IRGC/OECD/UCL Conference on Planned Adaptive Regulation
Panel 2.1 Synthetic Biology
8 January 2016

Synthetic Biology: Governing Risks of Emerging Applications

Professor Kenneth A. Oye
Program on Emerging Technologies
Massachusetts Institute of Technology

Outline

Introduction: Synthetic Biology Fundamentals
Case 1: Production of (relatively) Low Value Fuel and Metals
Case 2: Production of High Value Drugs, Scents and Flavors
Case 3: Control of Vector Borne Diseases and Invasive Species
Discussion of Risk - Precautionary, After-the-Fact or Planned Adaption

This presentation is based on research and workshops supported by NSF, EPA, MIT Center for Biomedical Innovation and IRGC; and on feedback on presentations and panels with WHO, UNBWC, NRC Life Sciences Board, NSABB, EMA and OECD.

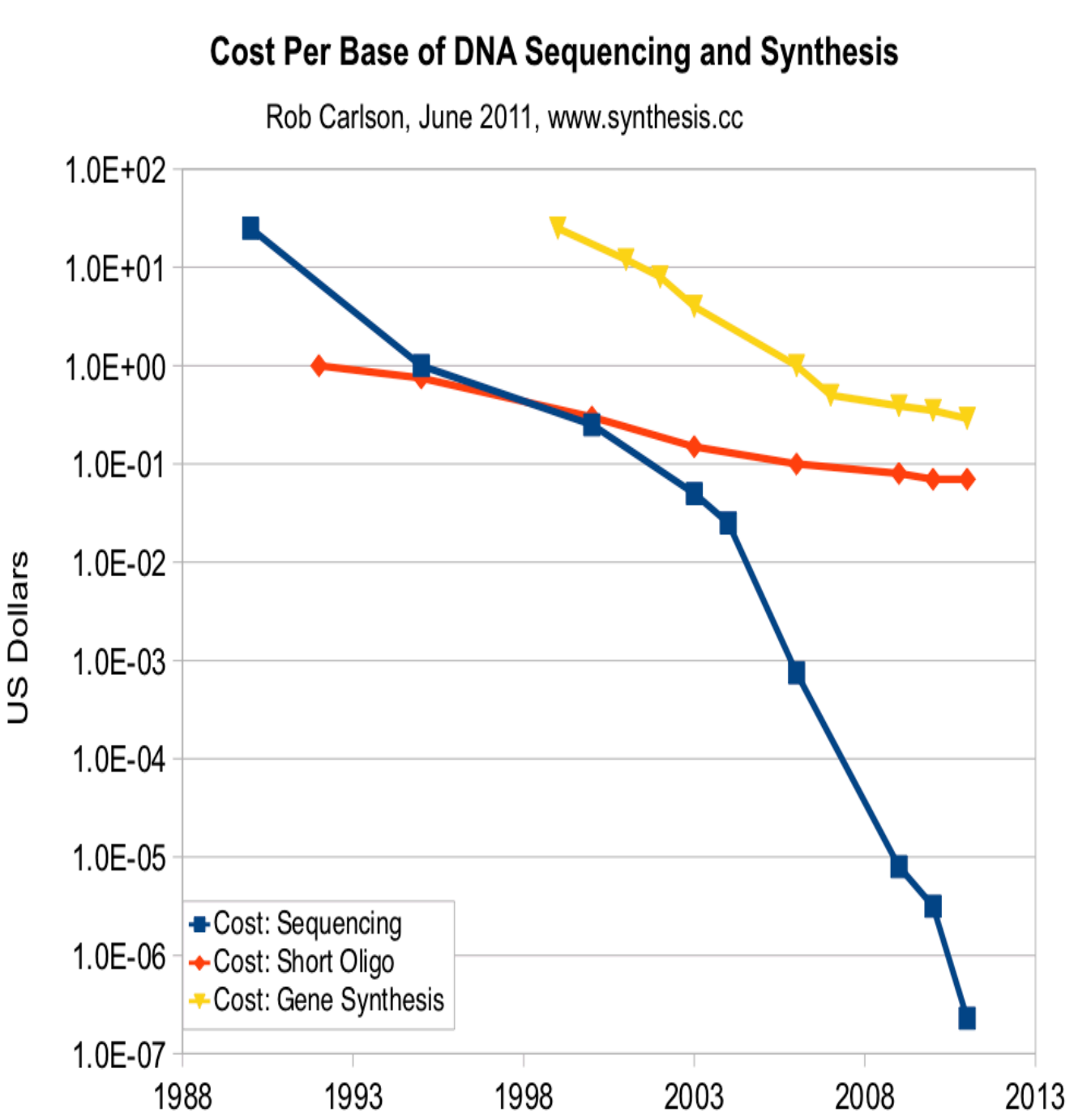
CARLSON'S CURVES

Exponential change through DNA sequencing and synthesis 1988-2011

Cost of short oligo synthesis

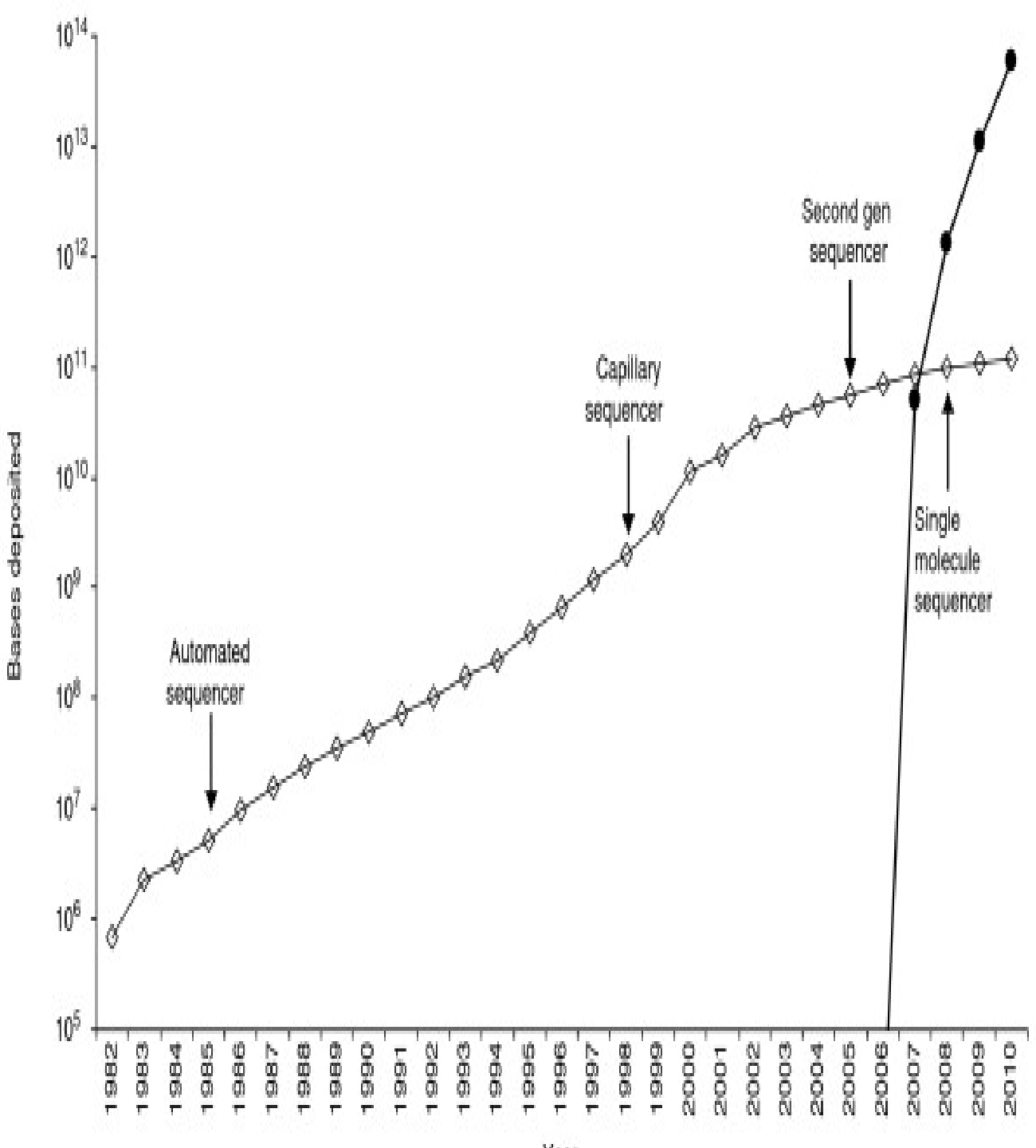
Cost per base sequenced

Cost of gene synthesis



DNA SEQUENCES IN DATA BANKS

Exponential increase in number of DNA sequences deposited in data banks



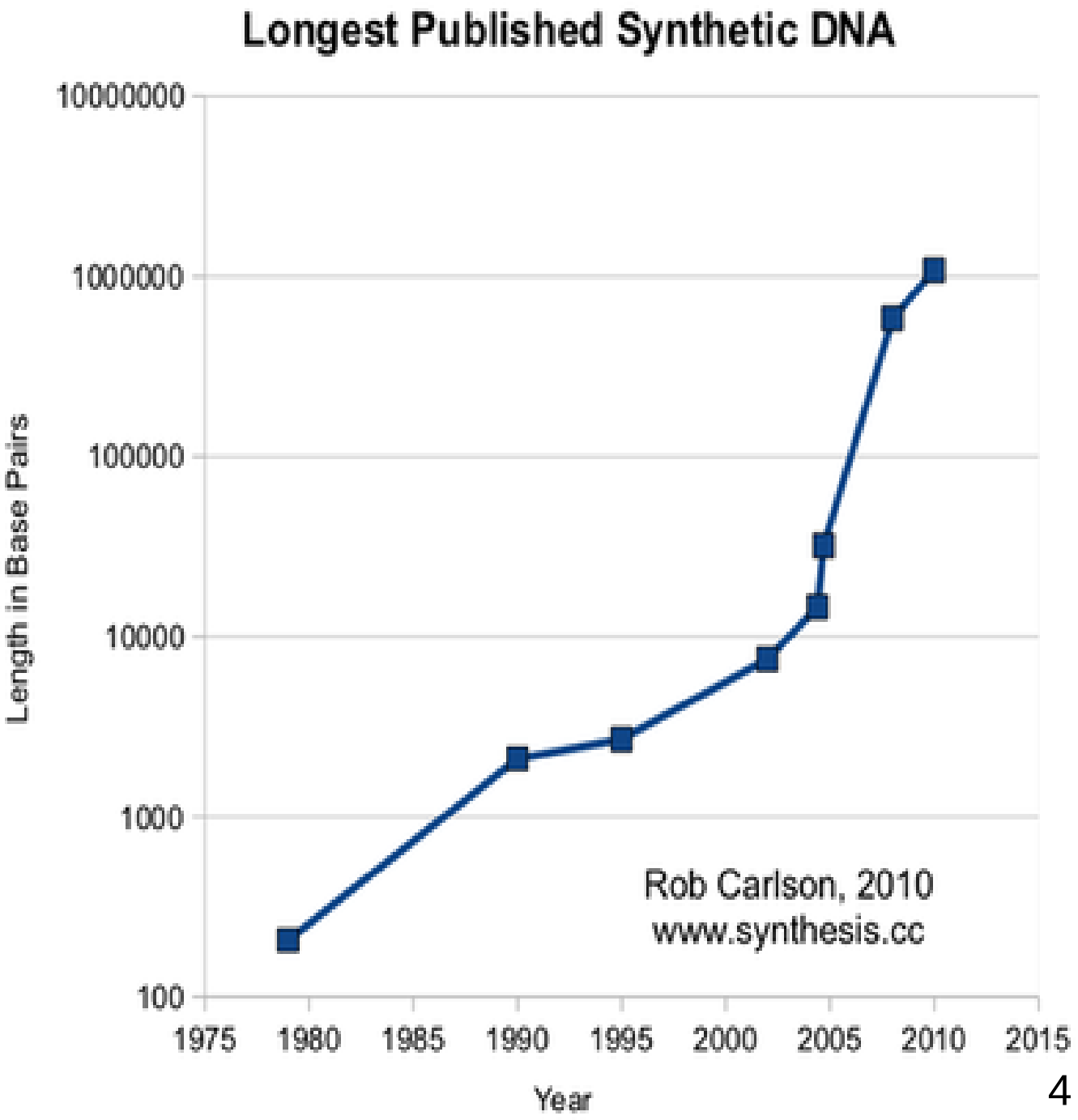
Thompson and Milos *Genome Biology* 2011

DNA SYNTHESIS

Exponential change in materials creation through DNA sequencing and synthesis

Length in Base Pairs of Longest Published Synthetic DNA

Carlson 2010



TWO DEFINITIONS OF SYNTHETIC BIOLOGY

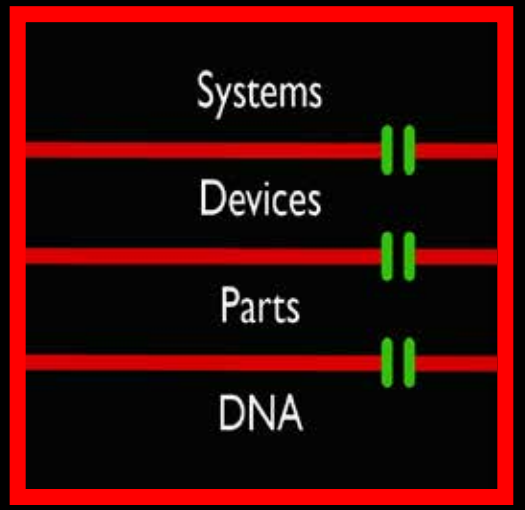
J CRAIG VENTER INSTITUTE VARIANT: ARTIFICIAL LIFE

- 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

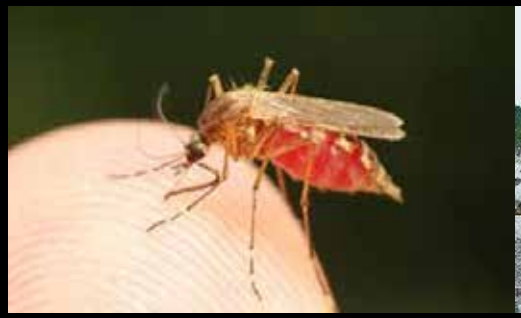


SYNTHETIC BIOLOGY EMERGING CASES

INDUSTRY — Synthesis of Licit and Illicit Organic Materials — Fuel, Opiates

AGRICULTURE — Conventional GM Plants and Animals — N Fixation

COMMONS MODIFICATION — Self-Propagating Genetic Elements — Gene Drives



AGRICULTURAL APPLICATIONS: CONVENTIONAL GM PLANTS ANIMALS

Dow Agrosciences	Enlist 2, 4-D & Glyphosphate Resistant Corn & Beans
Voigt	Nitrogen Fixation in Non Legumes
Kickstarter	Glowing Plants
AquaBounty	Salmon rapid weight gain using pout and chinook α-form of opAFP-GHc2 construct at α-locus in EO-1 α lineage of triploid hemizygous, all-female *Salmo salar* under specified conditions of use.

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INDUSTRIAL APPLICATIONS: MAKING LOW VALUE MATERIALS

SGI, Sapphire, Algenol — synthesis of biofuels

Universal Biomining — extraction and effluent treatment

Economics > low cost containment > environment release probable

Environmental effects

- Fitness / reproduction / propagation
- Horizontal gene flow
- Mutation > effects on fitness, gene flow?

Raceways and Sluices

Plastic Bags

Surface Ponds

LIMITING ENVIRONMENTAL EFFECTS OF INDUSTRIAL APPLICATIONS
DEVELOPMENTS IN BIOCONTAINMENT BY DESIGN

Fitness Isaacs multiple synthetic nutrient dependency
Gene Flow Church codon knockouts, orthogonality, syntheci proteins
Stability Silver monitoring of cumulative mutations, functionality
Unfilled gap - Credible independent demonstration and testing



ARTICLE

doi:10.1038/nature14121

Biocontainment of genetically modified organisms by synthetic protein design

Daniel J. Mandell[1]*, Marc J. Lajoie[1,2]*, Michael T. Mee[1,3], Ryo Takeuchi[4], Gleb Kuznetsov[1], Julie E. Norville[1], Christopher J. Gregg[1], Barry L. Stoddard[4] & George M. Church[1,5]

LETTER

doi:10.1038/nature14095

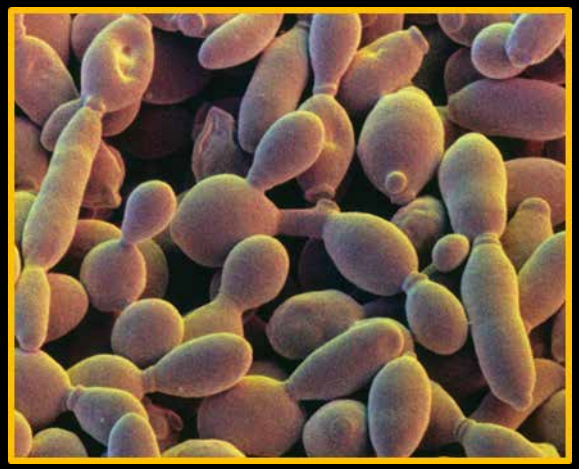
Recoded organisms engineered to depend on synthetic amino acids

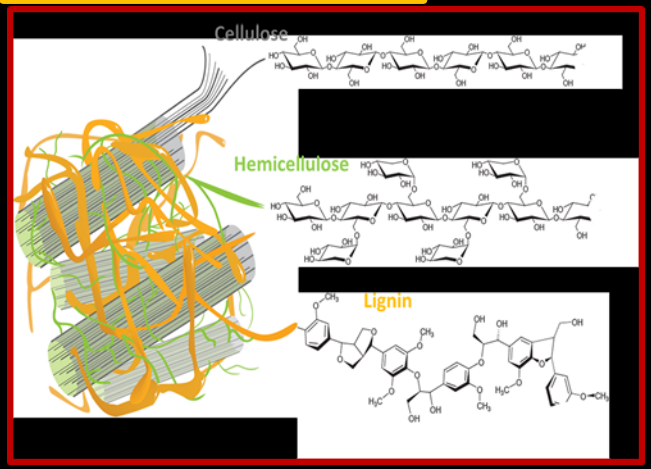
Alexis J. Rovner[1,2], Adrian D. Haimovich[1,2]*, Spencer R. Katz[1,2]*, Zhe Li[1,2], Michael W. Grome[1,2], Brandon M. Gassaway[2,3], Miriam Amiram[1,2], Jaymin R. Patel[1,2], Ryan R. Gallagher[1,2], Jesse Rinehart[2,3] & Farren J. Isaacs[1,2]

INDUSTRIAL APPLICATIONS: MAKING HIGH VALUE MATERIALS

Keasling/Amyris/Sanofi	amorphadien, artemisinen
Prather	glucaric acid
Evolva	vanillin
Smolke, Dueber, Martin, Facchini	reticuline, hydrocodone, morphine

evolva

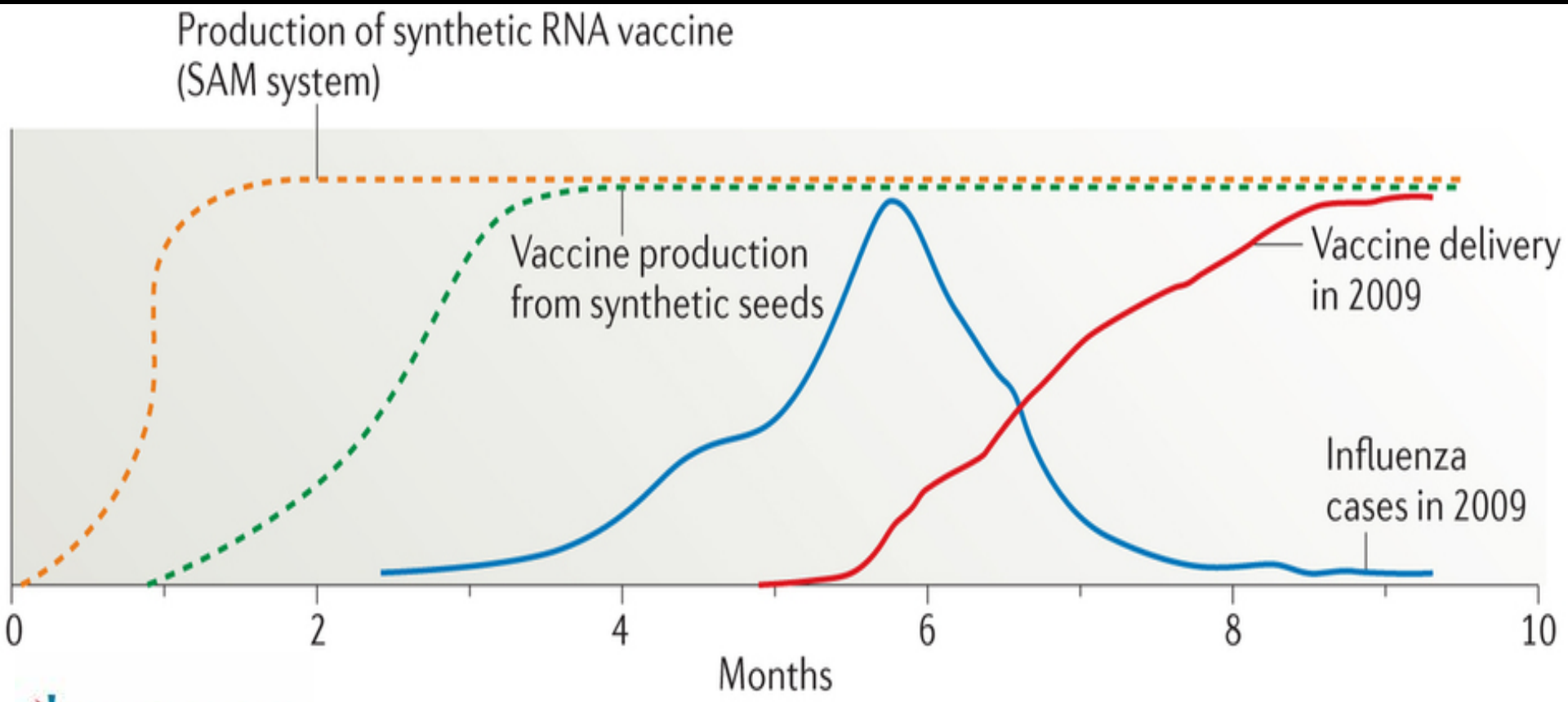




VACCINES DEVELOPMENT AND PRODUCTION

Benefit: strain > vaccine development > vaccine production

Ennio De Gregorio and Rino Rappuoli, “From empiricism to rational design: a personal perspective of the evolution of vaccine development,” Nature Reviews Immunology, 14, 505–514 (2014) doi:10.1038/nri3694



NOVARTIS VACCINES

Nature Reviews | Immunology

OPIATE PRODUCTION IN YEAST DUEBER, MARTIN, SMOLKE
Benefits: Ability to vary scaffolds, control intermediates, create novel analgesics
Hazard: Production beyond control of cartels and law enforcement
Technical Measures: markers, finicky strains, unappealing final product
Policy Measures: lab security, licensing, synthesis screening IEGBBR DEA FBI

nature International weekly journal of science

Illegal use of opiates such as heroin and morphine affects more than 16 million people worldwide.

Regulate 'home-brew' opiates

The research community and the public require a fast, flexible response to the synthesis of morphine by engineered yeasts, urge **Kenneth Oye**, **Tania Bubela** and **J. Chappell H. Lawson**.

Every year, thousands of students from across the world compete to build biological systems from pre-existing parts in a competition organized by the International Genetically Engineered Machine (iGEM) Foundation. Last November, to spark discussion on security and health risks raised by synthetic biology, FBI Special Agent Edward You presented an example: the production of opiates from sugar by yeast (*Saccharomyces cerevisiae*) that has been genetically modified.

You's hypothetical scenario is becoming a reality. One week after the iGEM competition, two developers of opiate-producing yeast strains approached us, specialists in biotechnology policy. They had results in advance of publication, and requested advice on how they might maximize the benefits of their research while mitigating the risks. Now, published papers by these researchers — John Dueber at the University of California, Berkeley, and his colleagues[1], and Vincent Martin ▶

Science

SYNTHETIC BIOLOGY

Complete biosynthesis of opioids in yeast

Stephanie Galanie,[1] Kate Thodey,[2] Isis J. Trenchard,[2] Maria Filsinger Interrante,[2] Christina D. Smolke[2]*

Opioids are the primary drugs used in Western medicine for pain management and palliative care. Farming of opium poppies remains the sole source of these essential medicines, despite diverse market demands and uncertainty in crop yields due to weather, climate change, and pests. We engineered yeast to produce the selected opioid compounds thebaine and hydrocodone starting from sugar. All work was conducted in a laboratory that is permitted and secured for work with controlled substances. We

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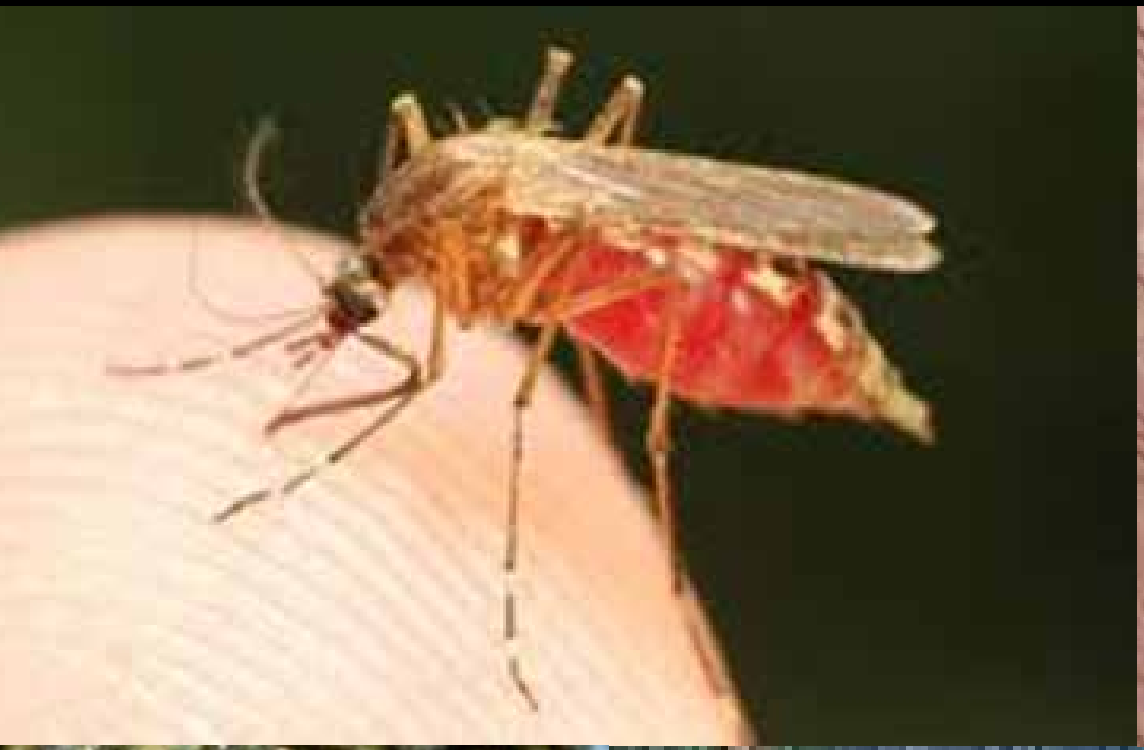
GENE DRIVES / SELF-PROPAGATING GENETIC ELEMENTS CONTROLLING VECTOR BORNE DISEASE AND INVASIVE SPECIES?



MENDELIAN AND GENE DRIVE INHERITANCE OF ALTERED GENE

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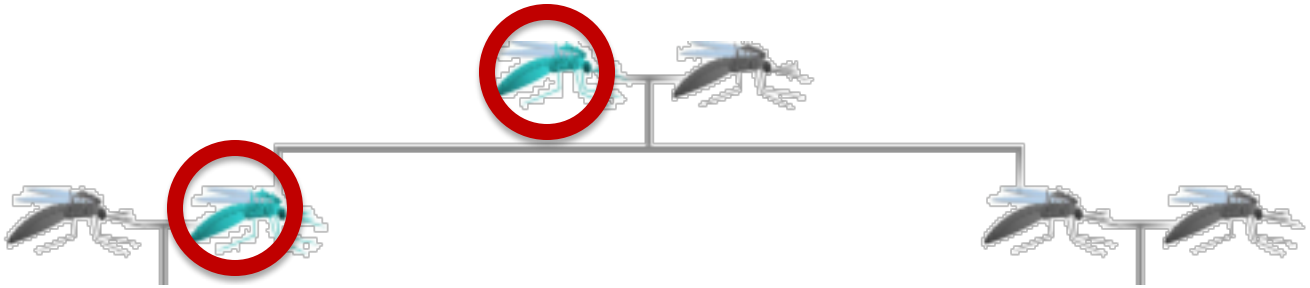

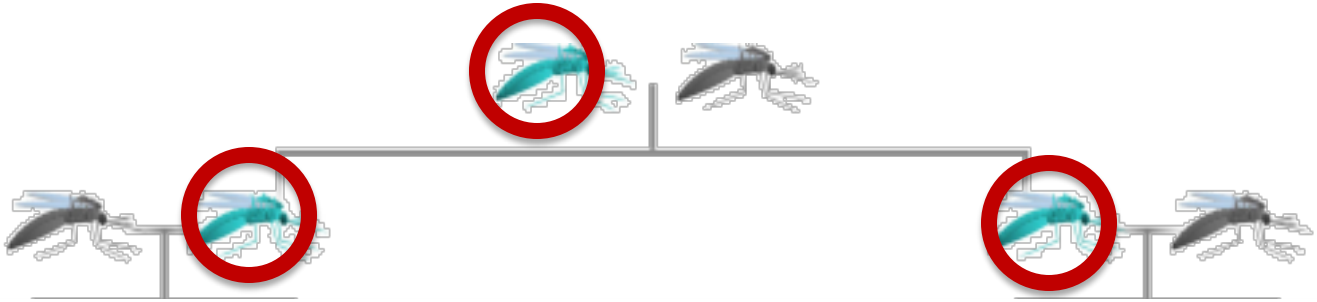

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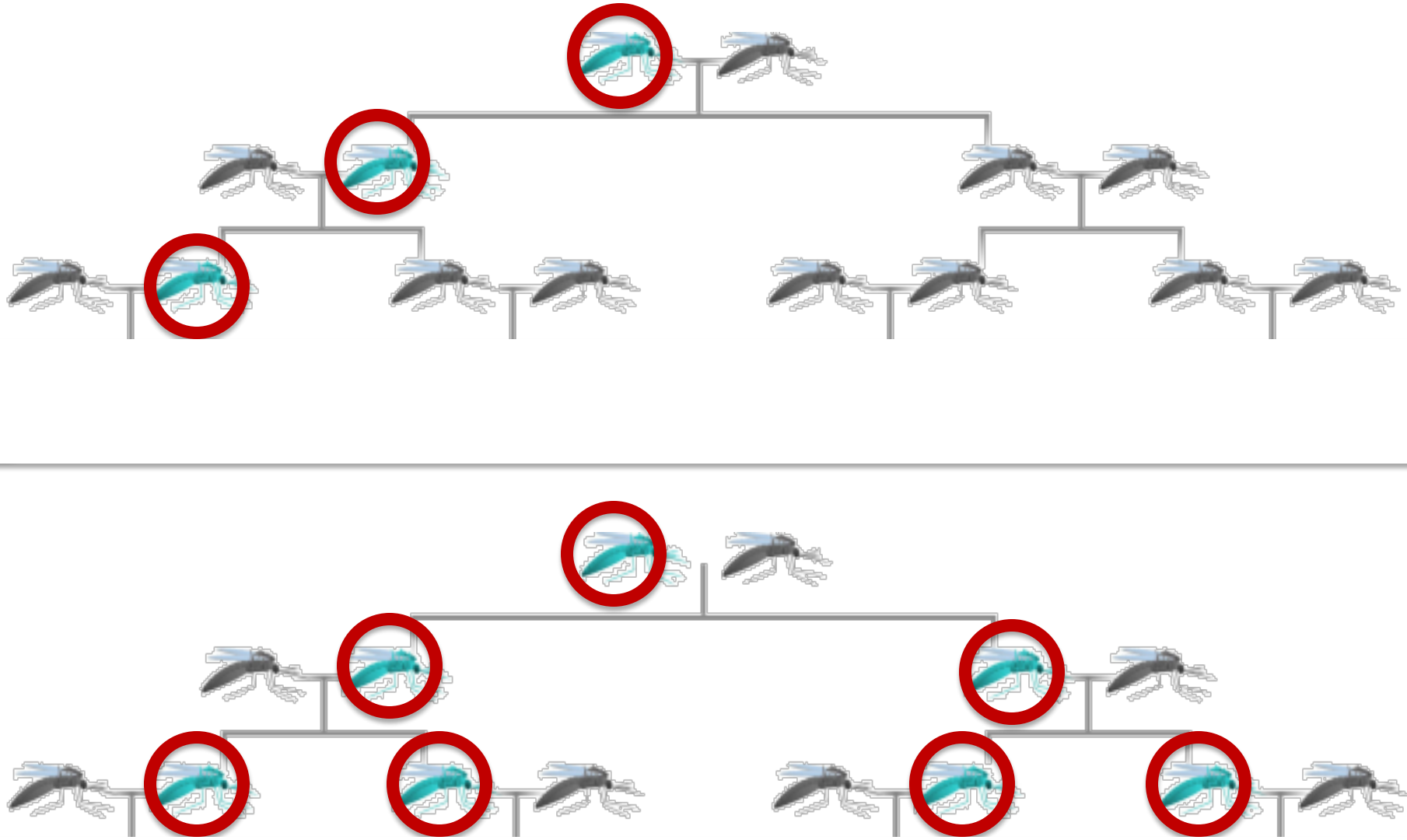

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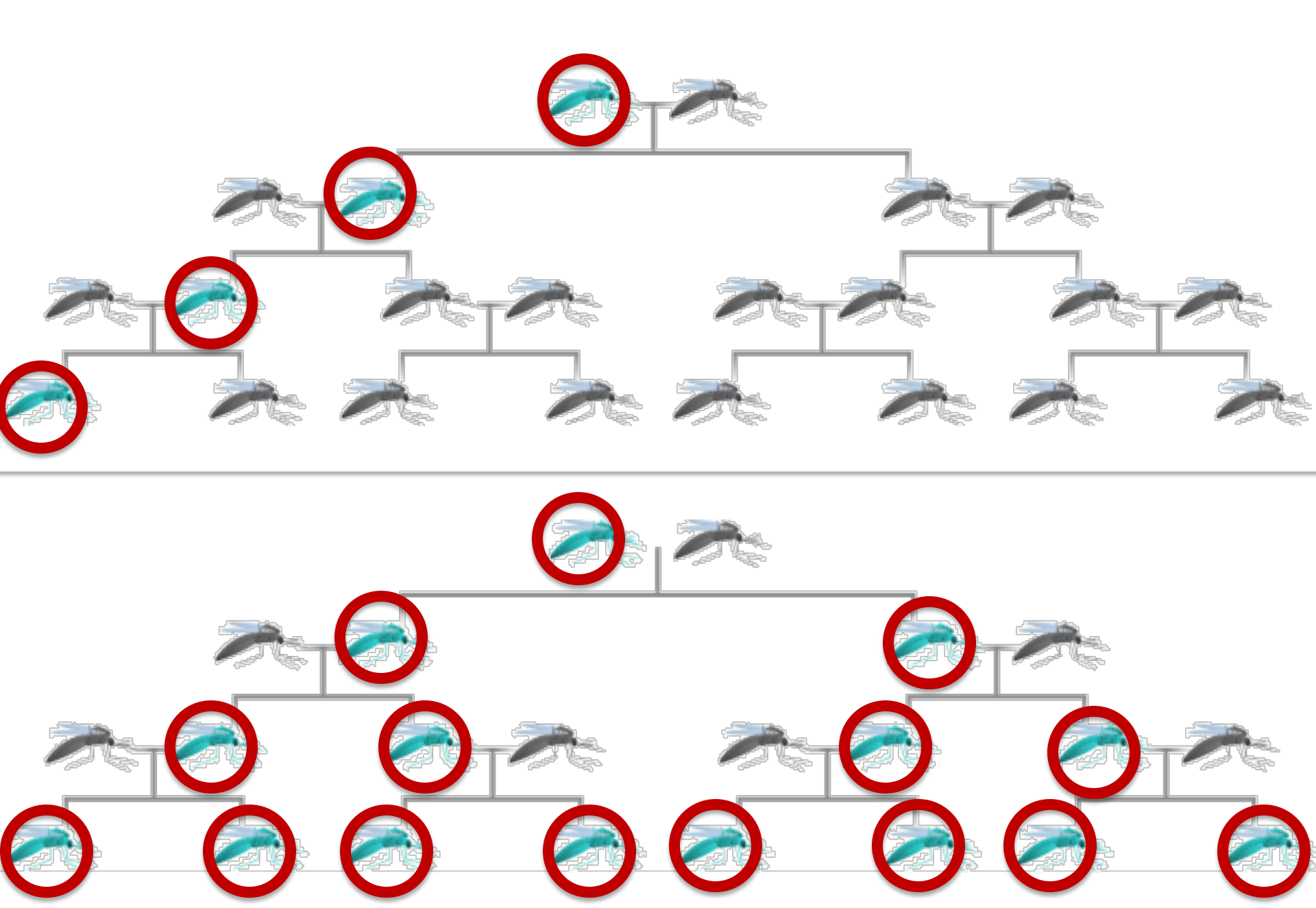
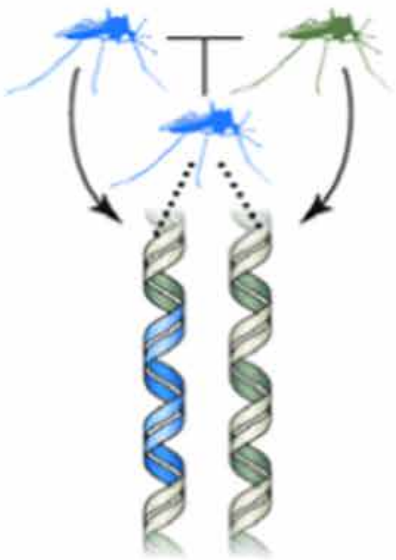


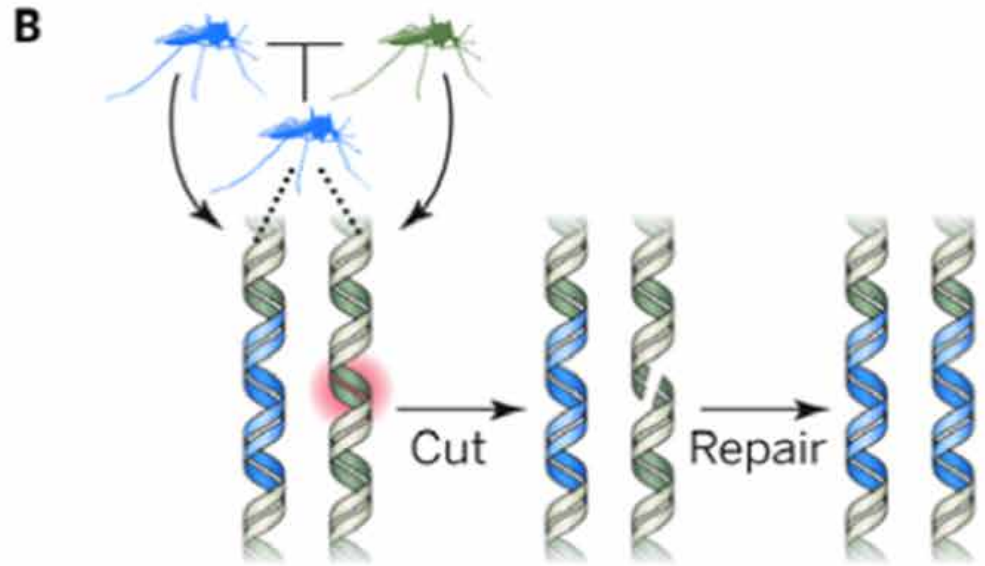
HOW GENE DRIVES BIAS INHERITANCE

A Altered genes (blue) and wild type (grey) ~ 50 % odds

B Altered gene with gene drive and wild type ~ 100 % odds
Gene drives cut homologous chromosomes lacking alteration and cause cell to copy altered gene and the gene drive



Standard altered gene
1 copy inherited from 1 parent
50% chance of passing it on



Altered gene + gene drive
1 copy → 2 copies
100% chance of passing it on

Sciencexpress

Policy Forum

Regulating gene drives

Kenneth A. Oye,[1,2*†] Kevin Esvelt,[3*] Evan Appleton,[4] Flaminia Catteruccia,[5,6] George Church,[3] Todd Kuiken,[7] Shlomiya Bar-Yam Lightfoot,[2] Julie McNamara,[2] Andrea Smidler,[5,8] James P. Collins[9]

[1]Political Science Department, Massachusetts Institute of Technology. [2]Engineering Systems Division, Massachusetts Institute of Technology. [3]Wyss Institute, Harvard University. [4]Bioinformatics, Boston University. [5]Harvard School of Public Health. [6]University of Perugia, Italy. [7]Woodrow Wilson International Center for Scholars. [8]Harvard Medical School. [9]School of Life Sciences, Arizona State University.

*Principal contributors to this piece.

†Corresponding author. oye@mit.edu

Regulatory gaps must be filled before gene drives could be used in the wild

Genes in sexually reproducing organisms normally have, on average, a 50% chance of being inherited, but some genes have a higher chance of being inherited. These genes can increase in relative frequency in a pop-

nome engineering that uses the CRISPR nuclease Cas9 to cut sequences specified by guide RNA molecules (5, 6). This technique is in widespread use and has already engineered the genomes of more than a dozen species. Cas9 may enable "RNA-guided gene drives" to edit nearly any gene in sexually reproducing populations (1).

To reduce potential negative effects in advance of construction and testing, Esvelt et al. have proposed several novel types of drives (1). Precision drives could exclusively affect particular species or subpopulations by targeting sequences unique to those groups. Immunizing drives could block the spread of unwanted gene drives by preemptively altering target sequences. Reversal drives could overwrite unwanted changes introduced by an initial drive or by conventional genome engineering, even restoring the original sequence. However, ecological effects would not necessarily be re-

ENVIRONMENTAL ISSUES

Mutation of gene drives inevitable, will alter effects
Lateral gene transfer may reduce discrimination
Immunization and reversal may not be effective
Diseases borne by vectors will evolve
Environmental effects will vary by species and alteration

SECURITY ISSUES

Gain-of-function enabling ability to host diseases
Suppression of crops and livestock in traditional agriculture
Suppression of pollinators and other keystone species
Immunization drives may protect self and allies from effects
Reversal drives may be withheld for economic or political gain
Security implications uncertain - note ingenuity and creativity

INTERNATIONAL ENVIRONMENT

Transborder movements inevitable, effects complex

CARTAGENA

- Article 17 “Unintentional Transboundary Movements and Emergency Measures” notify if released organism likely to have significant adverse effects on biodiversity or health.
- Other provisions treat movement of organisms as trade issue, with controls through ordinary border measures.

NAGOYA-KUALA LUMPUR SUPPLEMENT

- Article 27 - Parties to adopt process to define rules on liability and redress for damage from trans-border movements

INTERNATIONAL SECURITY

1925 GENEVA PROTOCOL

- Prohibits “bacteriological methods of warfare”
- Extends (by analogy) to viral agents . . . and more?

UN BIOLOGICAL WEAPONS CONVENTION

- Article 1 “general purpose criterion” bans development, production, or stockpiling of agents that have no justification for prophylactic, protective, and other peaceful purposes.
- National measures and Australia Group Guidelines rely on lists of organisms and toxins

2009 FDA GUIDANCE*

Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs

An rDNA construct in a genetically engineered animal and is intended to affect animal structure or function meets the definition of an animal drug . . .

Developers demonstrate that construct and new products expressed from construct are safe for the animal

>> Fit with suppression of Asian carp, zebra mussels or mice?

SOME REACTIONS AND EXTENSIONS

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OMG

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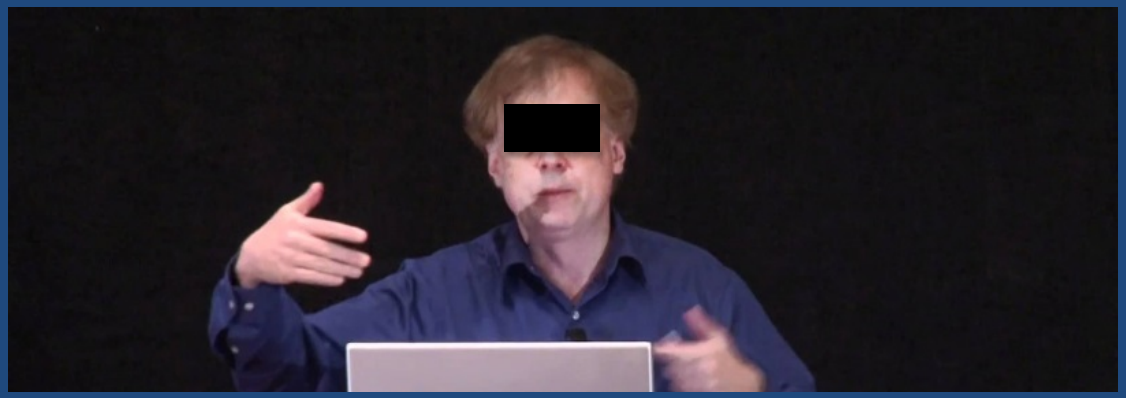
OMG

Don’t tell the muggles
They will panic



Besides the magic is not ready.

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Classify all information needed to create gene drives

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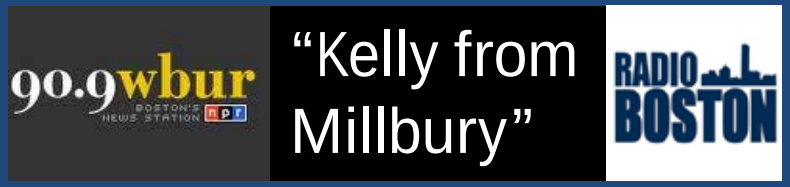
Malaria is nature's way of controlling human population
Don't eradicate malaria



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Gene drives will affect the global commons
We need global discussion of values and decision processes

USES OF LEAD TIME

Science nerds: Assess environmental and security effects, flag sources of uncertainty, direct research at uncertainty

- Effect of possible instability of drives on environment
- Effect of lateral gene flow on diffusion of alterations
- Improve test methods - mesocosms and microcosms

Technology geeks: Modify organisms and uses to minimize risks by designing, testing and incorporating safety features

- Develop and test immunization and reversal drives
- Design-degeneration to degrade efficiency, localize effect

Policy wonks: Identify and address gaps in policy, fund research, foster informed public debate . . . .

- Functional approach -- not just lists of pathogens
- Gaming / “white hat hacking” to flag misuses
- Public debate over benefit/risk in advance of release

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NSF Env Res Agenda; USDA Biotech Risk Assessment Grants

Technology geeks: Modify organisms and uses to minimize risks by designing, testing and incorporating safety features

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Gene drive labs adopt safety code on research
Church/Esvelt developing and testing safeguards

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US NSABB, UN BWC, NRC Gene Drive Study, IEGBRR

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APPROACHES TO RISK GOVERNANCE UNDER UNCERTAINTY

PERMISSIVE

Allow innovation unless environment, health, security are clearly compromised
After-the-fact reaction if crisis materializes; backlash may limit innovation
Examples: Post-Fukushima nuclear shutdown, US stasis on gene therapy

PRECAUTIONARY

Limit innovation unless environment, health and security are clearly protected
Diversion of innovation to less regulated areas may heighten risks
Examples: EU on GMOs, US on stem cell research, German genetic data protection

PLANNED ADAPTIVE

Prepare: Fund research to inform priors on benefits and risks
Discriminate: Foster initial applications with most favorable priors
Observe: Harvest and process information from initial experience
Adapt: Learn from experience and update/correct practices

QUESTIONS TO PANELISTS

How would apps be treated under existing European and US policies?

- H5N1 gain-of-function research
- Nitrogen fixation in non-legumes
- Lightly contained biofuels / mining / effluent treatment
- Technical measures to limit horizontal gene flow or reduce fitness
- Vanillin synthesis
- Opiate synthesis
- Human somatic gene therapy
- Human germline modification
- Gene drives to control vector borne disease (Lyme, malaria, dengue)
- Gene drives to suppress invasive species (Spanish slug, Asian carp)

What evidence do we need but lack on environmental, safety, security effects of apps? What research is needed? Who should fund research?

Should the US and Europe adopt general policies on synthetic biology or differentiated policies on applications of synthetic biology?