The Promises – and Potential Risks – of Synthetic Biology

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(Based on the article, "The Promise and Perils of Synthetic Biology," in *The New Atlantis*, Spring 2006, by Jonathan B. Tucker and Raymond A. Zilinskas)

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What is Synthetic Biology?

- New discipline at the frontier of biological science and engineering
  - Design and redesign of biological systems for greater efficiency
  - Design and assembly of functional genetic circuits and metabolic pathways
  - Offers scientists a way to test their theories
- Wide variety of potential applications

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Potential Benefits and Risks

- Created bioengineered synthetic organisms will be able to:
  - Produce pharmaceuticals
  - Detect toxic chemicals
  - Break down pollutants
  - Repair defective genes
  - Destroy cancer cells
  - Utilize carbon dioxide from the atmosphere for products
  - Generate hydrogen as a fuel source
- But synthetic biology may pose risks of inadvertent harm or deliberate misuse

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Current Status of Synthetic Biology

- Field is at roughly the same level of development as molecular genetics in the late 1970s, about five years after discovery of recombinant-DNA technology
- First international conference (SynBio 1.0) was held at MIT in June 2004; second conference (SynBio 2.0) was held at UC Berkeley May 21-23, 2006; SynBio 3.0 will be held in June 2007 in Zurich.

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Current Status of Synthetic Biology

- Most of current work on synthetic biology taking place in the U.S., but research groups are also active in Europe and Israel
- Over the next decade, the field will enter a phase of exponential growth and spread to many other countries
- Two private companies already founded to commercialize the technology - Codon Devices (Cambridge, MA) and Amyris Biotechnologies (Emeryville, CA)

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Four Subfields of Synthetic Biology

- Genome design and construction
- Natural product synthesis
- Design and operation of circuits
- Creation of standardized biological parts

1. Genome Design & Construction

- Can build known genes and genomes from short strands of DNA (*oligonucleotides*)
  - 2002 – poliovirus
  - 2003 – phage φX174
  - 2006 – Spanish flu virus
- Cost of DNA synthesis (per base-pair) dropping rapidly
  - From $10 in 2000 to $2 in 2005
  - Will drop to pennies in the next 5 years, making it possible to synthesize large genomes

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Redesign of Existing Genomes

- 2005 – LY Chan et al. at MIT simplified genome of phage T7 by removing complex gene overlaps and rationalizing DNA sequence
- Venter Institute is currently redesigning *Mycoplasma genitalium* genome (517 genes) to reduce it to the minimum number of genes required to support independent life
- Redesigned microbes could serve as “platforms” for bioengineered systems

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2. Natural Product Synthesis

- Aim is to develop bacteria that make natural products by transferring a “cassette” of plant or animal genes that code for all the enzymes in a metabolic pathway
- Jay Keasling et al.: designing a cassette coding for the multi-step synthesis of immediate precursor of artemisinin, a malaria drug extracted from sweet wormwood plant
- Goal is to reduce cost of artemisinin in Third World

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3. Construction of Genetic Circuits

- 2000 – proof of concept: first genetic circuit built by Michael Elowitz and Stanislas Leibler
- Two plasmids, one containing three repressor genes, the other Green-fluorescent protein (GFP) gene
- Inserted into bacteria, the circuit behaved like an artificial clock, causing cells to blink on and off

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4. MIT Registry of Biological Parts

- MIT developing a “tool box” of standardized genetic parts with known performance characteristics
- Parts (DNA sequences) known as “BioBricks”
- Goal is to assemble BioBricks into functional genetic circuits

Building Circuits from BioBricks

- Simple genetic circuit produced by assembly of several BioBricks
- Film of bacteria contains a genetic circuit that makes them sensitive to light, so that they function like a photographic negative

Educational Initiatives Generated by Synthetic Biology

- At MIT and other universities, synthetic biology is a catalyst for interdisciplinary research and teaching
  - Field bridges molecular biology, computer science, and electrical engineering
- In November 2005, MIT held first International Genetically Engineered Machine (iGEM) competition, with participation from 13 universities and institutes in the US, Canada, and Europe; second took place in November 2006 at MIT
  - Competition: to use BioBricks in the most innovative way

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Broad Goals of iGEM

- To enable the systematic engineering of biology
- To promote the open and transparent development of tools for engineering biology
- To help construct a society that can productively apply biological technology

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Potential Risks of Synthetic Biology

- At current state of development, synthetic biology poses certain “indefinable” risks
- Based on history of rDNA technology, three categories of risk are of primary concern:
  - Accidental release of synthetic microbes, with incalculable effects
  - Testing or applications of synthetic microbes in the open environment, with unintended effects
  - Potential for deliberate misuse

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Risk #1: Accidental Releases

- In near future, vast majority of synthetic biological systems will be engineered by transferring small genetic circuits into a well-understood bacterial host (e.g., *E. coli* bacterium)
- A decade from now, however, synthetic genomes may be assembled from BioBricks that have been redesigned or are entirely artificial, giving rise to new uncertainties about safety (emergent properties)
- Synthetic biology may require a new set of biosafety guidelines to prevent accidental release into environment

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Risk # 2: Intentional Releases

- Some proposed applications of synthetic biology, such as biosensors and bioremediation, would by definition involve the use of synthetic organisms in the open environment
- Need a means to assess possible ecological impact of synthetic microbes
  - One approach: ecosystem modeling with a “microcosm” (from a few ml to 15 m^3) or a “mesocosm” (> 15 m^3)
- Need for standardized testing methodology

Risk # 3: Misuse for Hostile Purposes

- Potential areas of misuse
  - Re-creation of known pathogens (e.g., Ebola virus)
  - Development of new, more lethal or effective BW agents
- Scenarios of concern
  - State-level BW program
  - Lone terrorist with advanced skills
  - “Biohacker”

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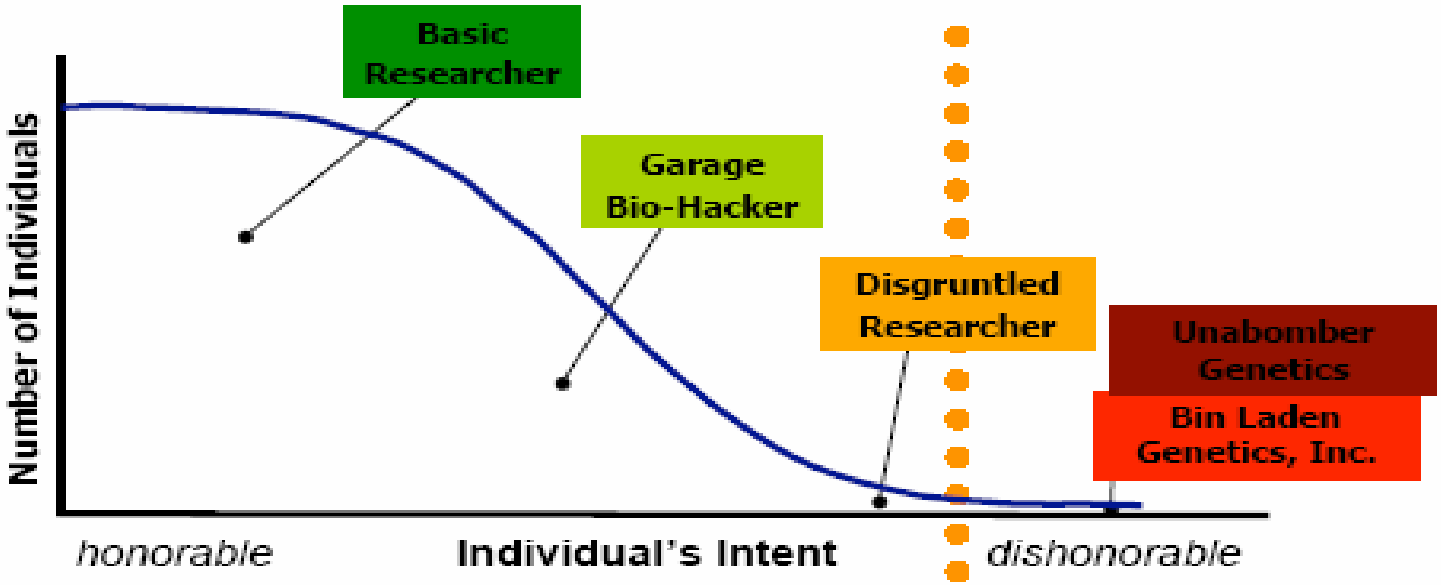
Suite of solutions



Source: Drew Endy, 2006

Policy Recommendations by Tucker and Zilinskas, 2006

- **Screening of oligonucleotide orders**
  - Pass law requiring suppliers to screen orders for pathogenic DNA sequences
- **Proactive oversight of scientific research**
  - Adopt guidelines being developed by NSABB and harmonize them internationally
- **Public outreach and education**
  - Educate public at early stage to avoid political backlash
- **Eventually - ecological modeling of synthetic microbes**
  - Conduct testing in enclosed microcosms or mesocosms

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Four Major Results of SynBio 2

Conference participants support:

1. **the organization of an open working group to undertake coordinated development of improved software tools to be used to check DNA synthesis orders for DNA sequences encoding hazardous biological systems; such software tools will be made freely available.**

2. **the adoption of best-practice sequence checking technology, including customer and order validation, by all commercial DNA synthesis companies; individuals and organizations are encouraged to avoid patronizing companies that do not systematically check their DNA synthesis orders.**

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Results of SynBio 2, cont'd

3. ongoing and future discussions within international and engineering research communities to develop creative solutions and frameworks that directly address challenges arising from the ongoing advances in biological technology, in particular, challenges to biological security and biological justice.

4. ongoing and future discussions with all stakeholders for the purpose of developing and analyzing inclusive governance options, including self-governance, that can be considered by policy-makers and others such that the development and application of biological technology remains overwhelmingly constructive (example: current CSIS, Venter Institute, and MIT project "Synthetic Genomics: Options for Governance."

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*Biological Weapons as Systems**

- *Pathogen*: active ingredient of the system; for pathogens, may be non-contagious or contagious
- *Formulation*: chemical mixed with pathogen for greater stability and effective dispersal; may be a "wet" or "dry" formulation (not necessarily needed for contagious)
- *Munition*: protect pathogens during transport and while in storage (not necessarily needed for contagious)
- *Dispersal device*: usually sprayer or atomizer for creating aerosol; may be a simple mechanism such as syringe, ladle, etc. (not needed for contagious)

*A pathogen (or chemical) by itself is not a weapon.

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What Makes an Ideal BW Agent?

Effective use depends on several characteristics:

- *Infectivity*: able to reliably infect exposed target personnel
- *Virulence*: capacity to incapacitate or kill
- *Stability*: able to live & maintain virulence over time & under difficult conditions (heat, dryness, shock, UV)
- *Incubation time*: time between exposure & onset effects
  - For military – should be short
  - For terrorism – might not matter
- *[Contagiousness*: person to person spread]

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BW Weaponization Challenges for Non-contagious Pathogens

Three key weaponization goals for aerosol dispersal:

- formulate pathogen for stability and virulence while in storage and delivery; formulation can be “wet” or “dry” (ex. encapsulation)
- formulation when dispersed should form aerosol whose particles are between 1 and 10 microns (μ)
- formulation should not block nozzle or clump after release

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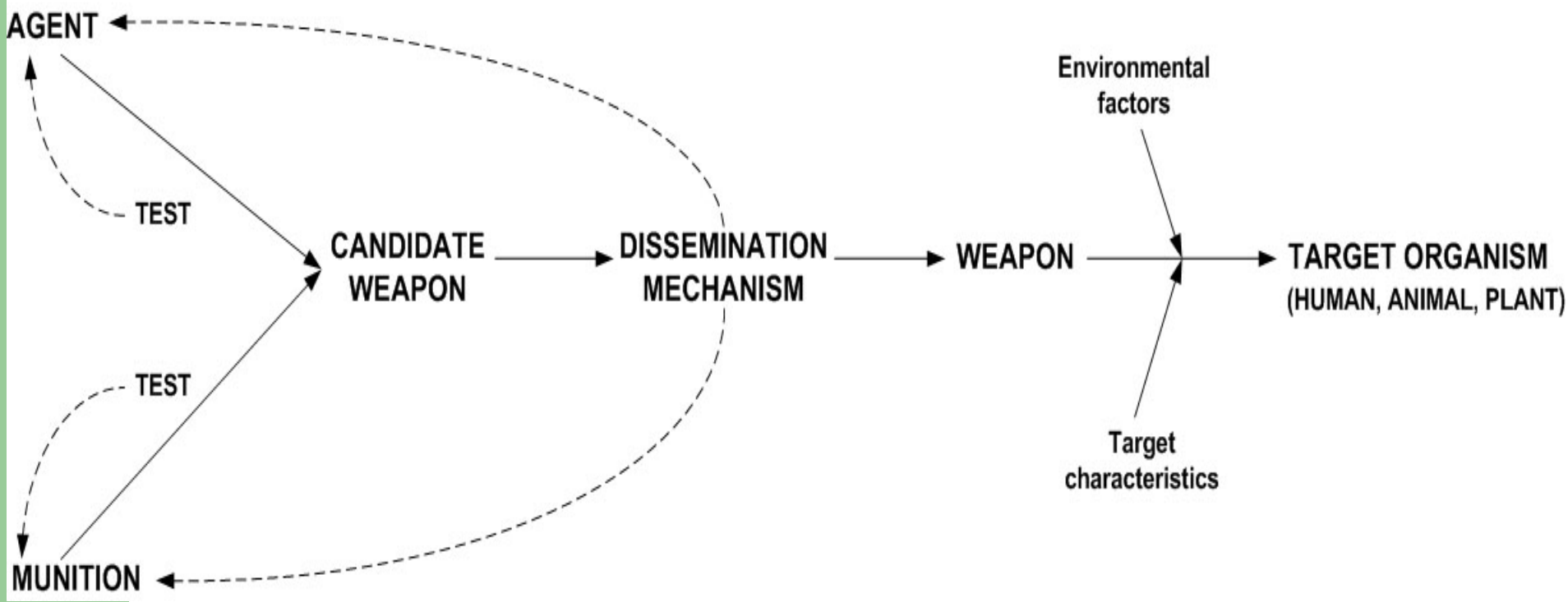
DEVELOPMENT OF BIOLOGICAL AND CHEMICAL WEAPONS



Synthetic Biology and International Law

- **Biological and Toxin Weapons Convention (BWC)**

  "…bans the development, production, stockpiling, possession, and transfer of "microbial or other biological agents, or toxins <u>whatever their origin or method of production</u>, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes."

- **Chemical Weapons Convention (CWC)**

  Only ricin and saxitoxin included in Schedule 1, but CWC commonly interpreted as covering all toxins.

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