PROACTIVE AND ADAPTIVE GOVERNANCE OF EMERGING RISKS THE CASE OF DNA SYNTHESIS AND SYNTHETIC BIOLOGY

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TWO DEFINITIONS OF SYNTHETIC BIOLOGY

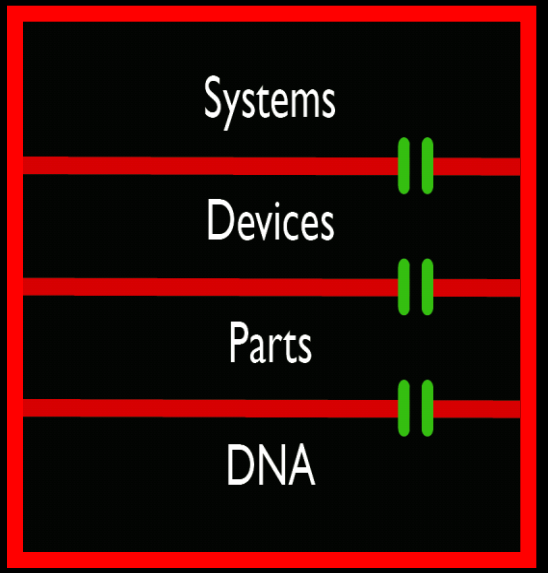
J CRAIG VENTER INSTITUTE VARIANT: ARTIFICIAL LIFE

- Prospect for and inventory natural sequences
- Simplify natural organisms; develop minimal organisms
- Fabricate customized whole artificial organisms

SynBERC VARIANT: ENGINEERING BIOLOGY

"Develop well characterized biological components easily assembled into larger functioning devices …."

- Develop and characterize standard parts
- Deposit standard parts in registries to allow reuse
- Deskill parts fabrication and assembly to cut costs
- Modularize designs to allow repurposing



BOTH VARIANTS ARE EXPERIMENTAL BIOLOGY

- Discover properties of natural biological systems by simplifying, decomposing, assembling synthetic systems
- Learn from failures as well as successes

COST OF CREATING KNOWLEDGE AND MATERIAL

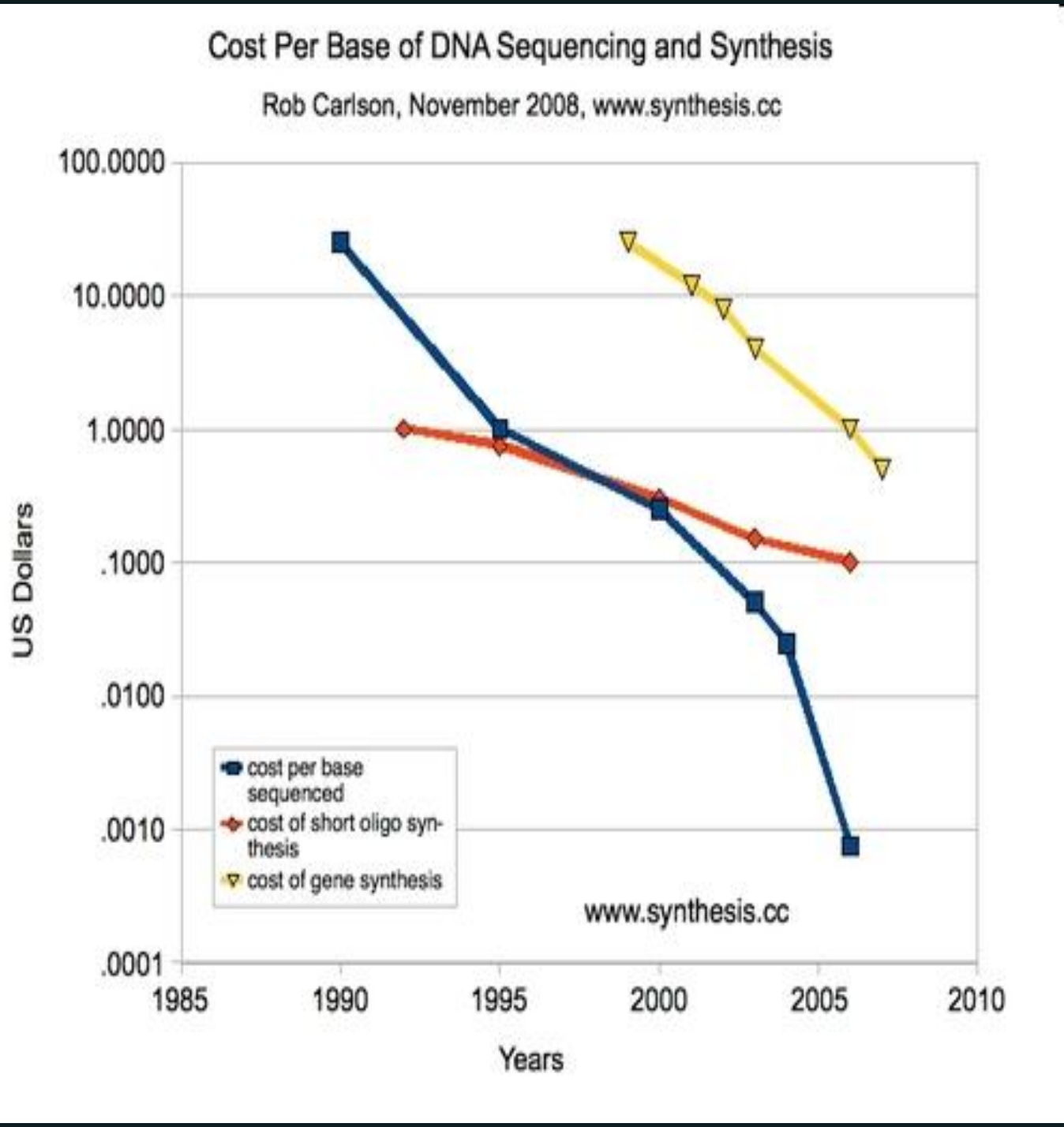
Exponential change through DNA sequencing and synthesis 1985-2007

Cost of short oligo synthesis

Cost per base sequenced

Cost of gene synthesis

Carlson 2008



DE-SKILLING MAY LEAD TO DIFFUSION OF CAPABILITIES

Synthetic Biology seeks to transform tacit to explicit knowledge

- Parts performance and couplings standardized
- Biobricks assembly standards and knowledge pooling
- Well characterized standardized chassis
- Automated assembly

This flattens the gradient between elite and mass practitioners

- Can do more in less time
- Cuts investment needed to do work
- Broadens pool of people capable of constructing a weapon
- Allows easier replication of cutting edge work

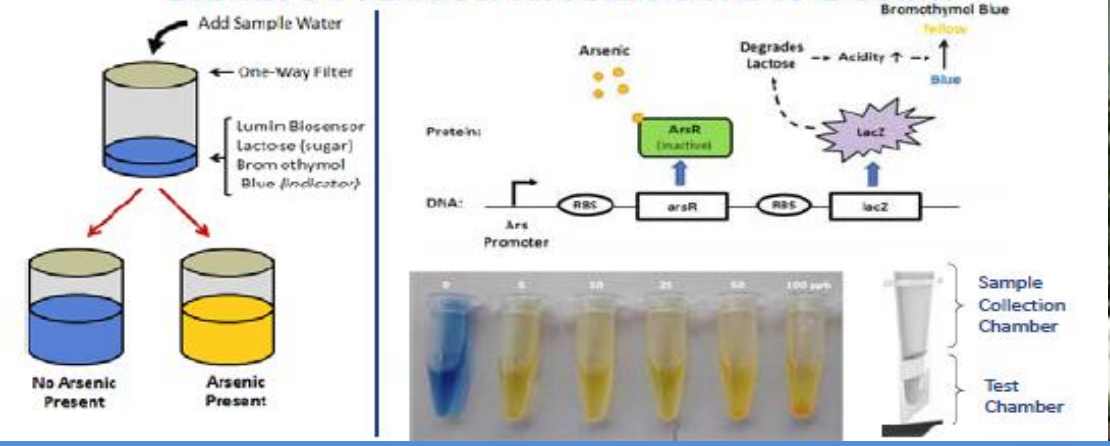
LOWER COSTS MAY ENABLE MASS USE WITH EFFECTS ON ECONOMIC , ENVIRONMENTAL AND SECURITY IMPACT OF SYNTHETIC BIOLOGY. . ..

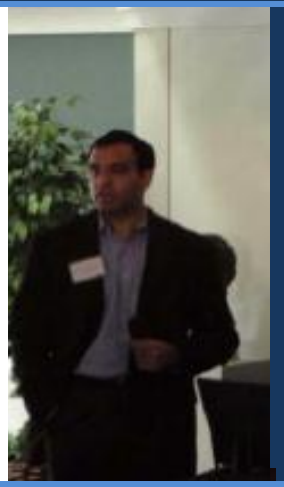
PROACTIVE ENVIRONMENTAL RISK MANAGEMENT WORKSHOPS

Organizers	Smithsonian Woodrow Wilson Center MIT Program on Emerging Technologies	
Sponsors	Sloan Foundation, NSF SynBERC, EPA	
Goals	Assess risks, redesign applications, develop tests Evaluate proactive risk management processes	
Objects	Specific synbio applications near rollout -- not blue sky Incidental release expected or deliberate release planned	
Participants	Synthetic Biologists, Environmental Microbiologists, Risk Analysts, Regulators, Insurers, Civil Society, Firms	
Workshops		
Jan 2011	E. coli arsenic biosensor rE. coli chassis	Edinburgh/Lumin Harvard/MIT
Jul 2011	Sucrose producing cyanobacteria	Harvard
Jun 2012	Testing cyanobacteria and rE. coli	Harvard/MIT
Future	eukaryotic algae	

DEVELOPERS PRESENT SPECIFIC SYNTHETIC BIOLOGY APPLICATIONS

Lumin's Product: Arsenic Sensor Design

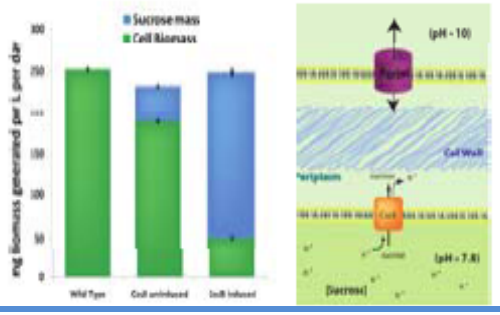




Gautam Mukunda
Lumin, MIT, HBS

Sucrose-producing Cyanobacteria

Because of large surface area required, cyanobacteria are often grown in outdoor environments for economical reasons. Genetic modification is also required for high yields. These needs present a unique issue for ecological containment.



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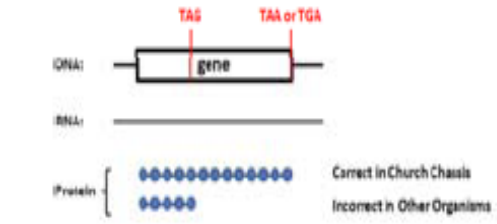
Patrick Boyle

Silver Lab
Harvard Medical

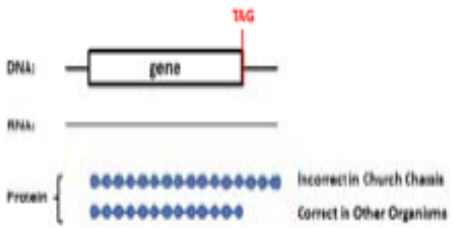
rE. coli Chassis

Removal of TAG stop codon limits horizontal gene transfer

Engineered Genes Isolated in *rE. coli*



Foreign Genes Not Functional in *rE. coli*



Peter Carr
Lincoln Lab

George Church
Harvard Medical

ENVIRONMENTAL MICROBIOLOGISTS

Allison Snow	Ohio State
Allen Place	U Maryland
Sarah Pacocha Preheim	MIT
Alan Tessier	NSF

Technologies that enable SynBio are changing understandings of effects

Sequencing: Observations on Fitness, Transfer, Stability of Genetic Elements

Computational Methods: Models of Networks and Communities

Survivability and Fitness

Conventional Wisdoms

- Engineered strains are at a fitness disadvantage compared with wild types because of additional metabolic burdens. Therefore, they will only survive at low levels in nature and won't do ecological damage.

Challenges

- It has not been demonstrated that engineered strains are regularly at a disadvantage; in some cases, the opposite has been found.
- Engineered traits may enable use of new resources, putting engineered strains at a competitive advantage.
- Engineered strains may alter their surroundings in ways that compromise locals.
- Whom do we compare with in assessing fitness: the engineered strain's own wild type version, or the local microflora? Which locals should we compare with? Most microorganisms can't be cultured.

Testing

- Theoretical fitness assessment uses wild type traits and genetic and phenotypic differences between wild type and engineered strains.
- Experimental fitness assessment involves comparing strains' growth rates or resource consumption.
- How do we know what the conditions will be and what factors to measure? Pinning down fitness is nontrivial. What should the conditions and timeframe of experiments be?

Design

- What should designing for compromised survival look like?
- Researchers are working on time- or conditions- linked killswitches.
- How do we design with mutation and natural selection in mind?

Horizontal Gene Transfer

Conventional Wisdoms

- Horizontal gene transfer is limited by phylogenetic proximity and occurs through a set of fairly well understood mechanisms.
- In order for transfer to matter, transferred genes must be adaptive.
- We can test whether or not a strain transfers DNA.

Challenges

- Recent research is dramatically changing our understanding of the frequency and importance of horizontal gene transfer, which is now considered to be a dominant force in evolution.
- Transfer occurs across phylogenetic distance, even between domains.
- Transfer does not require phages, F-factor, transposons, or plasmids.
- Methods of detecting transfer are not well developed.
- Transferred genes need not be beneficial, and genes that are not beneficial may remain in the population.

Testing

- How might we test for transfer? Tests are not yet well developed.
- What would a test look like to determine likelihood of future transfer?
- Some experiments involve growing strains together and measuring transfer of particular genes. How long should the experiment run? What about species that can't yet be cultured?

Design

- Groups are designing to prevent engineered genes from expressing properly in natural hosts and vice-versa.
- Is anyone engineering to avoid transfer?
- We have knowledge about conditions favorable and unfavorable for transfer, so the potential to engineer accordingly is there!

Stability and Evolution

Conventional Wisdoms

- Evolution affects lab work in that it introduces complications and can be harnessed for directed evolution. However, it does not create substantial safety or environmental risks in practice.
- Killswitches relieve concerns about evolution.
- Evolution is beyond the scope of current research; substantial risks, if any, can be addressed when products are closer to commercialization.

Challenges

- Microbes acquire new traits rapidly.
- For microbial populations, 'n' is very large, bringing "vanishingly rare" events into the realm of reasonable possibility that should be considered in designing for safety.
- Selective pressure to circumvent or break killswitches is strong.
- Engineered strains tend to "dump" added, burdensome genes.

Testing

- How might one test for the potential for evolution to occur? How long would the study run, and under what conditions?
- Evolutionary studies suggest that some types of traits arise more easily than others. How can this knowledge be applied here?

Design

- Researchers are working to engineer such that organisms that deviate too far from the original engineered strain die.
- Researchers are working to engineer killswitches and other traits more robust to mutation.
- Work can be done on applying the "ease of evolution" concept here.
- Is any of these a foolproof solution? What more can we do?

INDUSTRY | CIVIL SOCIETY | INSURANCE | PUBLIC SECTOR

Reto Schneider
SwissRe

Gwen McClung EPA, Alan Pearson USDA, Jessica Tucker HHS, Mark Segal EPA

Eric Hoffman, Friends of the Earth;
Jaydee Hanson, International Center for Technology Assessment

Sarah Carter, JCVI, Steve Evans, DowAgrosciences

Peter Jutro, EPA;
Diane DeEuliis, White House OSTP / NIH

Sucrose-producing Cyanobacteria

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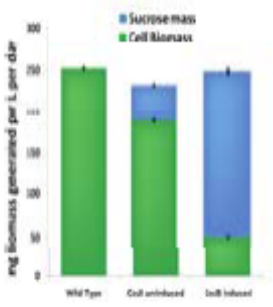

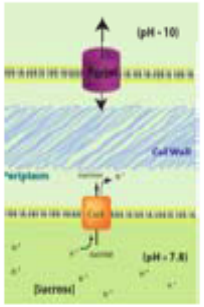

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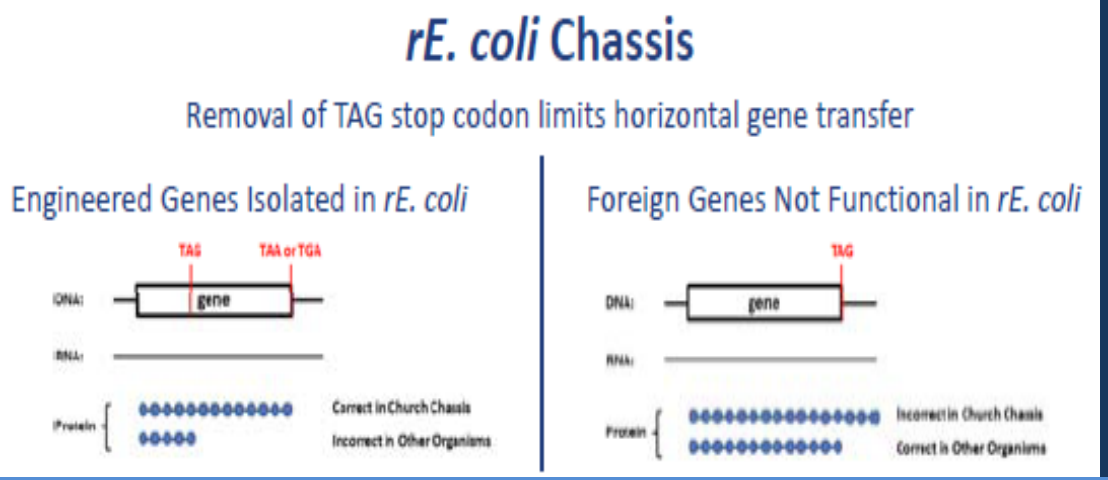
ECONOMICS DICTATE LIGHT CONTAINMENT TO PRODUCE LOW VALUE MATERIALS

- CONSEQUENCES OF INEVITABLE RELEASE?
- EFFECT OF METHODS OF INSERTION ON GENE FLOW?
- EFFECT OF INSTABILITY ON FUNCTIONALITY OF KILL SWITCHES?

Raceways and Sluices

Plastic Bags

Surface Ponds



Peter Carr
Lincoln Lab

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EFFECTS OF ORTHOGANALITY ON GENE FLOW?
GENE TRANSFER ACROSS UNLIKE ORGANISMS?
MODULAR CHASSIS CERTIFICATION INDEPENDENT OF PATHWAYS INSERTED?

A solar saltern, whose occupants benefit from archaea-to-bacteria transfer of salinity adaptations

Pea aphids, whose distinctive coloration is believed to result from fungus-to-animal gene transfer

In this bacteria-to-animal transfer, a nematode parasitizes plants using genes from parasitic bacteria.

GROUP TAKEAWAYS

Environmental microbiologists critical of risks and benefits of synbio

- Reproductive disadvantage / diminished fitness not enough
- Focus on interaction between engineered and wild type populations
- Focus on mutation and potential changing traits of organisms
- Context sensitivity, complexity, epigenetics, not modularity, simplicity

Civil society expressed concern and sought more information:

- Flagged uncertainty, potential irreversible changes, bio-economy
- Noted complexity barrier to engagement with civil society, regulators
- Requested boot camp to enable understanding and participation

Regulators and NSABB/RAC members

- Favored analysis of concrete examples, not blue sky discussion
- Flagged issue of evaluating and certifying modular safe chassis
- Favored algae fuel production and bioremediation for later workshops (immediate needs)
- Noted regulatory variation complicates product development
- Favored inclusion of AIC, NIC and LDC regulators and insurers

CONSENSUS TAKEAWAYS

AGREEMENT ON ADVANTAGES OF EARLY PROACTIVE ENGAGEMENT

Good at Flagging Broader Array of Risks
Good at Identifying Proactive Measures
Mutual exchange bolstered legitimacy and credibility
Good at identifying policy relevant sources of uncertainty

AGREEMENT ON NEED TO STRENGTHEN SENSING AND ADAPTING

Now: Form small technical working groups to address testing issues
Soon: EPA may use workshop as model to frame assessments
Later: NSF/OSTP/DARPA/EPA may fund research to reduce uncertainty

- Design and certification of microcosms for safe trials
- Assess effects of methods of insertion on stability and gene transfer
- Assess effect of genetic instability on functionality of kill switches
- Establish observational baselines for detection of environmental effects
- Assess effect of phylogenic difference on probability of gene transfer
- Continue work on gene flow, genetic stability, fitness with sequencing
- Evaluate effects on biomes using advanced computational methods

DNA SYNTHESIS SCREENING REGIME

IGSC international gene synthesis consortium™

IDT INTEGRATED DNA TECHNOLOGIES

IASB International Association Synthetic Biology

Intelechon

HYBRID REGIME

INTERGOVERNMENTAL - AUSTRALIA GROUP

NATIONAL – HHS SCREENING FRAMEWORK GUIDANCE

TRANSNATIONAL – TWO SCREENING CONSORTIA WITH TWO LEAD FIRMS

WHY DO VOLUNTARY ARRANGEMENTS WORK IN THIS CASE ?

CONCENTRATED INDUSTRIAL STRUCTURE – FOR NOW

FIRMS COSTS OF COMPLIANCE LOW – SCREENING COSTS, LOST CUSTOMERS

FIRMS ACT AS IF HHS GUIDELINES ARE REGULATIONS TO LIMIT COMPLAINTS

FIRMS FEAR OF LIABILITY IF IGNORE GUIDANCE

FIRMS SEEK TO REDUCE DEMANDS FOR MANDATORY REGULATIONS

DNA SYNTHESIS SCREENING REGIME

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IDT INTEGRATED DNA TECHNOLOGIES

IASB International Association Synthetic Biology

Intelechon

WILL HYBRID REGIME/VOLUNTARY ARRANGEMENTS CONTINUE TO WORK?

TRENDS IN INDUSTRIAL STRUCTURE . . .

HORIZONTAL DECONCENTRATION
VERTICAL DECONCENTRATION

FIRMS IN CHINA AND INDIA ENTER
HIGH END IN HOUSE OPTIONS
BIOFABS NTERMEDIATE CUSTOMERS

IRONY OF CONTROLS – INCENTIVES FOR INDEPENDENCE

IRAN, PAKISTAN BUILDING DNA SYNTHESIS CAPACITY
DIYBio SEEK SMALL DESKTOP UNITS

TRENDS IN TECHNOLOGY

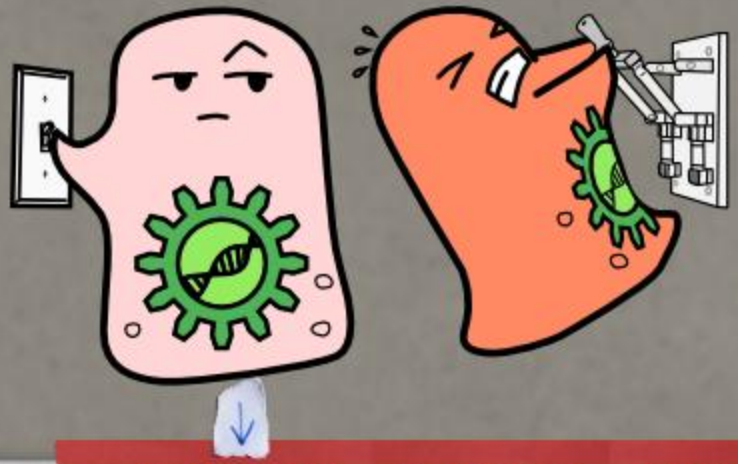
ORGANISM BASED CONTROLS OBSOLETE
NEED FUNCTIONAL SEQUENCE BASED CLASSIFICATIONS

IGEM International Genetically Engineered Machine Competition

2012 – 250 Teams

Year	Teams	Participants
2004	5	70
2005	12	130
2006	32	320
2007	54	540
2008	84	840
2009	112	1120
2010	130	1300
2011	165	1650

2010 130 teams 1300 participants from Asia, Europe, Americas, Africa



switch epfl 2012

Home

The "SWITCH" Project

The Problem

Producing complex therapeutic proteins requires biosynthesis in mammalian cells. Such proteins can sometimes have a certain level of toxicity for the cells and limit their productivity if they are produced constantly and are accumulating. To avoid this, the pharmaceutical industry use 'rewired' cells that synthesize toxic proteins only when a special molecule is added to the bioreactor. This solution has two disadvantages. First, cell rewiring affects several pathways and decreases cell productivity. Second, the 'special' molecule will mix with the final product and a purification will be needed to get

THE CASE OF IGEM SCREENING FOR SAFETY AND SECURITY – A PLAY IN THREE ACTS

Randy Rettberg, Meagan Lizarazo, Peter Carr	iGEM HQ & Head Judge
Kenneth Oye, Piers Millett, Todd Kuiken	iGEM Safety Committee
King Chow	iGEM Head Asia Region
Allen Lin, Ralph Turlington, Shlomiya Bar-Yam	MIT SynBIO Policy Group
Rocco Casagrande, Michael Imperiale, Jef Boeke	External Fast Reviewers
George Church	Parts Screen
Toby Richardson	Archetype Parts Screen

Archetype

ACT I - SCREENING PROJECTS

- Screen safety pages & projects of all iGEM teams with focus on pathogens
- Flag two projects, one lacking safeguards and IRB
- External biosafety experts fast reviews, insufficient info to determine safety
- iGEM SC and Head Asia Region query team & faculty advisor; inadequate response
- Disqualify team, recruit President Asia Pacific Biosafety Assoc to work with team
- Team redefines project as “software only / no wet lab work”

ACT II – SCREENING PARTS

- Review parts in registry, find team submitted parts to Registry in prior year
- Query US agencies re definition “genetic elements associated with pathogenicity”
- George Church screens parts, finds no problem (Not scalable)
- Toby Richardson uses Archetype to screen, no red flags (Scalable)

ACT III – LESSONS LEARNED?

- Implications for iGEM
- Implications for US and international policies and practices

DIFFUSION – GARAGE AND CLOSET BASED SYNBIO

Do-It-Yourself-Biology (DIYB)
Kay Aull's closet lab – low cost, self diagnostics
Low Cost Desk Top DNA Synthesis Units
Potential for bio-hackers and malevolent action?

DIYB

FBI

Kay's Closet

Amateurs Are New Fear in Creating Mutant Virus

Na Son Nguyen/Associated Press

WORRY An outbreak of the H5N1 bird flu virus was reported in Vietnam in February.

By CARL ZIMMER
Published: March 5, 2012

Just how easy is it to make a deadly virus?

Related

Genetically Altered Bird Flu Virus Not as Dangerous as Believed, Its Maker Asserts (March 1, 2012)

Despite Safety Worries, Work on Deadly Flu to Be Released (Februar

This disturbing question has been on the minds of many scientists recently, thanks to a pair of controversial experiments in which the H5N1 bird flu virus was transformed into mutant forms that spread among mammals.

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SIDE EFFECTS

D.I.Y. Biology, on the Wings of the Mockingjay

By JAMES GORMAN
Published: May 10, 2012 | 34 Comments

Genetically modified organisms are not wildly popular these days, except one: a fictional bird that is central to the hugely popular movie and book trilogy "The Hunger Games." That's the mockingjay, a cross between a mockingbird and a genetically engineered spy bird called a jabberjay.

Enlarge This Image

The action in "The Hunger Games" takes place in a fictional future in which teenagers are forced to hunt and kill one another in annual competitions designed to entertain and suppress a highly controlled population. The mockingjay first appears as a symbol, when Katniss Everdeen is given a pin that depicts the bird. Mockingj although not the birds, have spread to the rea

"They're funny birds and something of a slap the Capitol," Katniss explains in the first boo nature of that slap in face is a new twist on th

Chicago Tribune

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Publish and perish?

March 17, 2012

The Gazette

montrealgazette.com

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'Doomsday' virus revealed, along with DIY instructions

BY MARGARET MUNRO, POSTMEDIA NEWS MAY 3, 2012

8-Points (1)

- Striving for integration
  - Synthetic biology risk governance cases should be seen as cautionary tales with respect to integration across different impacts and risks

8-Points (2)

- Prioritizing risks
  - In practice, synthetic biology risks have been prioritized by the immediacy and potential severity of emerging threats
  - Prioritization is taking place within security and environmental domains, but not across domains

8-Points (3)

- Ascertaining accountability
  - Most of those generating risks in synthetic biology have been accepting responsibility for evaluating and managing foreseeable risks that they may be creating

8-Points (4)

- Ensuring flexibility and adaptability over time
  - Synthetic biology is a strong candidate for adaptive approaches to risk management
  - In the realm of biosecurity, DNA synthesis screening appears to be an exemplary case for adaptive risk management
  - In the realm of env. risks, with less immediate and clearly defined risks, the need for adaptive and proactive risk governance methods is even clearer

8-Points (5)

- Creating transparency
  - Synthetic biology cases include both exemplary and cautionary tales with respect to the transparency of risk assessment and management
  - As the focus of synthetic biology moves from academic actors to commercial firms, the heart of the problem rests confidential business information
  - IP claims and licensing provisions may be used to prevent some research by third parties on risks associated with synthetic biology

8-Points (6)

- Approaching inclusive governance
  - Bad News: increasing polarization and mutual isolation of civil society, biotechnology firms and academic synthetic biologists
  - Good News: workshops conducted at the Wilson Center have continued to engage constructively in identifying risks and setting priorities for next stage research on risks

8-Points (7)

- Providing convincing methods and procedures for evaluating threats and designing options to deal with threats
  - Cases described provide examples of reasonably convincing methods and procedures for dealing with threats
  - Succeeded in identifying areas of agreement on risks and benefits, in flagging uncertainty and tagging points where agreement would be difficult because of conflicting values

8-Points (8)

- Demonstrating the value of professional emerging risk identification, assessment and management
  - Professionals have played a key role in identifying, assessing and managing risks in the synthetic biology cases treated in this paper, with professional competencies including both risk governance processes and technical and scientific specializations needed to assess and manage risks

IDEA LAB

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