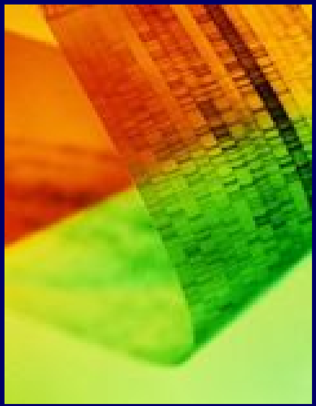
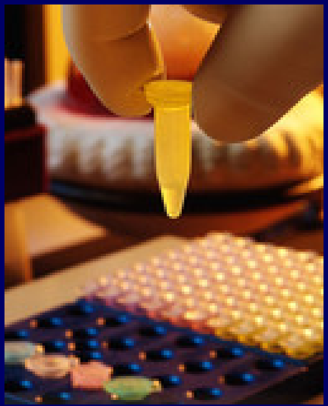
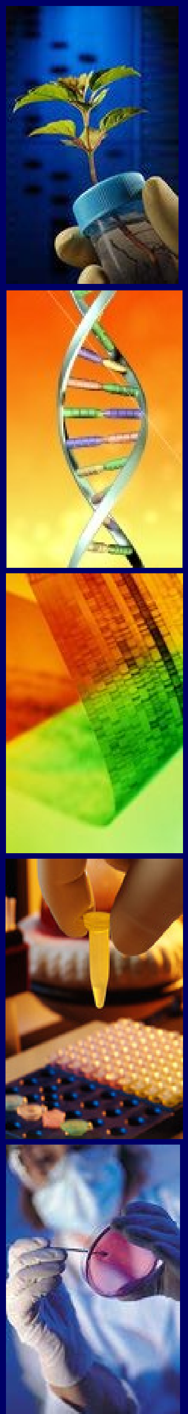
Addressing Biosecurity Concerns Related to Synthetic Biology




David Relman, M.D.

Chair, NSABB Working Group on Synthetic Biology



Charge to NSABB

- Two-part charge
  1. Synthetic Genomics

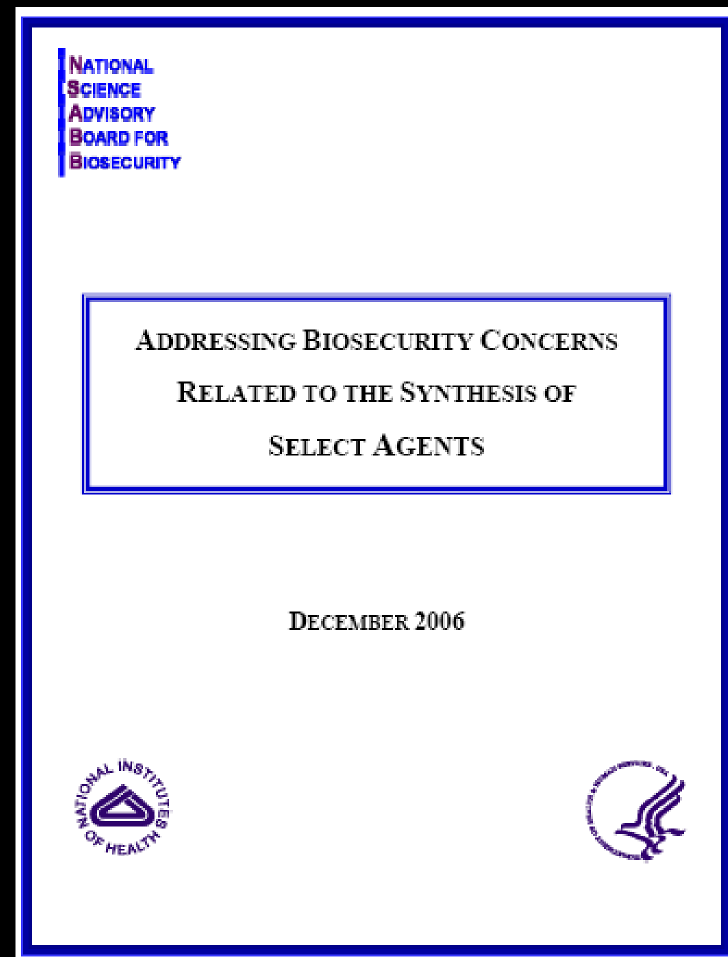
     ...to address whether synthetically derived Select Agents are adequately covered by the current regulatory framework...

  2. Synthetic Biology

     ...to identify, assess and recommend strategies to address any biosecurity or dual use research concerns that may arise from work being performed in the nascent field of synthetic biology

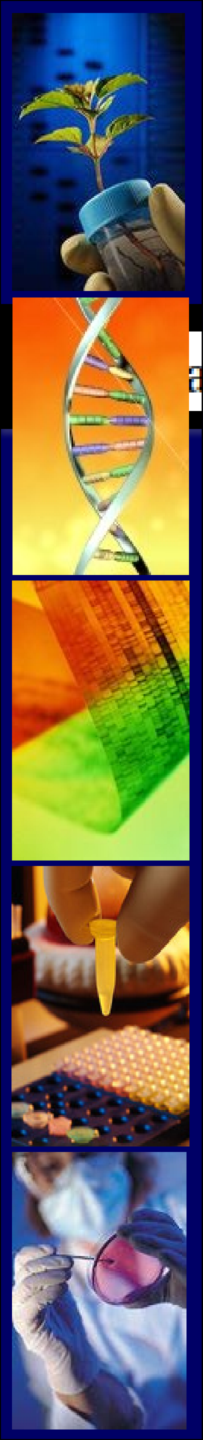
Synthetic Genomics

- NSABB recommended:
  - Development and dissemination of harmonized guidance
  - Development of standards & practices for sequence providers to include nucleic acid screening
  - A review of current biosafety guidelines to ensure that they are adequate for synthetically derived DNA
  - Continued consultation with experts to develop a framework for predicting pathogenicity


National
Science
Advisory
Board for
Biosecurity

Addressing Biosecurity Concerns Related to the Synthesis of Select Agents

December 2006



Recent development

al Register / Vol. 74, No. 227 / Friday, November 27, 2009 / Notices

DEPARTMENT OF HEALTH AND HUMAN SERVICES

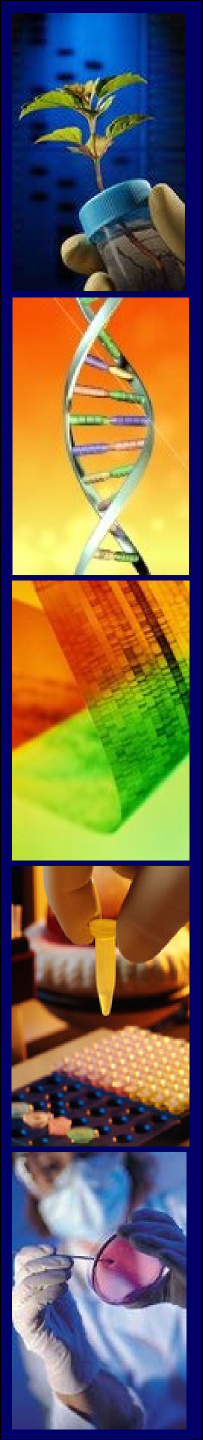
Office of the Secretary

Screening Framework Guidance for Synthetic Double-Stranded DNA Providers

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

ACTION: Notice.

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



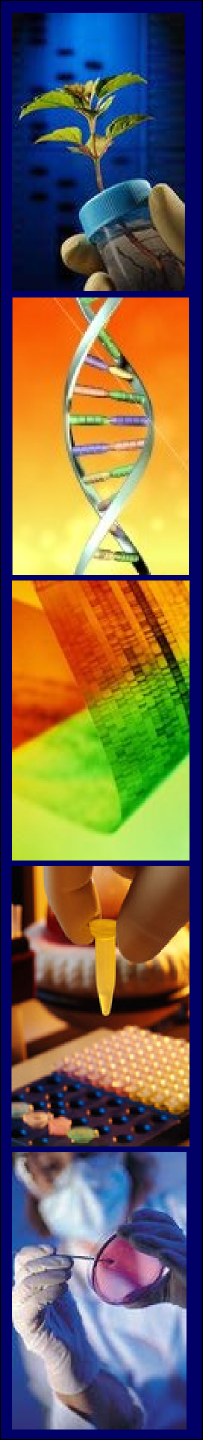
NSABB Working Group on Synthetic Biology

Voting Members

- David Relman (Chair)
- Susan Ehrlich
- Claire Fraser-Liggett
- Mike Imperiale
- Harvey Rubin
- Thomas Shenk

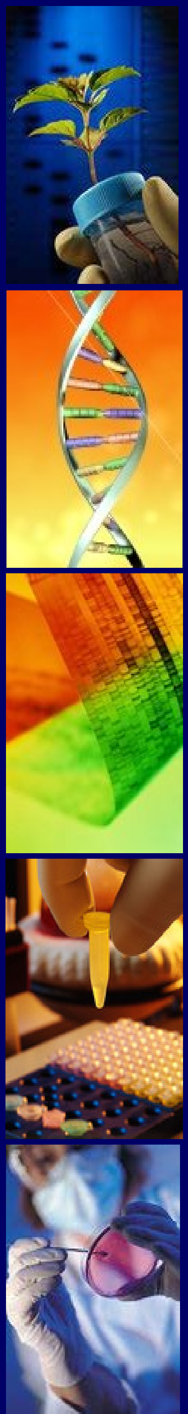
Agency Representatives

- FBI
- OGC
- Department of State
- Department of Defense
- OSTP
- NIH
- Dept. of Homeland Security
- EPA
- USDA
- Department of HHS
- CDC
- Department of Energy
- Intelligence Community



NSABB Approach to Synthetic Biology

- The Working Group considered
  - The potential that information and/or technology stemming from legitimate scientific research might be misused to threaten elements of national security
  - Biosecurity concerns presented by the ability to:
    - Synthesize new genes, metabolic pathways, and/or proteins
    - Design genetic systems and organisms with specified functions
  - Extant oversight frameworks
    - The NSABB's proposed oversight framework for dual use research of concern
    - The *NIH Guidelines for Research Involving Recombinant DNA Molecules*



Scientific Roundtable Hosted by NSABB and RAC (Oct 11, 2007)

- Expertise
  – Synthetic biology
  – Microbiology, immunology, molecular biology
  – Systems biology and bioinformatics
  – Evolutionary biology
  – Engineering, computer science
  – Biosafety
  – Private sector
  – Risk assessment of emerging technologies

- Topics addressed included
  – State of the science of synthetic biology
  – Goals of research in synthetic biology
  – Predicting biological function from sequence
  – Risk assessment and management in the context of uncertainty

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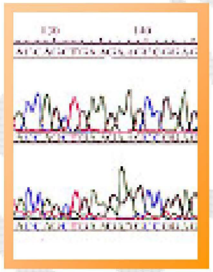
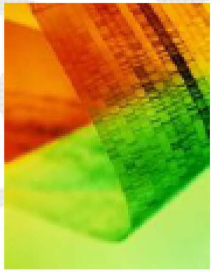
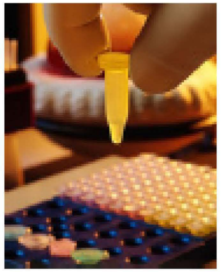
ADDRESSING BIOSECURITY CONCERNS RELATED TO SYNTHETIC BIOLOGY







DRAFT Report of the National Science Advisory Board for Biosecurity (NSABB)

What is synthetic biology?

- The design and construction of new biological parts and devices—including computational devices, and other functional nucleic acid-based structures
- The re-design of existing, natural biological systems for specific purposes, as well as
- The synthesis of self replicating entities from scratch

What is synthetic biology?

- Sometimes referred to as “engineering biology” since it often involves
  - characterizing and simplifying parts of natural biological systems and using them as components of an unnatural, engineered, biological system
  - creating novel biological structures with predictable properties and functions
  - seeking to understand the form and function of living organisms or their products and utilizing them in a predictable and controlled manner

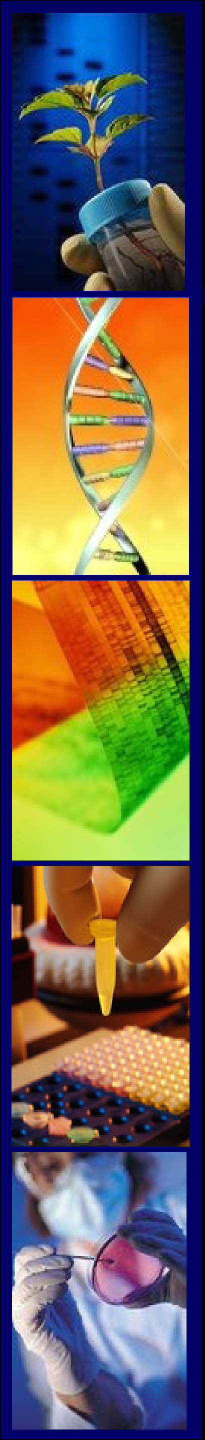
Synthetic biology approaches

Top Down

- Involves the re-engineering of existing organisms or genomes for defined purposes
- Interweaves classical recombinant techniques with increasingly powerful methods for sequencing and synthesizing DNA
- Examples:
  - Metabolic engineering of microbes
  - Genome shuffling

Bottom Up

- Involves assembling non-living biological components into novel systems to perform a desired function
- Predictability is based on an understanding of the fundamental nature of living organisms or biological materials
- Examples:
  - Biofabrication
  - Synthetic organism from scratch



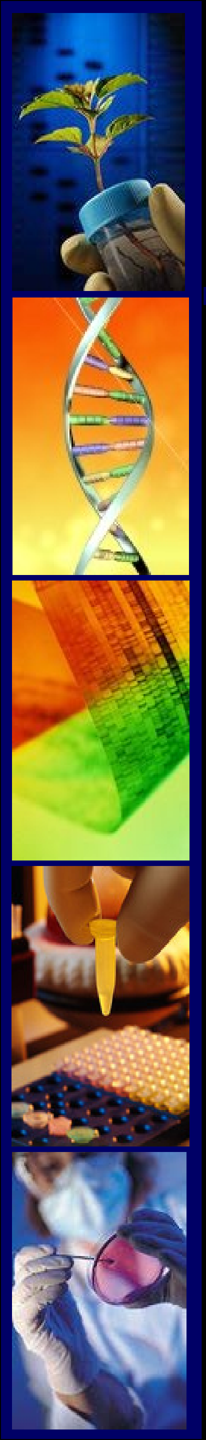
Who are synthetic biologists?

- Highly interdisciplinary
- Researchers from diverse fields
- Practitioners who may not consider their work "biological"
- Practitioners with diverse research aims

- Life scientists
- Engineers
- Chemists
- Computer modelers
- Materials scientists
- "Re-writers"
- Students
- Non-traditional scientists, unaffiliated with universities or institutes
- Private industry

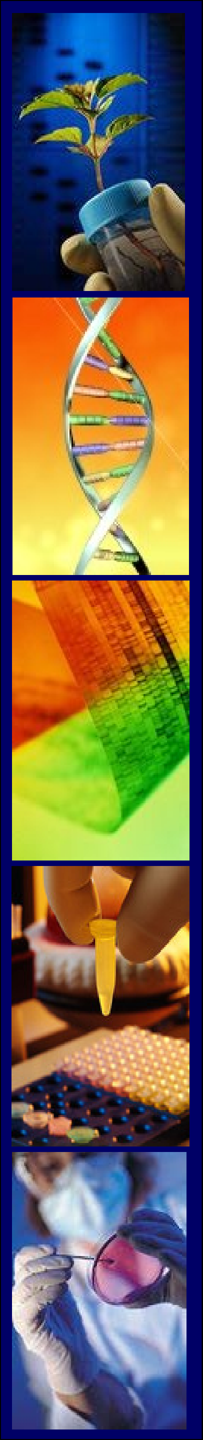
The promise of synthetic biology

- Synthetic biology:
  - A relatively nascent discipline
  - Rapidly evolving
  - Benefits from advances in related fields
- Numerous successes, both proofs of concept and commercial applications
- The more ambitious goals have yet to be achieved



Significant uncertainties

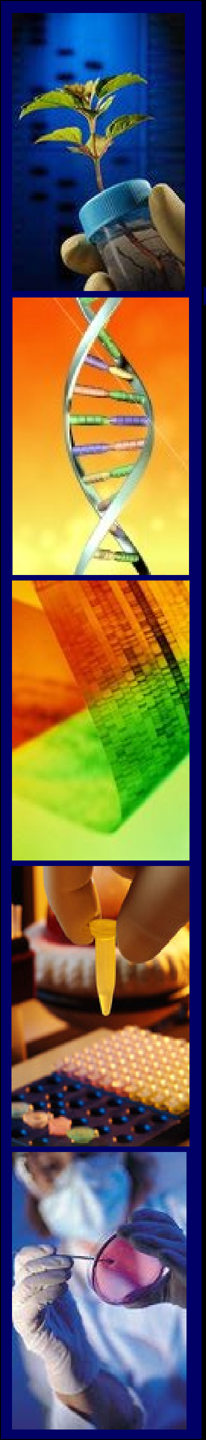
- Synthetic biology is associated with several uncertainties stemming from
  - Present state of the science
  - Rapidly evolving nature of synthetic biology
  - Diverse practitioners attracted to synthetic biology



Predicting biological function

- Synthetic biology relies heavily on the ability to predict biological function from nucleic acid or protein sequence/structure
- State of the science
  - Accurately predicting biological properties from sequence or structure is very difficult
  - A better understanding of how biological context determines function is still needed

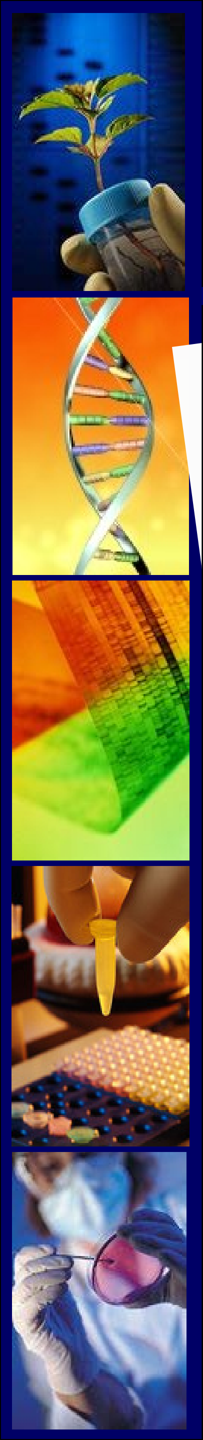
It will continue to be difficult to predict the biological risk of a synthetic entity, especially one that bears little resemblance to natural organisms.



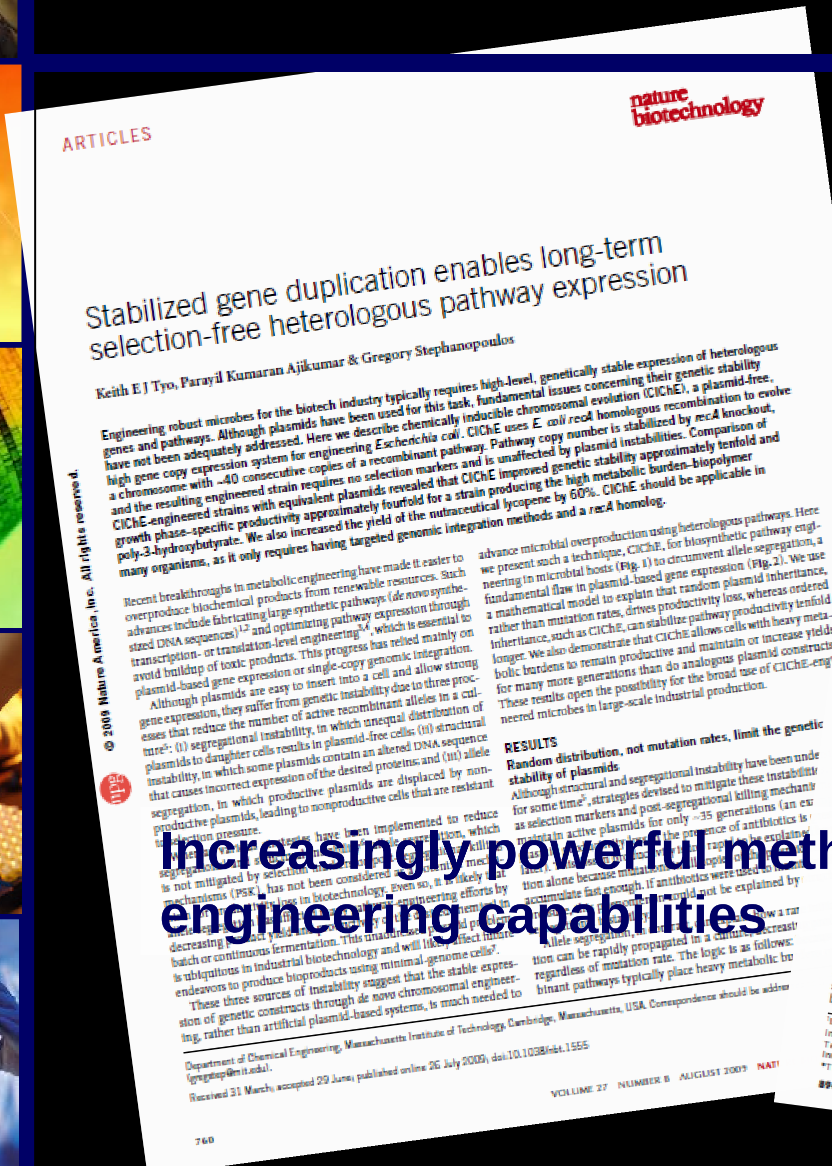
An evolving field

- Science is evolving rapidly
  - Example: Novel genetic modules and functional RNA devices
- Cost is decreasing
  - Example: Massively parallel DNA synthesis and assembly
- Increasing rate at which information is generated
  - Example: >1000 bacterial genomes sequenced

It will remain challenging to predict the new discoveries, information and technologies generated by a rapidly changing field.



An evolving field



ARTICLES

nature biotechnology

Stabilized gene duplication enables long-term selection-free heterologous pathway expression

Keith E J Tyo, Parayil Kumaran Ajikumar & Gregory Stephanopoulos

Engineering robust microbes for the biotech industry typically requires high-level, genetically stable expression of heterologous genes and pathways. Although plasmids have been used for this task, fundamental issues concerning their genetic stability have not been adequately addressed. Here we describe chemically inducible chromosomal evolution (CIChE), a plasmid-free, high gene copy expression system for engineering *Escherichia coli*. CIChE uses *E. coli recA* homologous recombination to evolve a chromosome with ~40 consecutive copies of a recombinant pathway. Pathway copy number is stabilized by *recA* knockout, and the resulting engineered strain requires no selection markers and is unaffected by plasmid instabilities. Comparison of CIChE-engineered strains with equivalent plasmids revealed that CIChE improved genetic stability approximately tenfold and growth phase–specific productivity approximately fourfold for a strain producing the high metabolic burden–biopolymer poly-3-hydroxybutyrate. We also increased the yield of the nutraceutical lycopene by 60%. CIChE should be applicable in many organisms, as it only requires having targeted genomic integration methods and a *recA* homolog.

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RESULTS

Random distribution, not mutation rates, limit the genetic stability of plasmids

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760 VOLUME 27 NUMBER 8 AUGUST 2009 NATURE BIOTECHNOLOGY

nature

LETTERS

Vol 460 | 13 August 2009 | doi:10.1038/nature08187

Programming cells by multiplex genome engineering and accelerated evolution

Harris H. Wang[1,2,3]*, Farren J. Isaacs[1]*, Peter A. Carr[4,5], Zachary Z. Sun[6], George Xu[6], Craig R. Forest[7] & George M. Church[1]

Figure 1 | Multiplex automated genome engineering enables the rapid and continuous generation of sequence diversity at many targeted chromosomal locations across a large population of cells through the repeated introduction of synthetic DNA.

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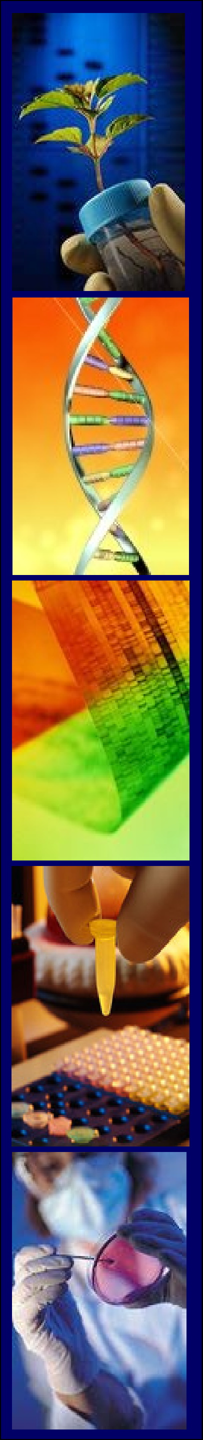
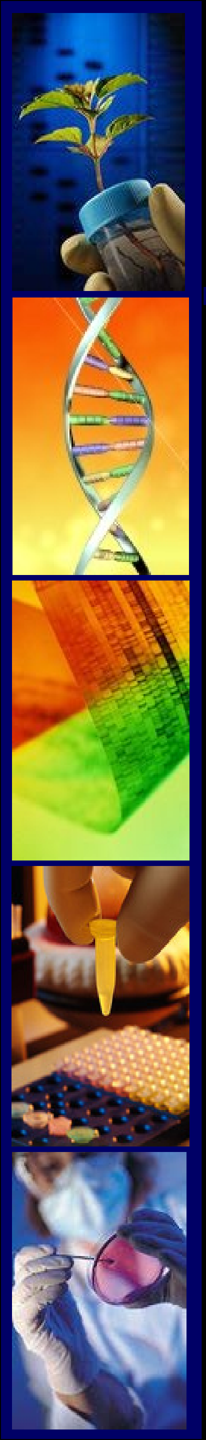
Increasingly powerful methods significantly accelerate re-engineering capabilities



Diverse practitioners, diverse applications

- Synthetic biology is attracting a growing number of diverse practitioners
  - Diverse disciplines and interdisciplinary collaborations
  - Different research interests and goals
    - Discovery-based
    - Application-driven
    - Technology optimization and development
- Diversity is good for the scientific enterprise as it leads to the convergence of expertise and leads to new findings

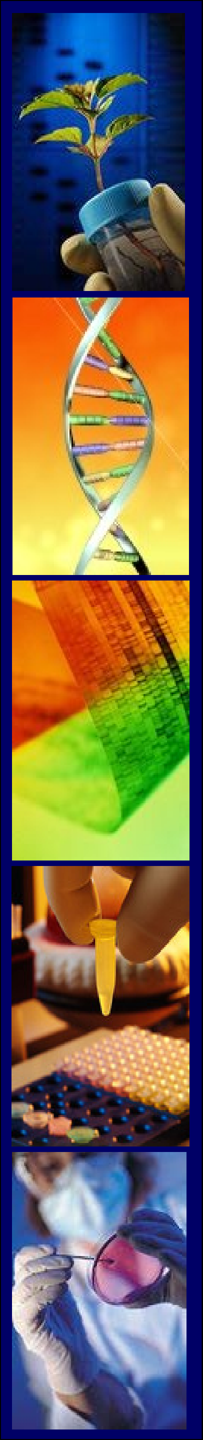


Significant uncertainties

- It is impossible to predict the information, technologies, and new applications that will be developed by, or applied to this relatively new field
- Calls for
  - Greater awareness of biosecurity (and biosafety) risks
  - Pursuit of methods for predicting functions associated with DNA constructs and engineered proteins and organisms

Current oversight paradigms

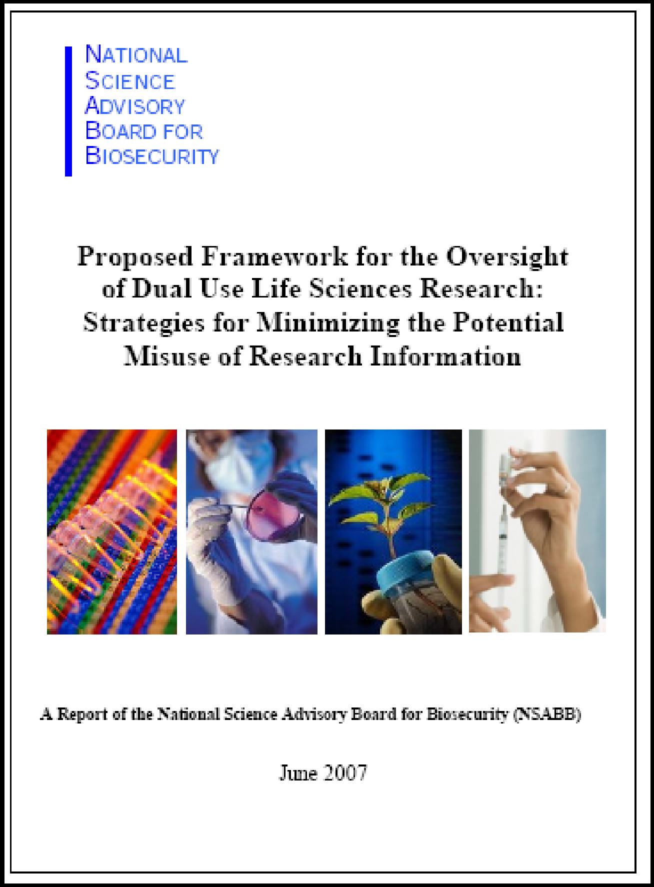
- *NIH Guidelines for Research Involving Recombinant DNA Molecules*
  - Outline principles for safe research with recombinant DNA molecules
  - Detail procedures for handling and containment of genetically modified microorganisms, plants, and animals
  - Institutional Biosafety Committees (IBCs) review research involving rDNA
  - Recombinant DNA Advisory Committee (RAC):
    - Provides in-depth review of scientific, safety, and ethical dimensions of human gene transfer experiments
    - Advises NIH Director on content and implementation of *NIH Guidelines*



Current oversight paradigms

- Proposed updates to the *NIH Guidelines* address synthetic biology by including nucleic acid molecules made by synthetic means
- The RAC has found that
  - In most cases, research with synthetic nucleic acids presents biosafety risks that are comparable to recombinant DNA research
  - Current risk assessment framework can be used to evaluate synthetically produced nucleic acids
  - Safety issues surrounding synthetic nucleic acids will likely need to be revisited in the near future since the field is evolving so rapidly

Current oversight paradigms



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Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information

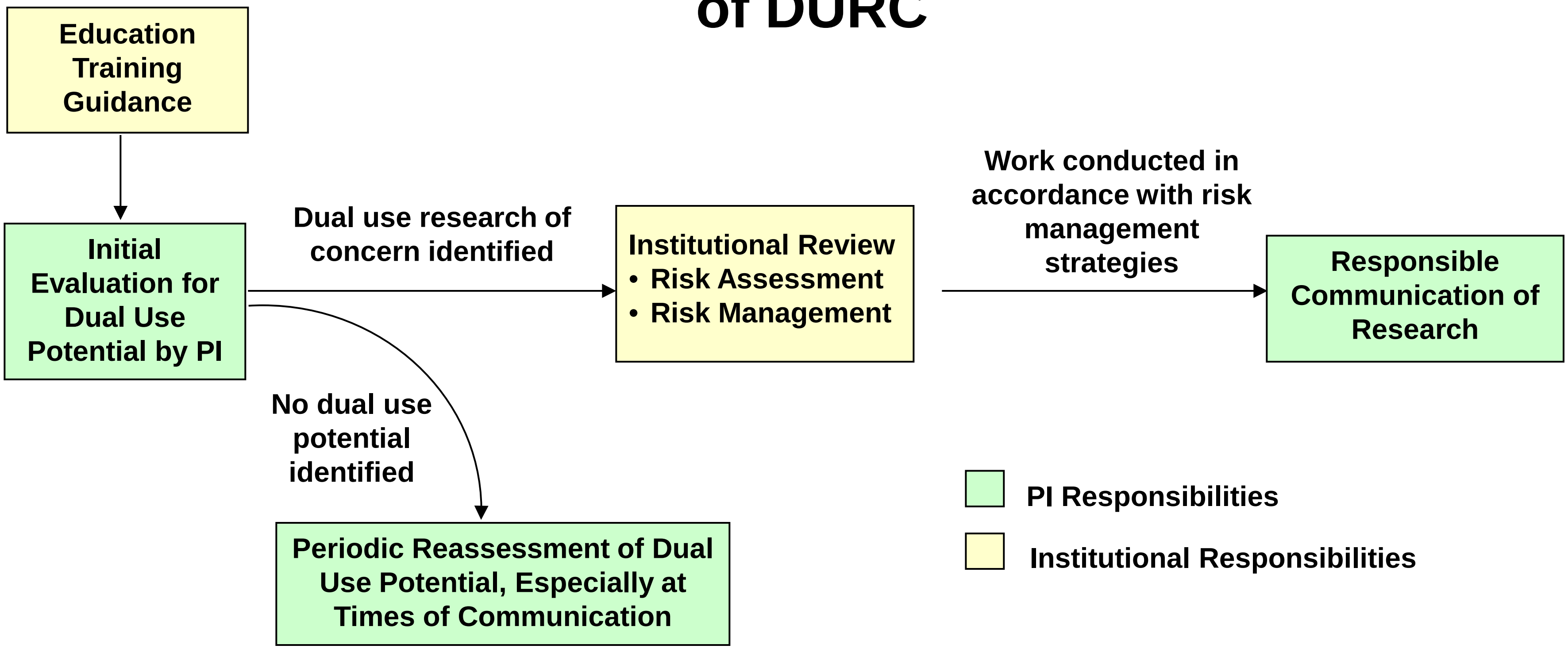
A Report of the National Science Advisory Board for Biosecurity (NSABB)

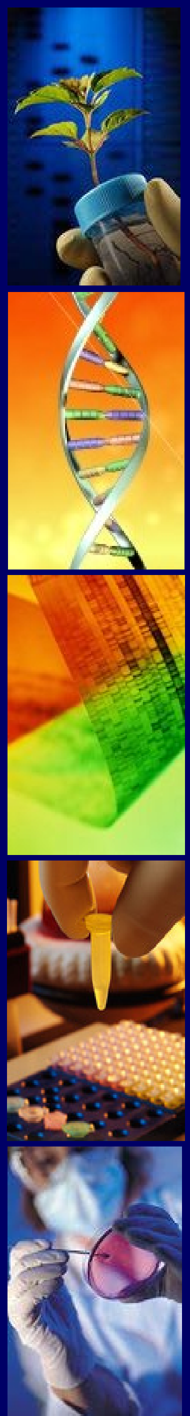
June 2007

- NSABB has recommended a framework for the oversight of dual use life sciences research including
  - Steps in the local oversight of DURC
  - Criterion and guidance for identifying DURC
  - Tools to assess and manage the dual use risk associated with certain research
  - Tools for the responsible communication of research
  - Responsibilities of those conducting life sciences research

NSABB's Recommended Oversight Framework for DURC

Proposed Steps in Local Oversight of DURC





Biosafety and biosecurity concerns

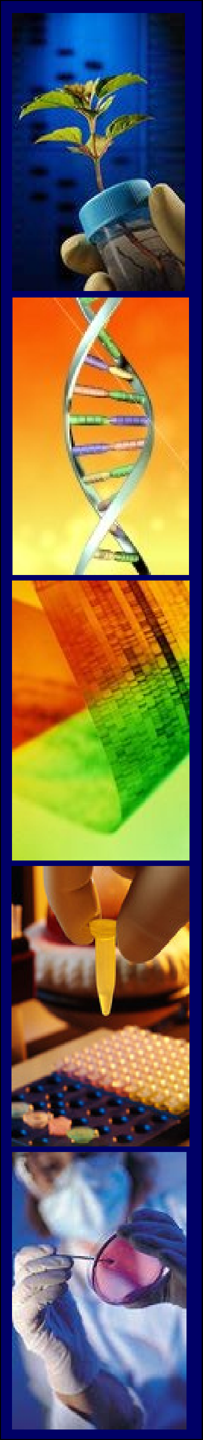
- Biosafety and biosecurity are distinct but related concepts
- Biosafety – refers to the prevention of accidental exposure to hazardous materials
- Biosecurity – refers to the prevention of unauthorized possession, loss, theft, misuse or diversion of hazardous agents; and the misuse of scientific information to threaten elements of national security
- NSABB's focus is biosecurity, but the two concepts converge since they both require the assessment and management of laboratory risks

Overarching biosafety and biosecurity concerns

- Biosafety concerns: recombinant techniques typically utilized in synthetic biology would be adequately covered by the *NIH Guidelines*
- Biosecurity concerns: should be adequately addressed by PI and institutional review in NSABB's oversight framework for dual use research

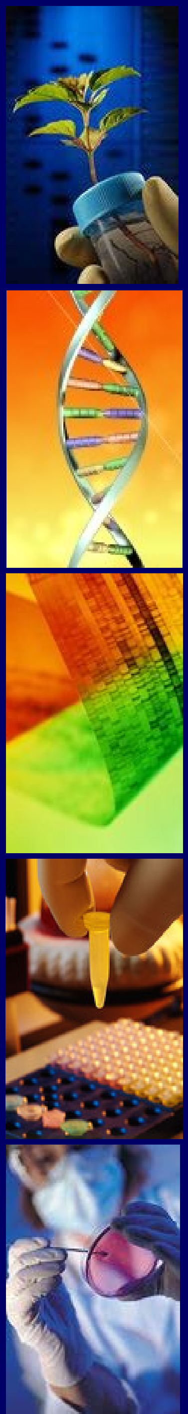
Current oversight addresses individuals conducting life sciences research within universities or institutional settings but…

- Not all synthetic biologists operate within these settings
- Many practitioners have backgrounds that are not rooted in the life sciences
- Not all practitioners consider their work "biological" in nature and may not regularly consider the biological or public, plant and animal health implications of their work



Recommendation 1

- **Synthetic biology should be subject to institutional review and oversight since some aspects of this field pose biosecurity risks**
  - NSABB has proposed an oversight paradigm that should adequately address dual use research issues associated with synthetic biology and strongly urges the federal government to develop and implement such policy

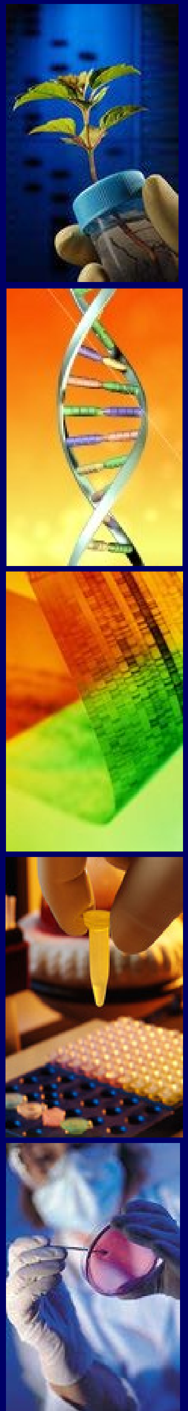


Recommendation 2

- **Oversight of dual use research should extend beyond the boundaries of life sciences and academia**
  - Gaps in oversight remain, primarily due to the large numbers of synthetic biology practitioners who come from backgrounds that are not traditionally considered life sciences or who lack formal institutional affiliations

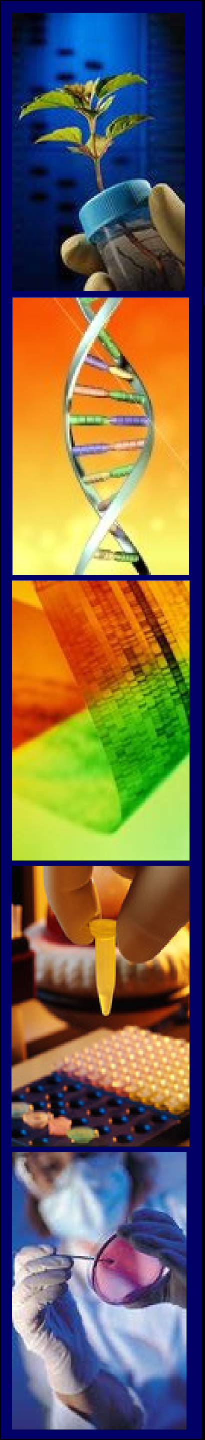
Recommendation 3

- **Outreach and education strategies should be developed that address dual use research issues and engage the research communities that are most likely to undertake work under the umbrella of synthetic biology**
  - Education efforts should be developed that target synthetic biology researchers who are
    - a) not subject to federal biosafety and biosecurity requirements,
    - b) not formally affiliated with universities or research institutions, and
    - c) students (at all levels)



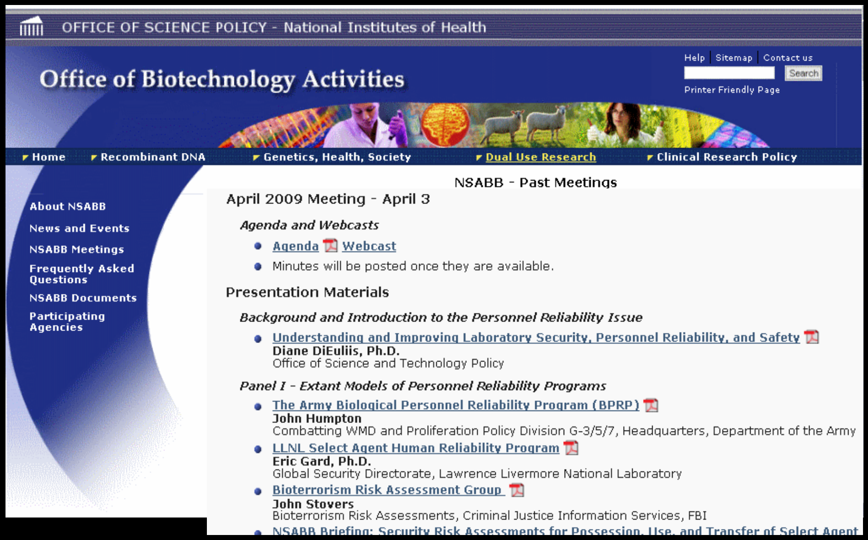
Recommendation 4

- **The US Government should include advances in synthetic biology and advances in our understanding of virulence/pathogenicity in “tech-watch” or “science-watch” endeavors**
  - It is appropriate for tech-watch or science-watch activities to identify emerging dual use technologies and new knowledge that could change the calculus about dual use risks and biosecurity concerns



More information

www.biosecurityboard.gov



nsabb@od.nih.gov