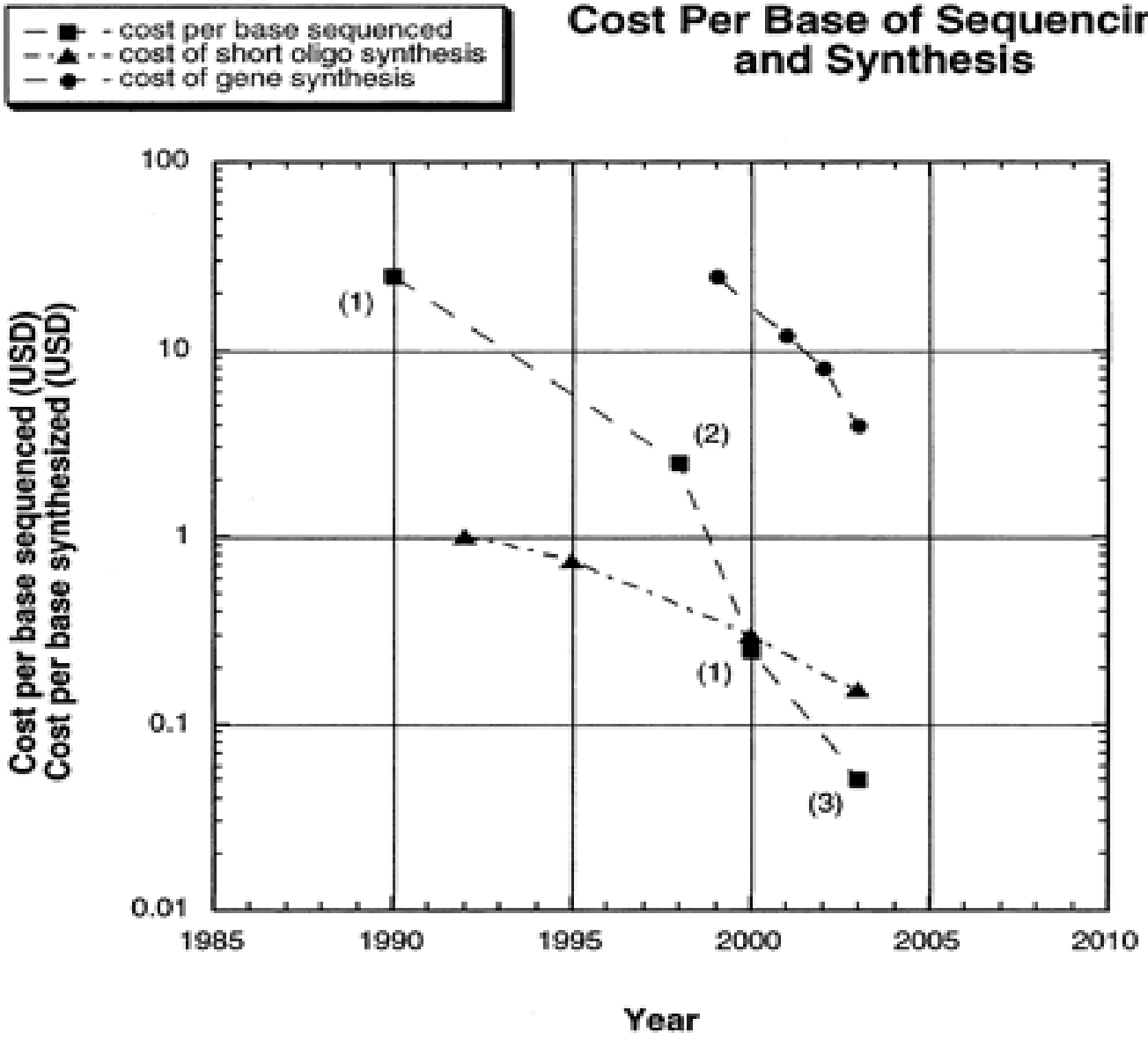
Action Items

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

Questions for Board/Points for Discussion

- Given the international nature of this field, who 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



Carlson, R. “Pace and Proliferation of Biological Technologies”,

Biosecurity and Bioterrorism Vol. 1 No. 3, 2003