SESSION III: FORECASTING IMPLICATIONS OF EMERGING BIOTECHNOLOGIES

THE CASE FOR PROACTIVE AND ADAPTIVE CONSIDERATION OF RISKS AND BENEFITS

Kenneth A. Oye
Professor of Political Science and Data, Systems and Society
Director, Program on Emerging Technologies
Massachusetts Institute of Technology

I. Lessons from the NIH Guidelines Workshop

David Baltimore Keynote: Asilomar and NIH Guidelines

Panel on Emerging Biotechnologies: New Stuff Undermines Premises

II. Approaches to Risk Governance

Permissive and Precautionary Risk Governance

Forecasting Failures: Laser, GPS, Automobile

Proactive and Adaptive Risk Governance: Exemplary US EU Cases

III. Applications to Current Biotech: Uncertainty, Observability and Reversibility

Business-As-Usual? SCGT human and animal, regenerative medicines

Not sure? Opiate production

Unique Risks? Xeno-transplantation, HGGT, gene drives

IV. Conclusions: Implications for Funders and Researchers

LESSONS FROM 2017 NIH GUIDELINES WORKSHOP

KEYNOTE ADDRESS BY DAVID BALTIMORE

ASILOMAR 1975: THE GREAT DEBATE

- WATSON: FULL SPEED AHEAD
- BALTIMORE: UNCERTAINTY / MORATORIUM / RESTRAINT

ROCKVILLE 2017: NOTHING BAD HAPPENED. WAS WATSON RIGHT?

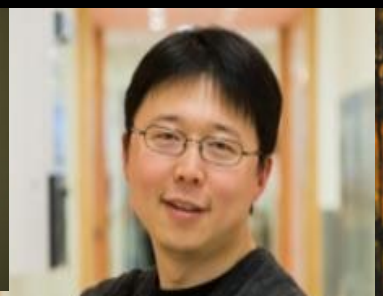
- NIH FUNDED UNIVERSITIES INSTITUTIONALIZED OVERSIGHT
- RESEARCHERS ACTED RESPONSIBLY, LIMITED RELEASES
- MENDEL AND NATURAL SELECTION TOOK CARE OF THE REST

SESSION IV – EMERGING BIOTECHNOLOGY – WILL THE SYSTEM KEEP WORKING?

DREW ENDY: SYN BIOLOGY >>> SKILL THRESHOLDS FALL, BIOTECH DIFFUSES

FENG ZHENG: CRISPR >>> POWERFUL AND EFFICIENT GENE EDITING

ZACH ADELMAN: GENE DRIVES >>> SUPER-MENDELIAN PROPAGATION



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APPROACHES TO RISK GOVERNANCE

Permissive

- Rebuttable presumption of benefit
- Allow unless evidence of harm
- If problems materialize, react after-the-fact

Precautionary

- Rebuttable presumption of harm
- Restrict unless evidence of safety
- Restrictions may limit experiential learning on benefits and harms

Proactive and 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

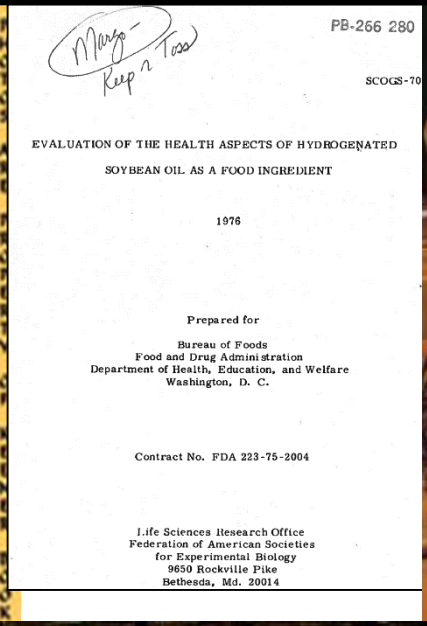
Exemplary Cases	Cautionary Tales
FAA-NTSB air safety	NASA shuttle
EU TSE policy	USDA BSE policy
EPA PM2.5	FDA Transfats

PERMISSIVE: ALLOW UNLESS EVIDENCE OF HARM, REACT AFTER-THE-FACT

DDT
Transfats

Widespread use
Satfats bad. Transfats GRAS.

Silent Spring
Tranfats cause CHD


PB-266 280

SCOGS-70

EVALUATION OF THE HEALTH ASPECTS OF HYDROGENATED SOYBEAN OIL AS A FOOD INGREDIENT

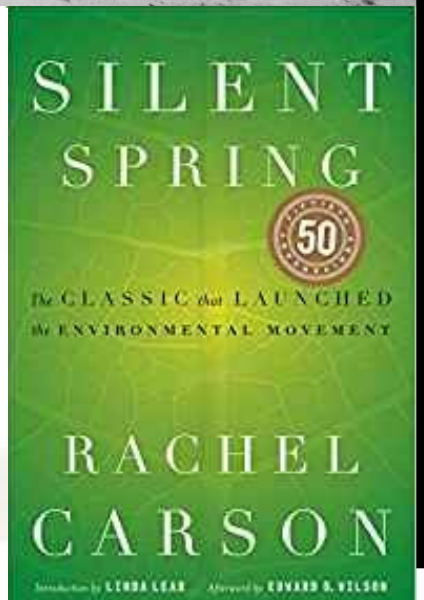
1976

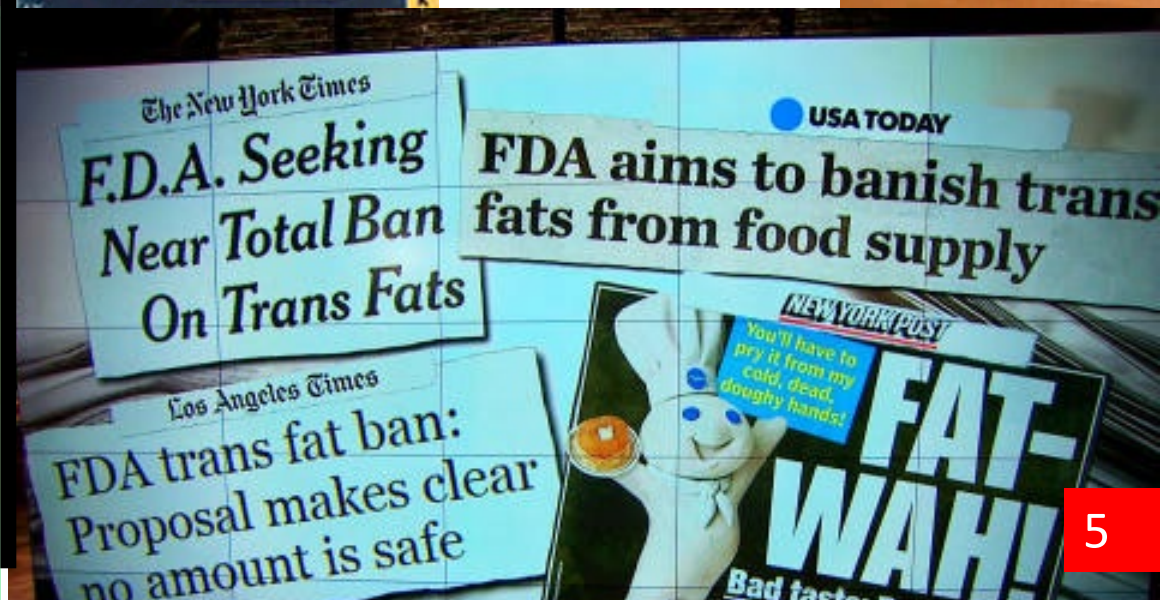
Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D. C.

Contract No. FDA 223-75-2004

Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Md. 20014





PRECAUTION: ACT ON WARNING, DISALLOW WITHOUT PROOF OF SAFETY

Y2K	US imposed standards and invested in infrastructure
GMO release	EU limits GMO field release
Pathogenic DNA elements	HHS DNA Screening Guidance (voluntary) + IGSC
Iran nuclear weapon	US-Israel attack Iran with Stuxnet and assassinations

11:59:59 31 DECEMBER 1999
12:00:00 01 JANUARY 2000

GMO-free Europe

theguardian

Revealed: the lax laws that could allow assembly of deadly virus DNA

Urgent calls for regulation after Guardian buys part of smallpox genome through mail order

IGSC
international gene synthesis consortium

IASB
International Association Synthetic Biology

6-A

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WARNING

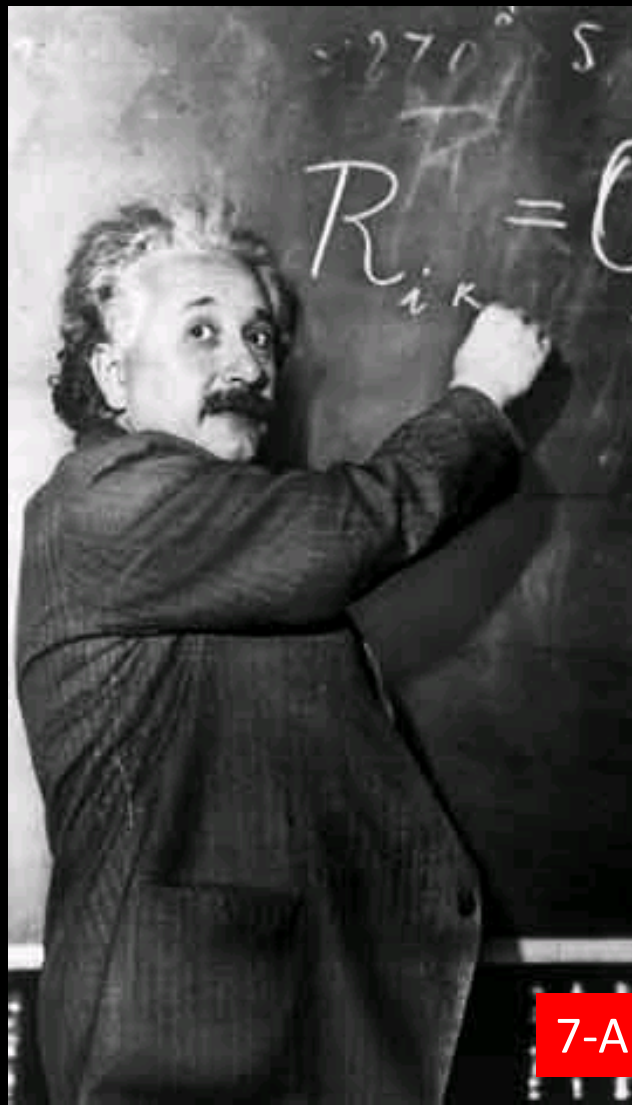
BOTH PERMISSIVE AND PRECAUTIONARY APPROACHES
REST ON PRESUMPTIVE ABILITY TO ANTICIPATE BENEFITS / RISKS

IGSC
international gene synthesis consortium

IASE
International Association Synthetic Biola

Technology Forecasting: Looking Back at Past Projections . . .

"There is not the slightest indication that nuclear power will ever be obtainable."
Albert Einstein 1932



New York Times Monday January 10, 2005 Page C4

Technology Forecasting: Looking Back at Past Projections . . .

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Thomas Watson 1943

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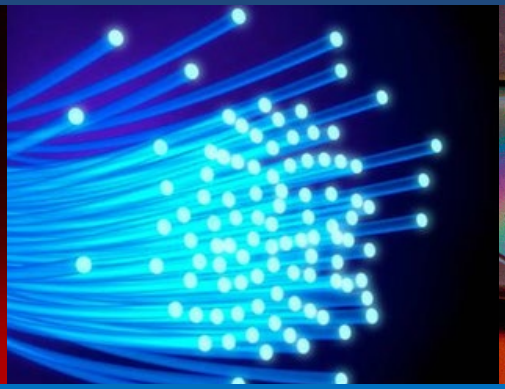
Albert Einstein 1932

"I think there is a world market for maybe five computers."
Thomas Watson 1943

"Two years from now, spam will be solved."
Bill Gates 2004

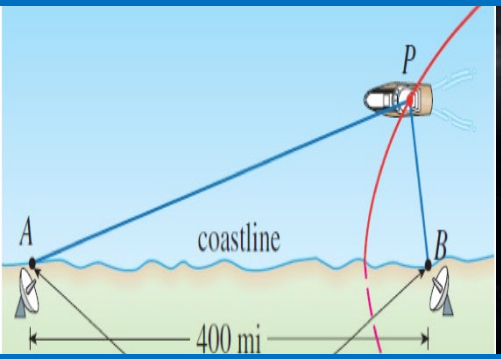
New York Times Monday January 10, 2005 Page C4

UNCERTAINTY OVER APPLICATIONS AND EFFECTS OF EMERGING TECHNOLOGIES CONTEMPORANEOUS FORECASTS ARE TYPICALLY WRONG



LASER CASE

LAWRENCE MCCRAY AND MARK AVNET



GPS CASE

DANIEL HASTINGS AND SPENCER LEWIS

AUTOMOBILE CASE

MERRITT ROE SMITH AND CHRISTINE NG

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FAA-NTSB air safety	NASA shuttle
EPA PM 2.5	USDA BSE policy
EU TSE & EMA adaptive licensing	FDA transfats

COMMERCIAL AVIATION

1975 US LEGISLATIVE REFORM

"No Federal agency can properly perform such functions unless it is totally separate."

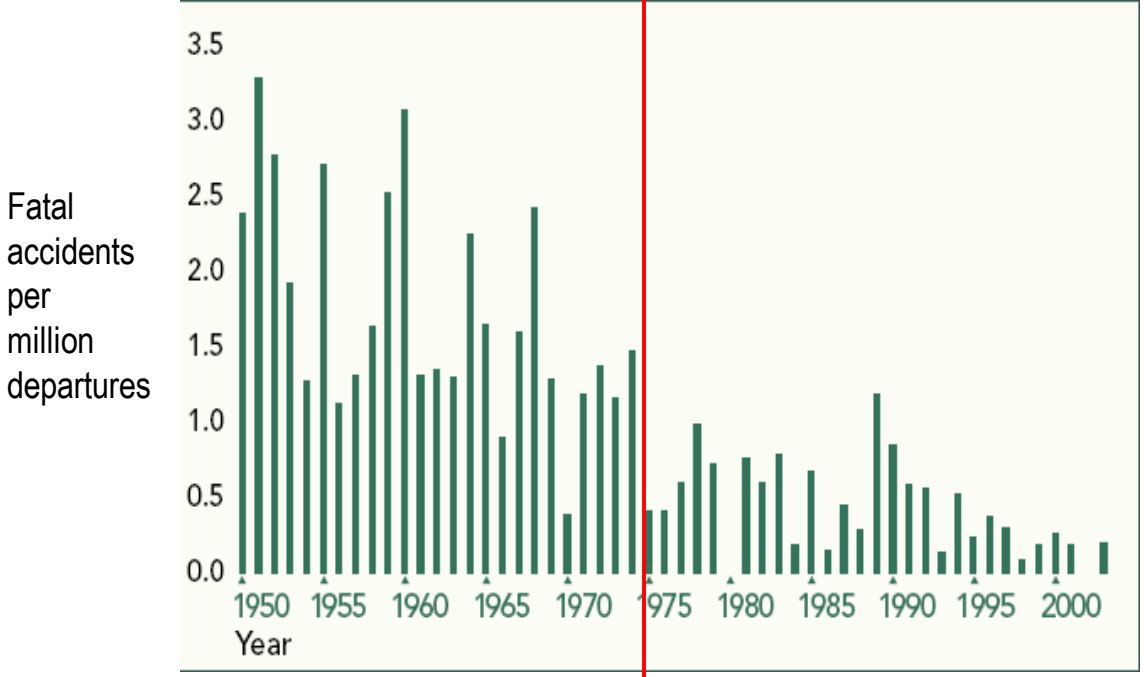
FAA certifies, NTSB investigates

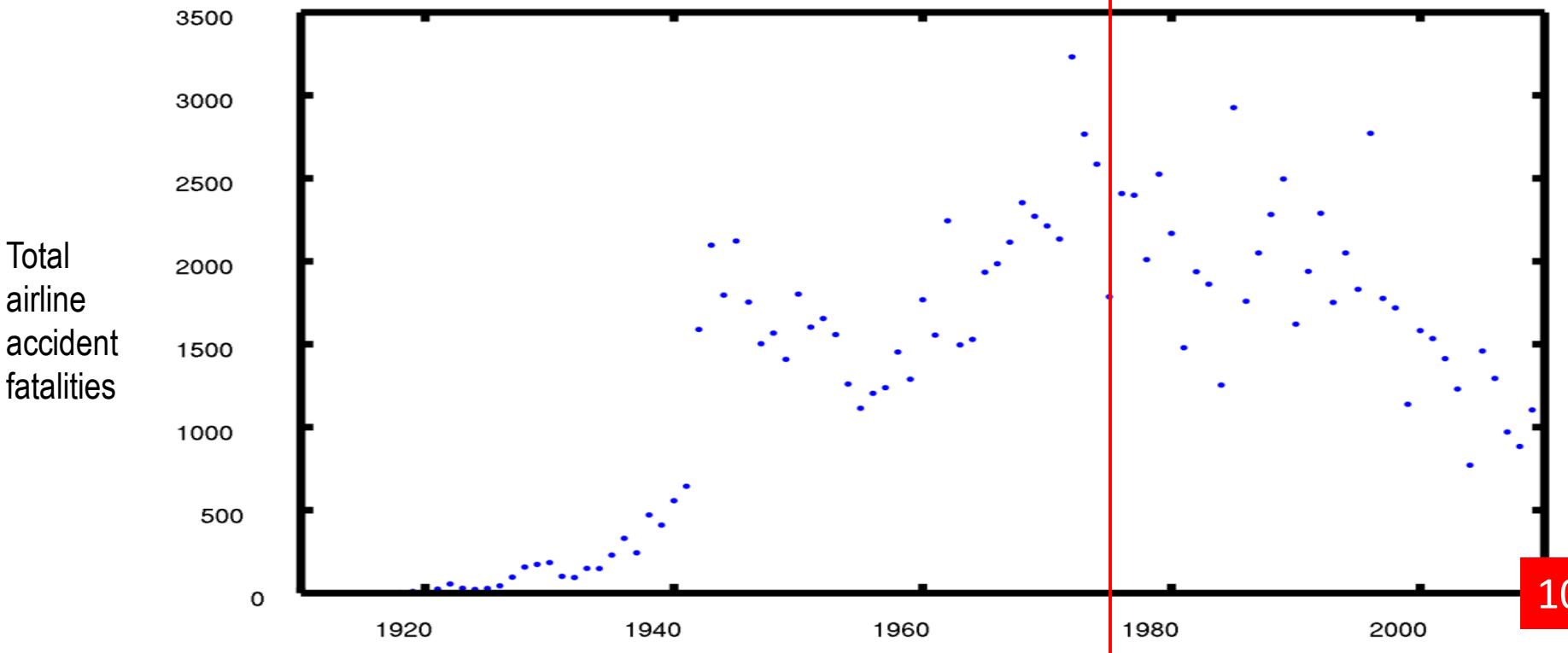
Examine accidents + near misses

NTSB recommends

FAA/makers/airlines usually act

- Why was reform demanded?
- Did the reform work?





EPA NATIONAL AMBIENT AIR QUALITY STANDARDS

- Review process to reassess standards based on best available evidence
- Research funding to reduce uncertainty and improve best available evidence

HARVARD SIX CITIES

8000+ subjects in panels

Adjusted mortality risk ratios

- Age, Sex
- Cigarette Smoking
- Occupational Exposure
- Education
- Body Mass Index
- Chronic Disease

STUDIES IN 80S AND 90S CAPTURE POLICY EFFECTS

Figure 17a: Annual Mean Ambient Sulfate Concentration, 1989 through 1991

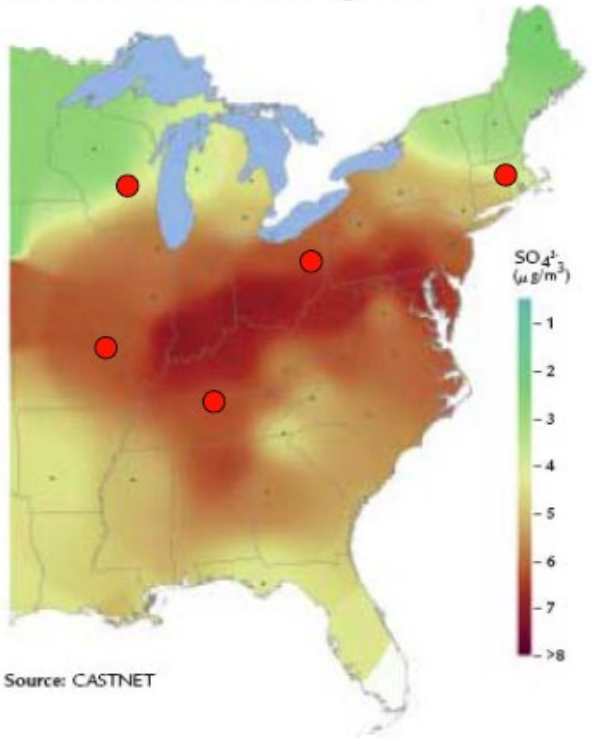
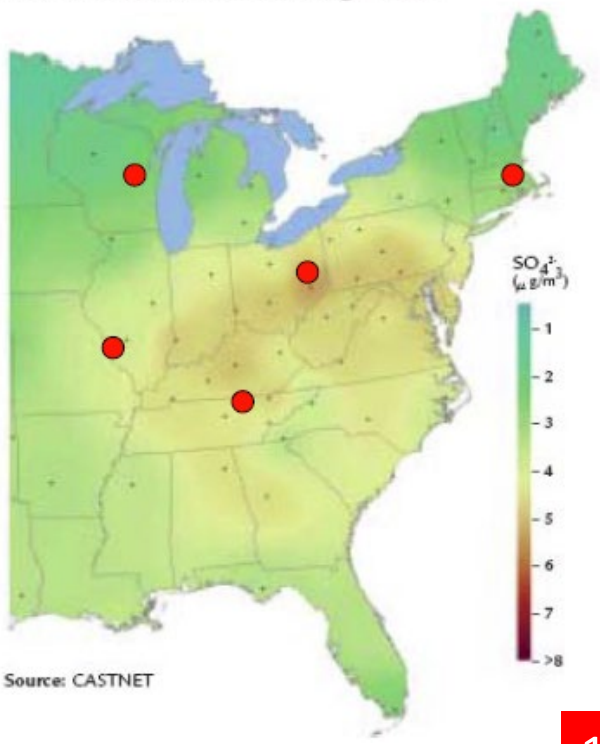


Figure 17b: Annual Mean Ambient Sulfate Concentration, 2002 through 2004



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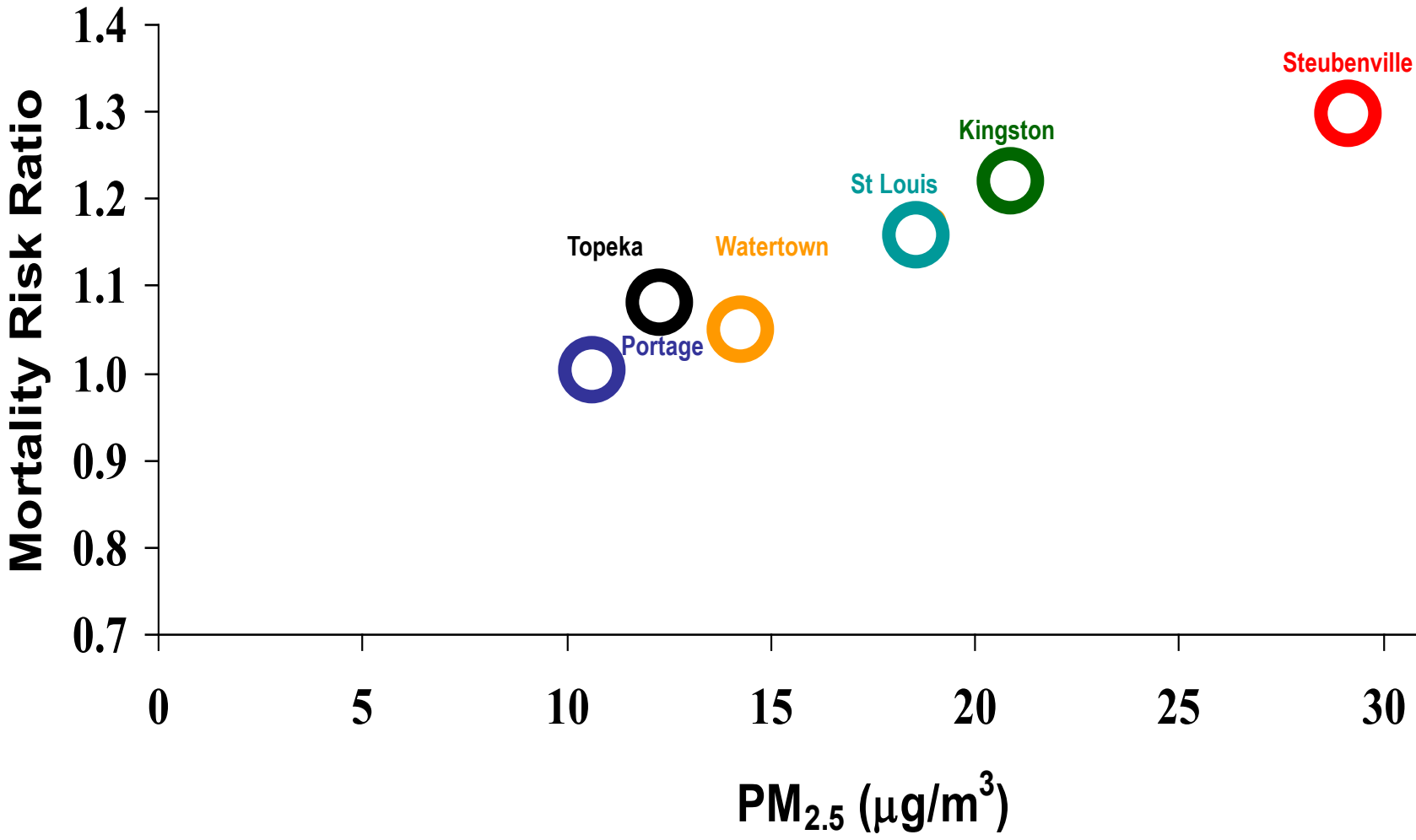
Six Cities Cohort Follow-up Study
1990 - 1998

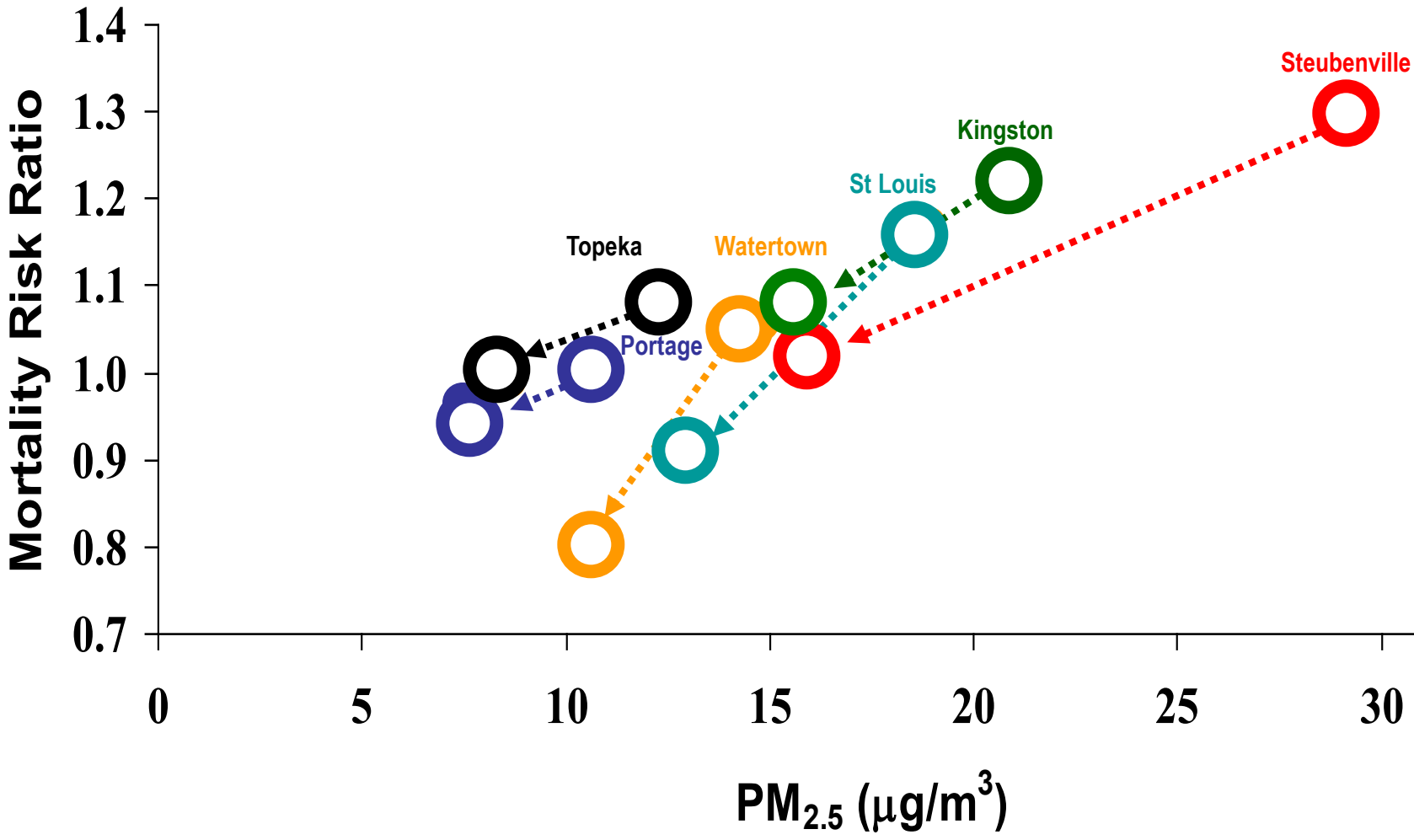


12-A

EPA NATIONAL AMBIENT AIR QUALITY STANDARDS

- Review process to reassess standards based on best available evidence
- Research funding to reduce uncertainty and improve best available evidence

Six Cities Cohort Follow-up Study
1990 - 1998



12-B

EPA NATIONAL AMBIENT AIR QUALITY STANDARDS

- Review process to reassess standards based on best available evidence
- Research funding to reduce uncertainty and improve best available evidence

HEI

SPECIAL REPORT

HEALTH EFFECTS INSTITUTE

July 2000

Includes Errata Sheet Of 11-01-01

Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality

A Special Report of the Institute's Particle Epidemiology Reanalysis Project

Executive Summaries and Commentary

EU TSE ROADMAP – STRUCTURED SENSING AND POLICY FEEDBACK

We have come to the stage that amendments of certain measures could be envisaged without endangering the health of the consumer or the policy of eradicating BSE, provided that the positive trend continues and scientific conditions are in place. Indeed different indicators already suggest a favourable trend in the BSE epidemic and a clear improvement of the situation in recent years due to the risk reducing measures in place. Furthermore, inspection reports indicate that implementation of BSE requirements in the Member States has improved. The main indicators are presented in Charts 1 -3 of Annex I.

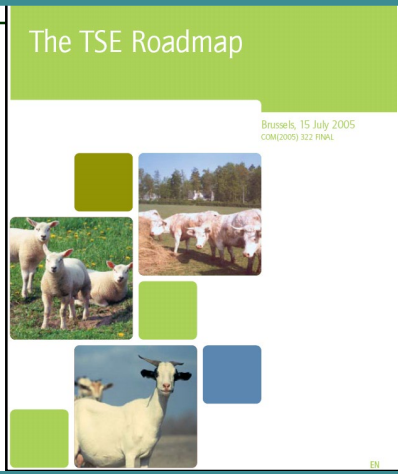
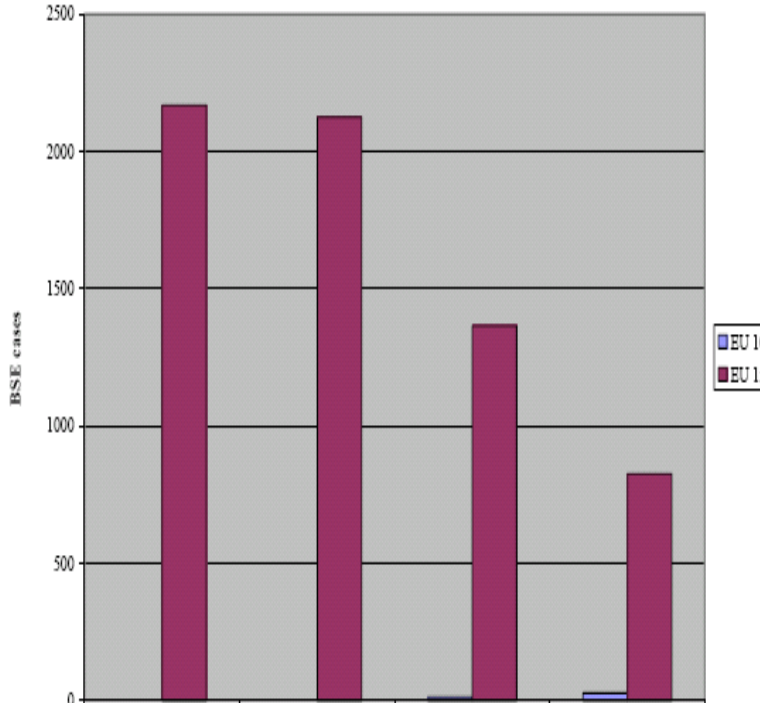
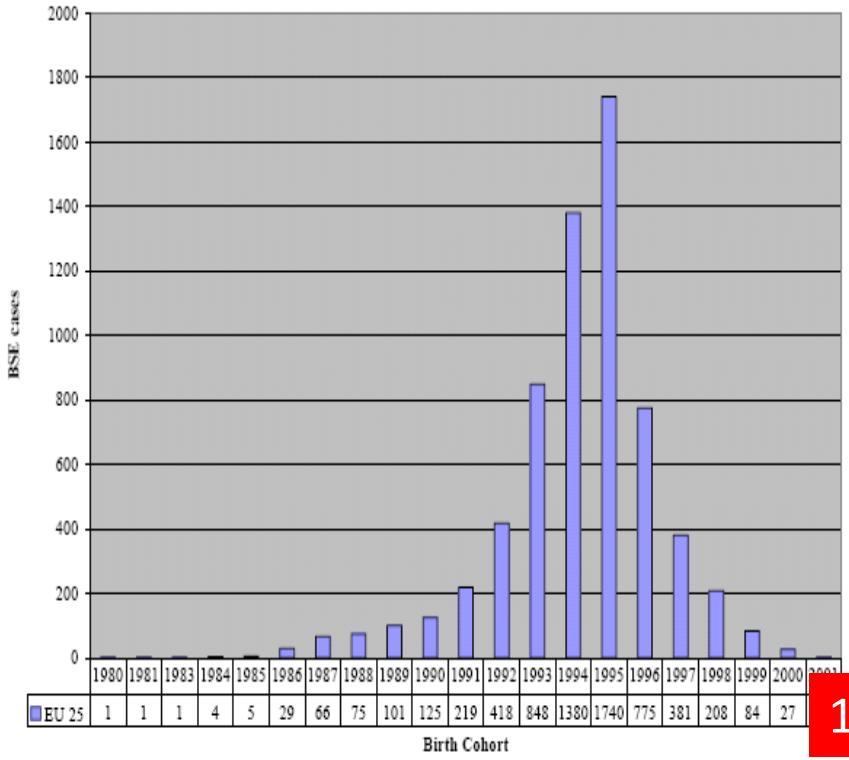


CHART 1: EU BSE CASES 2001 TO 2004



	2001	2002	2003	2004
EU 10			12	27
EU 15	2167	2124	1364	825

CHART 2: EU BSE CASES BY BIRTH COHORTS



	1980	1981	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
EU 25	1	1	1	4	5	29	66	75	101	125	219	418	848	1380	1740	775	381	208	84	27	

EMA ADAPTIVE ;LICENSING PILOT AND POLICY

- Evidence on safety and efficacy up front
- Limits on initial applications to balance benefits and risks
- Monitoring and updating based on drugs in use

STATE OF THE ART

nature publishing group

Open

See COMMENTARY page 378

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[2]

Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive licensing (AL) approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of perspectives. Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformative framework that may require legislative action before implementation. This article summarizes recent AL proposals;

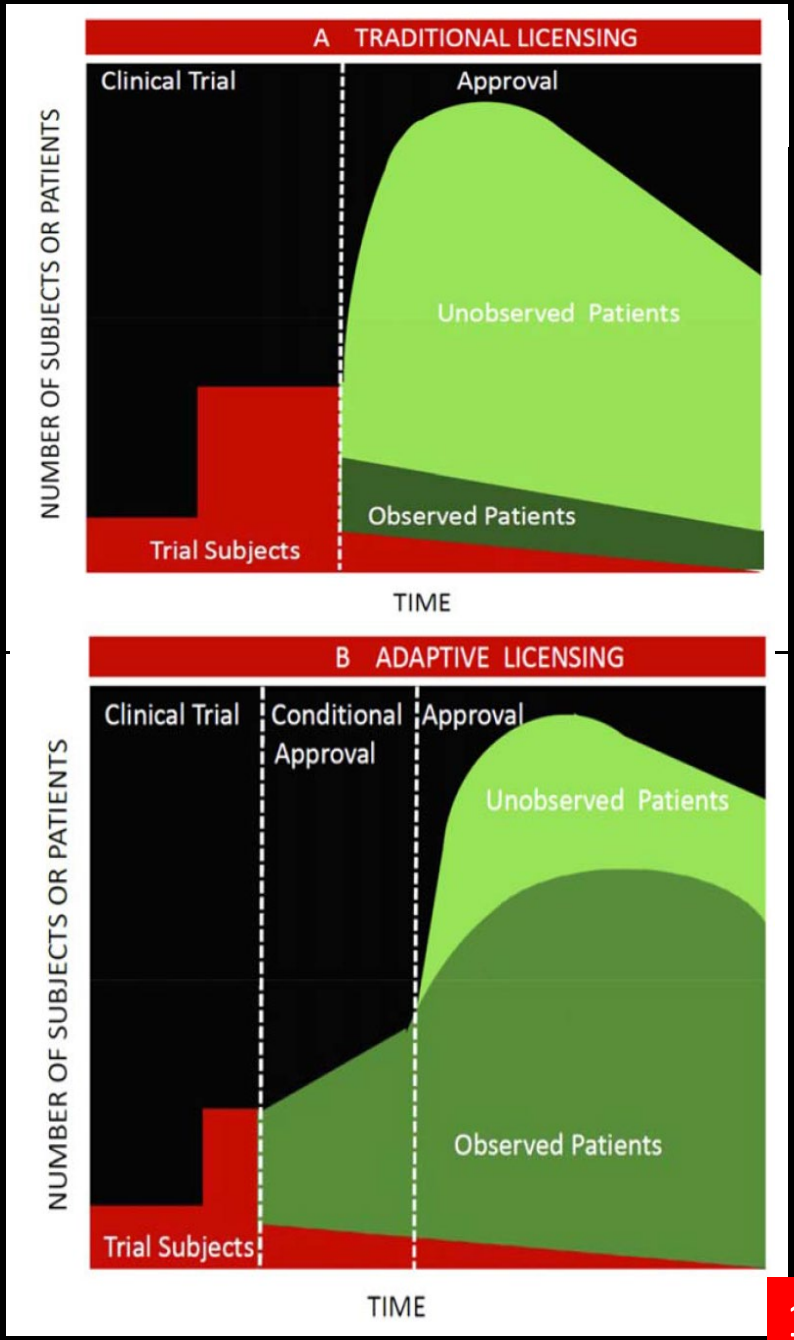
EU ADAPTIVE LICENSING
Patient experience contributes to evidence development

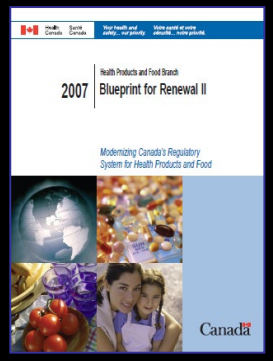
<u>FRONT END – PRE MARKET</u>
Earlier approval
Conditional
Limit to patient subset on benefit/risk

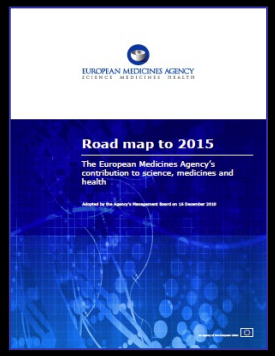
<u>BACK END – ON MARKET</u>
Strengthen observation
- Registries
- EHRs

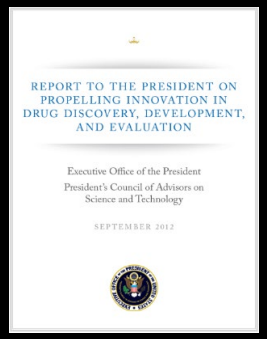
Analyze safety and effectiveness
Adapt label and license

KEY
Patients in interventional studies
Patients treated but unobserved
Patients treated and observed









pmda
aceuticals and Medical Devices Agency

STEPS TOWARD ADAPTIVE PATHWAYS

Health Canada

Progressive Licensing Exercise (not approved)	2008
Parliament enacts safety reform /adaptive licensing	2014

European Medicines Agency

Pharmacovigilance legislation	2010
EFPIA planning IMI project on AL/MAPPs	2013
EMA/EUnetHTA 3 year post market data plan	2013
EMA AL Pilots	2015
EMA Adaptive Pathways as policy	2016

US IOM PCAST AND FDA

PCAST report recommends exploring SMU and AL	2013
Breakthrough product designation established	2012
• 64 requests for designation in year 1, 24 granted	2013
• 2 FDA-CMS parallel review pilot projects	2013

JAPAN PMDA

Conditional limited approval regenerative medicine	2014
Forerunner Review Assignment	2014

ELEMENTARY PRINCIPLES FOR GOVERNING EMERGING RISKS

PROSPECTIVELY PLAN ADAPTATION

- Phenomena regulated and effects of policies not well understood upfront.
- Understandings change with observations on use.
- Act on priors on risks/benefit and update as understandings evolve.

OBSERVING/SENSING/REVEALING

- Parties must have interest in harvesting and sharing info on benefits/risks.
- Create incentives to reveal info (funding, liability waivers, IP protections).

CREDIBLE ASSESSMENT OF SCIENTIFIC AND TECHNICAL KNOWLEDGE

- Conflicts of interest, inertia and prior beliefs bias assessments.
- Complexity, uncertainty, controversy typical
- Consider both neutral technocratic and adversarial methods of assessment

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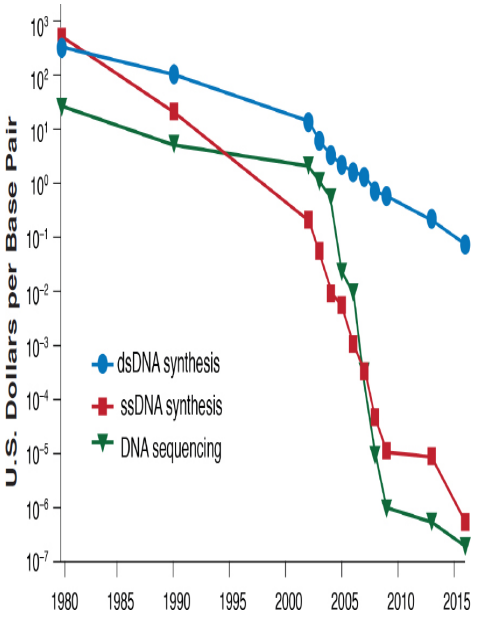
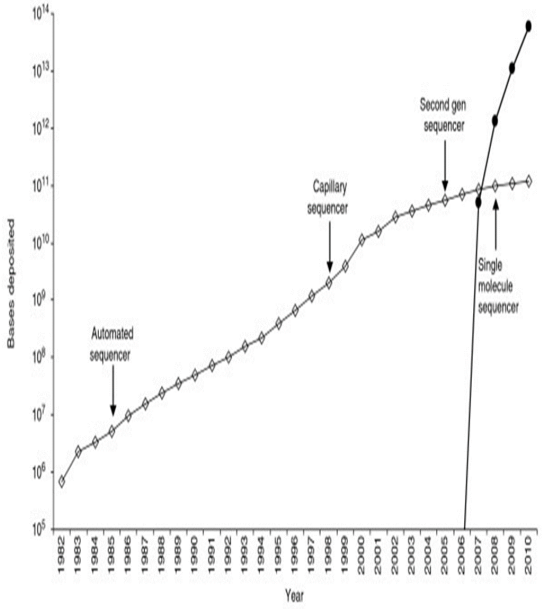
ENABLING TECHNOLOGIES

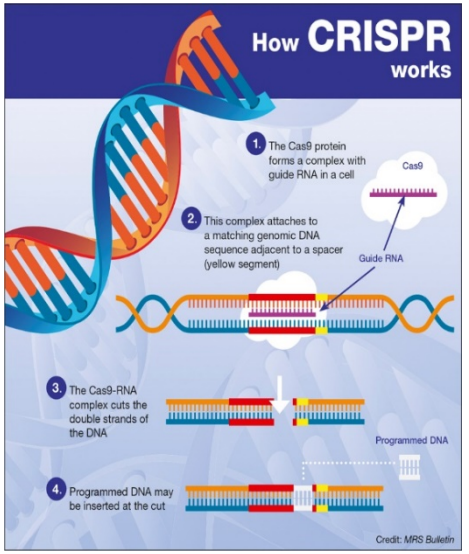
DNA SEQUENCING: EXPONENTIAL DECLINE IN COST AND EXPANSION OF DATA
INFORMATION TECHNOLOGY: EXPONENTIAL GROWTH IN DATA ANALYSIS AND DESIGN
DNA SYNTHESIS: EXPONENTIAL ADVANCES IN EFFICIENCY AND LENGTH
GENE EDITING TOOLS: FROM ZINC FINGERS AND TALENS TO CRISPR CAS9 AND PRIME



COST OF DNA SEQUENCING & SYNTHESIS



GENOMIC INFORMATION DEPOSITED IN DATA BANKS

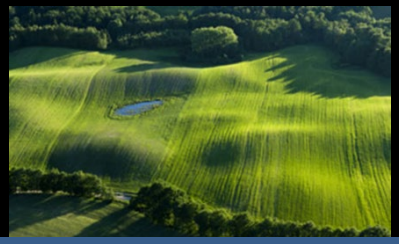


ANALYTIC, DESIGN AND EDITING TOOLS

EMERGING APPLICATIONS

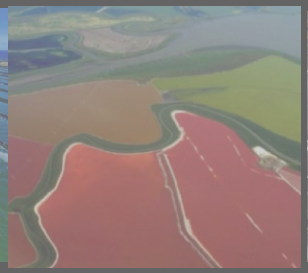
AGRICULTURE

GM Crops and Livestock N Fixation, Glowing Plants, Aquabounty



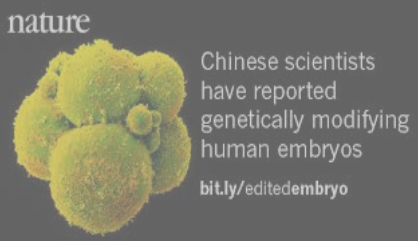
INDUSTRY

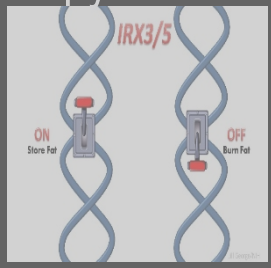
Synthesis of Organic Materials Fuel, Flavors, Drugs



MEDICINE

Regenerative Medicine, Somatic and Germline Cell Therapy





ENVIRONMENT

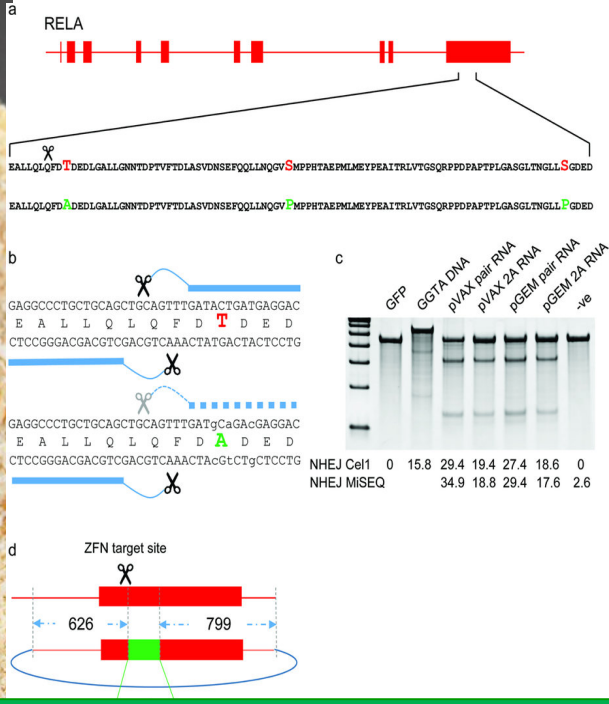
Remediation; Control Vector Borne Disease and Invasive Species

FDA LICENSING OF GE SALMON: FDA APPROVAL 11/12/2015

FOOD SAFETY: FDA compared non-GE farmed and GM salmon, with focus on estradiol, testosterone, 11-ketotestosterone, T3, T4 and insulin-like growth factor 1 (IGF1). No biologically relevant differences.

ENVIRONMENT: FDA issued "Finding of No Significant Impact" (FONSI)
Physical containment: Broodstock in land based tanks with safeguards
Geophysical containment: High water temp, no wild salmon near farms
Biological containment – organism design

- Adults sterile triploid (diploid broodstock)
- Adults all female
- Fitness disadvantage relative to wild type



Mammalian interspecies substitution of immune modulatory alleles by genome editing

Simon G. Lillico[1], Chris Proudfoot[1], Tim J. King[1], Wenfang Tan[1], Lei Zhang[2], Rachel Mardjuki[2], David E. Paschon[2], Edward J. Rebar[2], Fyodor D. Urnov[2], Alan J. Mileham[3], David G. McLaren[3] & C. Bruce A. Whitelaw[1]

Zinc finger nuclease in-embryo editing of the RELA locus generated live born domestic pigs with the warthog RELA orthologue, associated with resilience to African Swine Fever.
Roslin Institute, University of Edinburgh

Scientific Reports 6, 21645 (2016)
DOI:10.1038/srep21645

Disruption of *FGF5* in Cashmere Goats Using CRISPR/Cas9 Results in More Secondary Hair Follicles and Longer Fibers

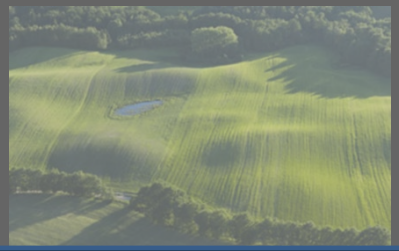
Xiaolong Wang[1☯], Bei Cai[1☯], Jiankui Zhou[2,3☯], Haijing Zhu[4,5], Yiyuan Niu[1], Baohua Ma[6], Honghao Yu[4,5], Anmin Lei[6], Hailong Yan[1,4,5], Qiaoyan Shen[6], Lei Shi[4,5], Xiaoe Zhao[6], Jinlian Hua[6], Xingxu Huang[2,3]*, Lei Qu[4,5]*, Yulin Chen[1]*

Cas9 mRNA and sgRNAs targeting the MSTN and FGF5 genes in goat embryos results in increased number of second hair follicles and enhanced fiber length, suggesting more cashmere will be produced. Knockout alleles were likely capable of germline transmission.
Northwest A&F U Nanling China PLOS ONE Oct 15, 2016
DOI:10:1371/journal.pone.0164640

EMERGING APPLICATIONS

AGRICULTURE

GM Crops and Livestock N Fixation, Glowing Plants, Aquabounty

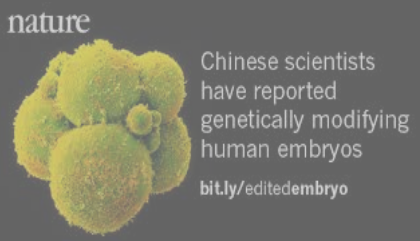


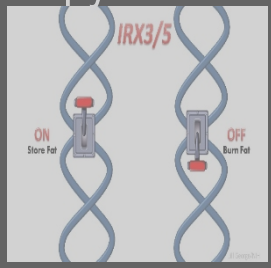
INDUSTRY

Synthesis of Organic Materials Fuel, Flavors, Drugs

MEDICINE

Regenerative Medicine, Somatic and Germline Cell Therapy





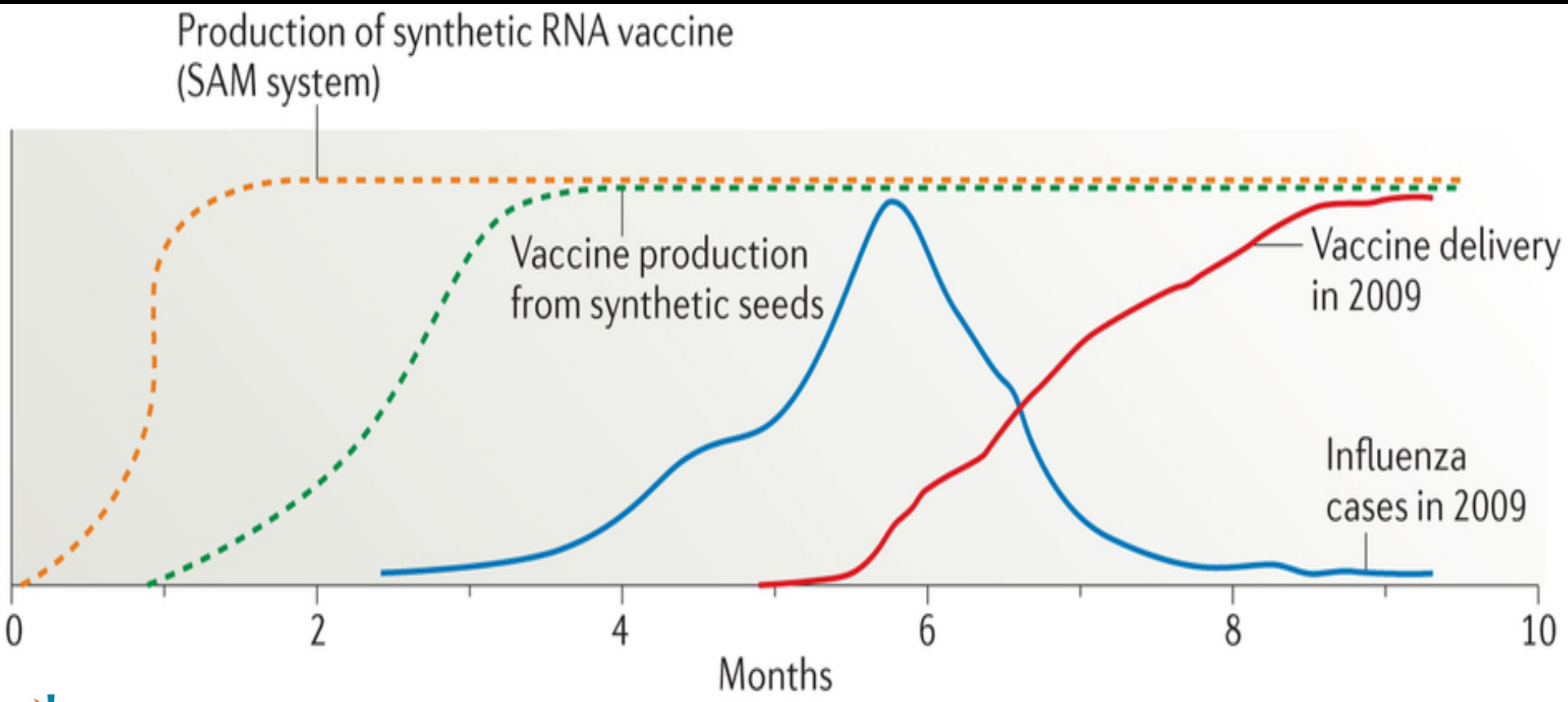
ENVIRONMENT

Remediation; Control Vector Borne Disease and Invasive Species

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

Why? Alter pathways to create safer less addictive analgesics

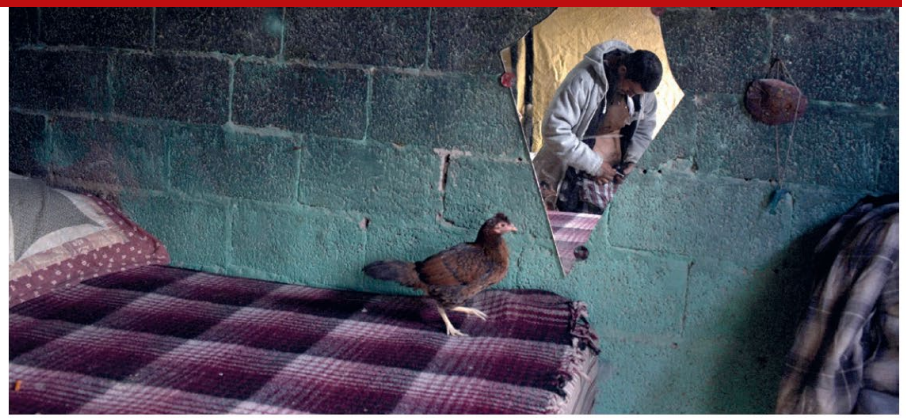
How? From low titer wimpy strains to high titer robust strains

Dueber/Martin tech papers 2015

Oye/Bubela/Lawson Nature 2015

Galanie/Thodey/Smolke Science 2015

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 ▶

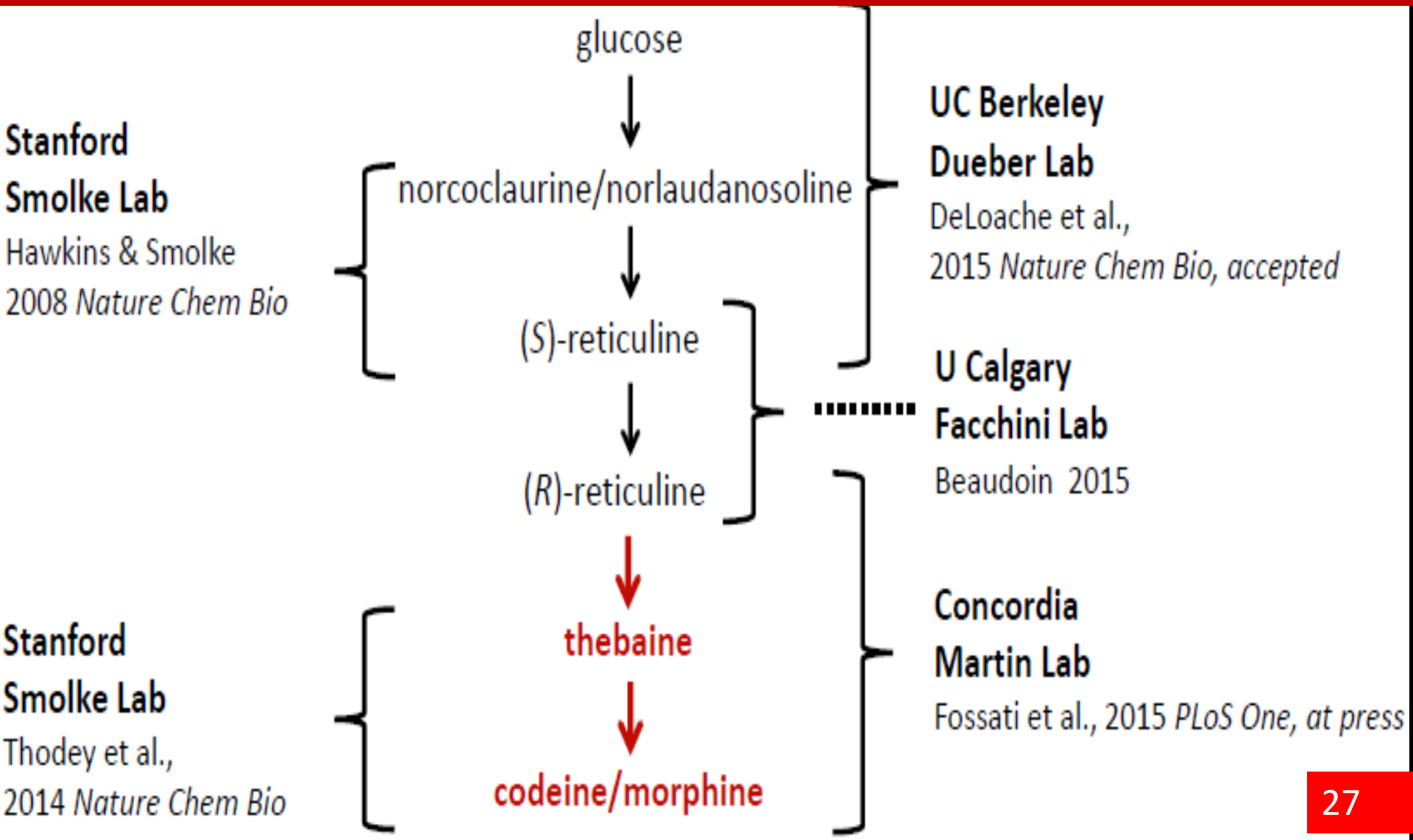
Science

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

OPIATE PRODUCTION IN YEAST: TWO RESEARCH GROUPS
Smolke, Thodey, Hawkins (Stanford)
Dueber (UCB), Facchini (Calgary), Martin (Concordia)



(NOT) BREWING BAD: LIMITING DIFFUSION?

PERSONNEL SECURITY

Psychological disorders

- Psychopathy
- Borderline personality disorder
- Narcissistic personality disorder

Other Risk Factors

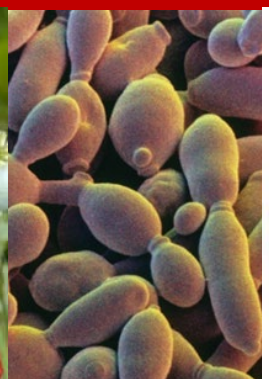
- Financial stress
- Status insecurity
- Sleep deprivation
- Perceived unfairness

LAB SECURITY

- Entry and exit control
- Materials access
- Inventory management
- Information controls

REDUCE APPEAL OF STRAINS

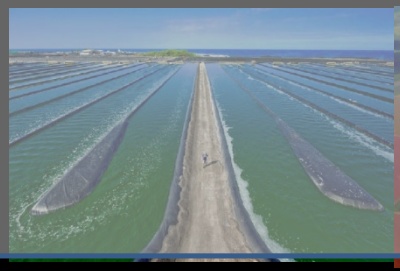
- Insert markers for traceability
- Make hard to cultivate
- Stop short of opiates
- Make distasteful to consume

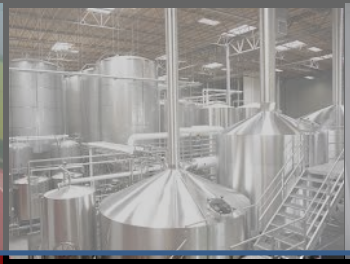


EMERGING APPLICATIONS

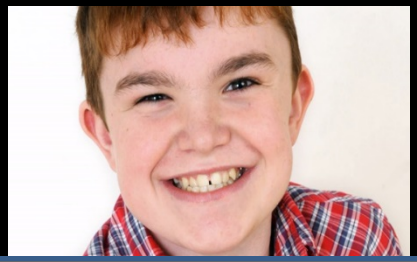
AGRICULTURE — GM Crops and Livestock — N Fixation, — Glowing Plants, Aquabounty

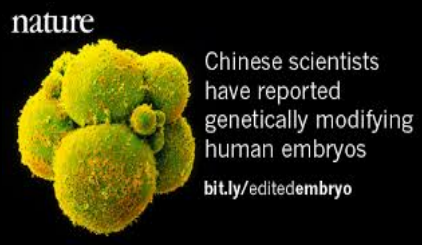
INDUSTRY — Synthesis of Organic Materials — Fuel, Flavors, Drugs

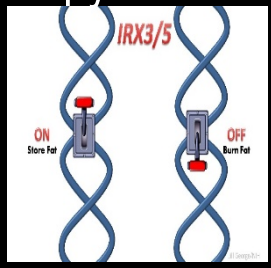




MEDICINE — Regenerative Medicine, Somatic and Germline Cell Therapy







ENVIRONMENT — Remediation; Control Vector Borne Disease and Invasive Species

SOMATIC CELL GENE THERAPY (SCGT)

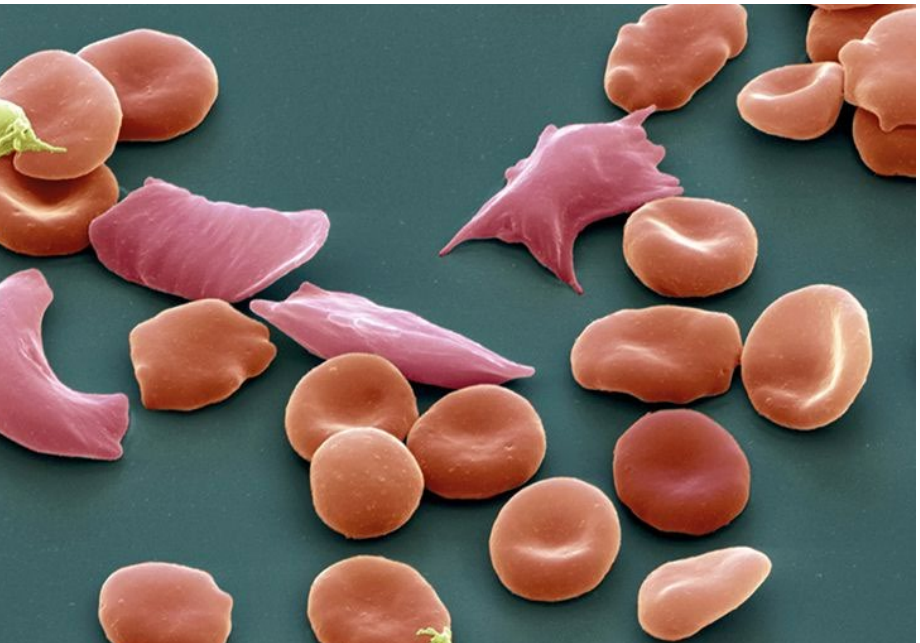
Gene alterations to cure sickle cell, thalassemia, cystic fibrosis, hemophilia.

Example: Bluebird Bio LentiGlobin BB305

- cure ß-thalassemia (approved by European Medicines Agency and US FDA)
- cure sickle cell by inserting healthy β-globin gene into blood stem cells (in trials)

bluebirdbio™

41



MENU nature International journal of science Subscribe Search

OUTLOOK · 12 DECEMBER 2018

Gene therapy targets sickle-cell disease

The research is promising, but a true cure for this painful condition could be years away.

Anna Nowogrodzki

DATA SCIENCES AND SOMATIC CELL GENE THERAPY (SCGT)

Example - "Obesity switch" NEJM September 2015

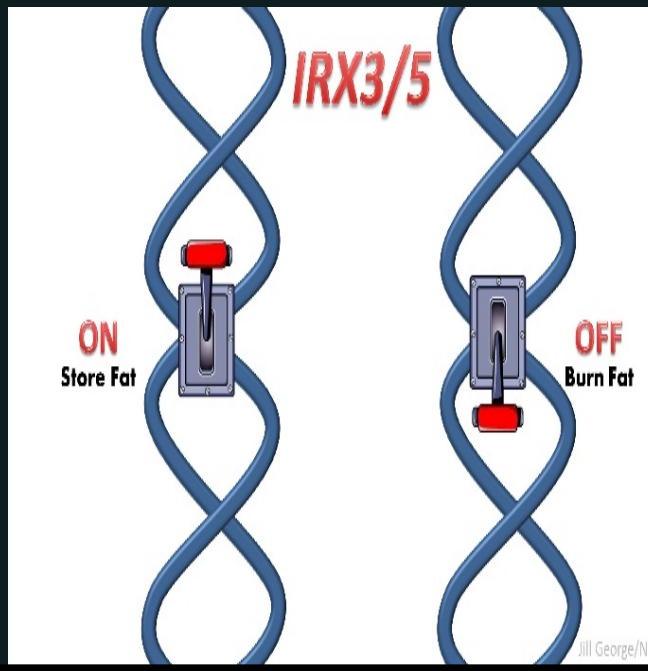
- MIT CSAIL Kellis lab decoded regulatory circuitry FTO obesity locus.
  - Integrated genomic info and health records
  - Applied AI methods to generate hypotheses on targets
- ID path for adipocyte thermogenesis ARID5B, rs1421085, IRX3, IRX5.
- Manipulated genetic switch with pro-obesity & anti-obesity effects.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 3, 2015 VOL. 373 NO. 10

FTO Obesity Variant Circuitry and Adipocyte Browning in Humans

Melina Claussnitzer, Ph.D., Simon N. Dankel, Ph.D., Kyoung-Han Kim, Ph.D., Gerald Quon, Ph.D., Wouter Meuleman, Ph.D., Christine Haugen, M.Sc., Viktoria Glunk, M.Sc., Isabel S. Sousa, M.Sc., Jacqueline L. Beaudry, Ph.D., Vijitha Puviindran, B.Sc., Nezar A. Abdennur, M.Sc., Jannel Liu, B.Sc., Per-Arne Svensson, Ph.D., Yi-Hsiang Hsu, Ph.D., Daniel J. Drucker, M.D., Gunnar Mellgren, M.D., Ph.D., Chi-Chung Hui, Ph.D., Hans Hauner, M.D., and Manolis Kellis, Ph.D.



REGENERATIVE MEDICINE

REPLACE

Engineer differentiated tissue/organ

Insert/transplant in subject

- Tracheal implants - Macchiarrini 2008, 2011
- Retinal Tissue Implant – Kurimoto 2011

REGENERATE

Trigger internal healing in subject

Insert extracellular matrix, modified stem cells

* Own cord blood stem cells

* Donor stem cells, marrow

Procymal for graft-versus-host disease

XENOTRANSPLANTATION

Old Regulatory Issues

- FDA regulates human cells or tissues intended for transplantation.
- FDA does not regulate transplantation of vascularized organs
- Health Resources Services Administration oversees (scarce) organs

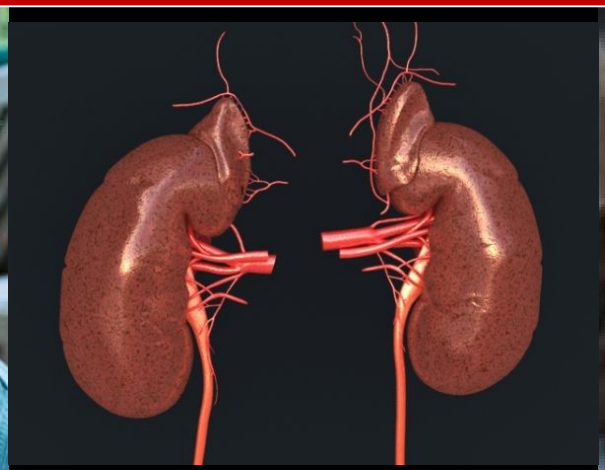
Technological Development – October 2015

- Pig organs with embedded viruses and immune response not usable
- Church Lab edited pig genome, inactivating 62 PERVs* that cause disease & 20 protein encoding genes that trigger immune response

Future Regulatory Issues

- Frame as informed consent: If you need organ, you make the call.
- Frame as health externality: Will retrovirus cross species barrier?

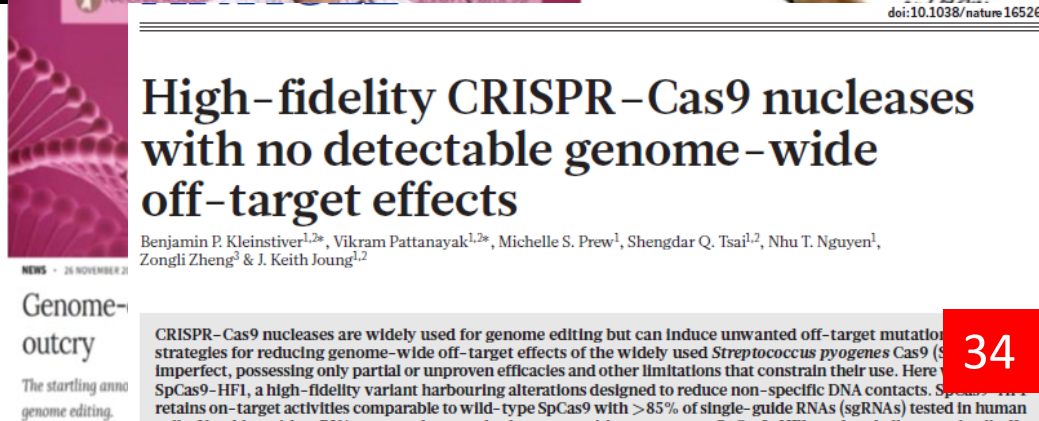
* PERV = Porcine Embedded Retrovirus



GERMLINE GENE THERAPY (GGT)

SCGT works in individual, GGT changes in germline will be heritable

- Huang@Sun Yat-sen edited β-thalassaemia gene 28 embryos. Experiment failed with many off-target effects (4/2015 Protein&Cell)
- Zhang@Broad Improved Cas9 Specificity (12/2015 Science)
- Joung@MGH Hi-fi CRISPR no off-target effects (1/2016 Nature)
- He@Shenzen creates CRISPR babies wi HIV resistance (11/2018)



OPEN

Citation: Transl Psychiatry (2015) 5, e681; doi:10.1038/tp.2015.170

www.nature.com/tp

ORIGINAL ARTICLE

Impulsive alcohol-related risk-behavior and emotional dysregulation among individuals with a serotonin 2B receptor stop codon

R Tikkanen[1,2], J Tiihonen[3,4,5], MR Rautiainen[5], T Paunio[1,5,6], L Bevilacqua[7], R Panarsky[8], D Goldman[8] and M Virkkunen[1,6]

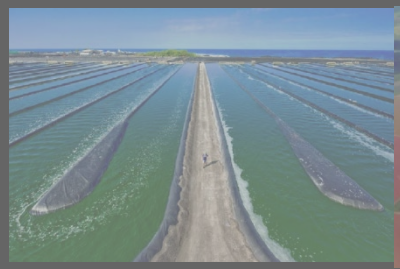
A relatively common stop codon (Q20*) was identified in the serotonin 2B receptor gene (*HTR2B*) in a Finnish founder population in 2010 and it was associated with impulsivity. Here we examine the phenotype of *HTR2B* Q20* carriers in a setting comprising 14 heterozygous *HTR2B* Q20* carriers and 156 healthy controls without the *HTR2B* Q20*. The tridimensional personality questionnaire, Brown–Goodwin lifetime aggression scale, the Michigan alcoholism screening test and lifetime drinking history were used to measure personality traits, impulsive and aggressive behavior, both while sober and under the influence of alcohol, and alcohol consumption. Regression analyses showed that among the *HTR2B* Q20* carriers, temperamental traits resembled a passive-dependent personality profile, and the presence of the *HTR2B* Q20* predicted impulsive and aggressive behaviors particularly under the influence of alcohol. Results present examples of how one gene may contribute to personality structure and behaviors in a founder population and how personality may translate into behavior.

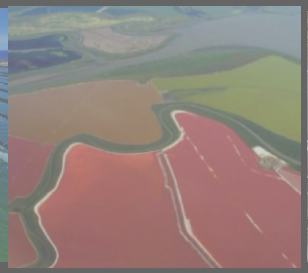
Translational Psychiatry (2015) **5,** e681; doi:10.1038/tp.2015.170; published online 17 November 2015

EMERGING APPLICATIONS

AGRICULTURE — GM Crops and Livestock — N Fixation, Glowing Plants, Aquabounty

INDUSTRY — Synthesis of Organic Materials — Fuel, Flavors, Drugs





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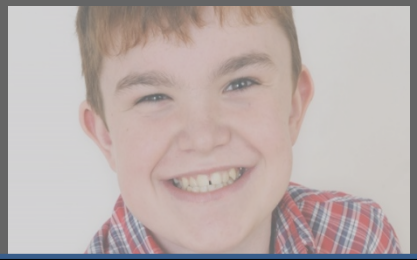
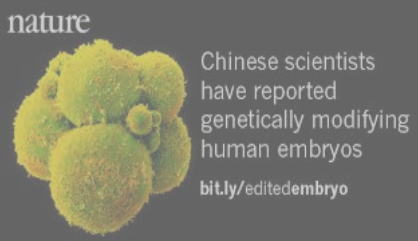
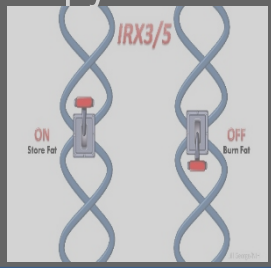






ENVIRONMENT — Remediation; Control Vector Borne Disease and Invasive Species

NOVEL PATHOGENS: MOUSE POX UNINTENDED GAIN-OF-FUNCTION

Journal of Virology
jvi.asm.org

doi: 10.1128/JVI.75.3.1205-1210.2001
J. Virol. February 2001 vol. 75 no. 3 1205-1210

Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox

Ronald J. Jackson[1,2,*], Alistair J. Ramsay[2,†], Carina D. Christensen[2], Sandra Beaton[1], Diana F. Hall[1,‡], and Ian A. Ramshaw[2]

Author Affiliations

ABSTRACT

Genetic resistance to clinical mousepox (ectromelia virus) varies among inbred laboratory mice and is characterized by an effective natural killer (NK) response and the early onset of a strong $CD8^+$ cytotoxic T-lymphocyte (CTL) response in resistant mice. We have investigated the influence of virus-expressed mouse interleukin-4 (IL-4) on the cell-mediated response during infection. It was observed that expression of IL-4 by a thymidine kinase-positive ectromelia virus suppressed cytolytic responses of NK and CTL and the expression of gamma interferon by the latter. Genetically resistant mice infected with the IL-4-expressing virus developed symptoms of acute mousepox accompanied by high mortality, similar to the disease seen when genetically sensitive mice are infected with the virulent Moscow strain. Strikingly, infection of recently immunized genetically resistant mice with the virus expressing IL-4 also resulted in significant mortality due to fulminant mousepox. These data therefore suggest that virus-encoded IL-4 not only suppresses primary antiviral cell-mediated immune responses but also can inhibit the expression of immune memory responses.

GENE DRIVES

WHAT IS A GENE DRIVE / SELF PROPAGATING GENETIC ELEMENT

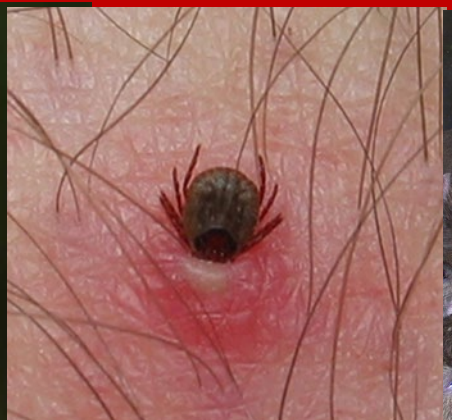
Mendelian: 50% odds genetic alteration will pass to next generation
IFF fitness or reproductive edge, THEN propagate

Gene drive: 99.5% odds alteration will pass to next generation
Edit whole population without fitness or reproductive edge

FOR WHAT APPLICATIONS?

Control vector borne diseases like malaria, dengue, zika, lyme
- Editing vector to not carry disease . . .
- Eradicating vector by altering sex ratios . . .

Control invasive species
- Eradicate invader by reducing fitness / reproductive success

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-

MOST RESEARCHERS ARE ACTING RESPONSIBLY
Code of Conduct

CHERS CODE OF CONDUCT SCIENCE AUGUST 2015

BIOSAFETY

Safeguarding gene drive experiments in the laboratory

Multiple stringent confinement strategies should be used whenever possible

By **Omar S. Akbari[1,2], Hugo J. Bellen[3,4], Ethan Bier[5,*], Simon L. Bullock[6], Austin Burt[7], George M. Church[8,9], Kevin R. Cook[10], Peter Duchek[11], Owain R. Edwards[12], Kevin M. Esvelt[8,*], Valentino M. Gantz[5], Kent G. Golic[13], Scott J. Gratz[14], Melissa M. Harrison[15], Keith R. Hayes[16], Anthony A. James[17], Thomas C. Kaufman[10], Juergen Knoblich[11], Harmit S. Malik[18,19], Kathy A. Matthews[10], Kate M. O'Connor-Giles[14,20], Annette L. Parks[10], Norbert Perrimon[9,21], Fillip Port[6], Steven Russell[22], Ryu Ueda[23,24], Jill Wildonger[25]**

Gene drive systems promote the spread of genetic elements through popula-

fore used institutionally approved stringent barrier methods. Only one experimenter

research involving potential gene drive systems while formal national guidelines are developed. Although we cannot claim to represent all researchers, we share a commitment to the safe and responsible development of gene drive technology. Although we differ in our assessments of the types of precaution needed, we recognize that any single confinement strategy could fail. We therefore unanimously recommend that future studies use a combination of stringent confinement strategies (see the table) whenever possible and always use safeguards adequate for preventing the unintentional release of synthetic gene drive systems into natural populations.

RECOMMENDATIONS. RNA-guided gene drive systems are created by delivering i the germline a DNA cassette encoding C and a single synthetic guide RNA (sgRNA)

MOST RESEARCHERS ARE ACTING RESPONSIBLY

Code of Conduct

Potentially stringent confinement strategies for gene drive research

Multiple stringent confinement strategies should be used whenever possible.

TYPE	STRINGENT CONFINEMENT STRATEGY	EXAMPLES
Molecular	Separate components required for genetic drive	sgRNA and Cas9 in separate loci (*8*)
	Target synthetic sequences absent from wild organisms	Drive targets a sequence unique to laboratory organisms (*3*,*4*,*8*)
Ecological	Perform experiments outside the habitable range of the organism	*Anopheles* mosquitoes in Boston
	Perform experiments in areas without potential wild mates	*Anopheles* mosquitoes in Los Angeles
Reproductive	Use a laboratory strain that cannot reproduce with wild organisms	*Drosophila* with compound autosomes*
Barrier	Physical barriers between organisms and the environment	Triply nested containers, >3 doors (*6*)
	•Remove barriers only when organisms are inactive	Anesthetize before opening (*6*)
	•Impose environmental constraints	Low-temperature room, air-blast fans
	•Take precautions to minimize breaches due to human error	Keep careful records of organisms, one investigator performs all experiments (*6*)

*An example of reproductive confinement would be *Drosophila* laboratory strains with a compound autosome, where both copies of a large autosome are conjoined at a single centromere. These strains are fertile when crossed inter se but are sterile when outcrossed to any normal or wild-type strain because all progeny are monosomic or trisomic and die early in development.

FUNDERS ARE SETTING GUIDELINES FOR RESEARCH

Science, Policy Forum December 1, 2017

Principles for gene drive research

Sponsors and supporters of gene drive research respond to a National Ac

By **Claudia Emerson,[1] Stephanie James,[2] Katherine Littler,[3] Filippo (Fil) Randazzo[4]**

The recent outbreak of Zika virus in the Americas renewed attention on the importance of vector-control strategies to fight the many vector-borne diseases that continue to inflict suffering around the world. In 2015, there were ~212 million infections and a death every minute from malaria alone (*1*). Gene drive technology is being explored as a potentially durable and cost-effective strategy for controlling the transmission of deadly and debilitating vector-borne diseases that affect millions of people worldwide, such as Zika virus and malaria. Additionally, its suitability is being evaluated for various potential applications in conservation biology, including a highly specific and humane method for eliminating invasive species from sensitive ecosystems (*2, 3*).

The use of gene drives is an emerging technology that promotes the preferential inheritance of a gene of interest, thereby increasing its prevalence in a population. A gene drive is distinct from genome editing, in which the genetic change is not preferentially inherited. A variety of gene drives occur in nature that can cause genetic elements to spread throughout populations to varying degrees, and researchers have been studying how to harness these to solve some of society's most intractable problems (*4*). Aided by CRISPR gene-editing technology, the rapid pace with which the research is progressing is demonstrated by recent successes in laboratory experiments (*5, 6*), although observation of resistance developing in one instance highlights the need for further research (*7*).

In recognition of the rapid advances of research in this field, the U.S. National Institutes of Health (NIH) and the Foundation for the NIH requested that the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM) conduct a study that would "summarize current understanding of the scientific discoveries related to gene drives and their accompanying ethical, legal, and social implications," which was published in 2016 [(*2*), p. vii)]. The authors noted that the promise of gene drives is tempered by uncertainties regarding potential for harm from unintended consequences or misuse of the technology. The potential persistence of genetic change in the target population caused by a gene drive is both the source of optimism for a durable and affordable tool to combat a variety of pernicious public health and environmental problems as well as the source of concern about the possibility for irreversible harm to the ecosystem that has prompted some to call for a moratorium on the research (*2, 8, 9*). This led the authors of the National Academies report to advocate for a precautionary contextual approach to the science—i.e., concluding that currently there is insufficient evidence to support deployment of gene drive–modified organisms into the environment but that the potential benefits justify proceeding with laboratory research and highly controlled field trials (*2, 10*).

The report issues a number of recommendations aimed at researchers, funders, and policy-makers on actions important for minimizing potential risks, averting preventable harm, and earning the confidence and support of the public. Of the 32

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[1]Institute on Ethics and Policy for Innovation, McMaster University, Hamilton, Ontario L8S 4L8, Canada. [2]Foundation for the National Institutes of Health, North Bethesda, MD 20852.

Guiding principles for the sponsors and supporters of gene drive research

Advance quality science to promote the public good

The pursuit of gene drive research must be motivated by, and aim to promote, the public good and social value. Funded research shall embody the highest quality science and ethical integrity, consistent with the current best practice guidance set by the research community and relevant decision-making bodies [(*2*), p. 106)].

Promote stewardship, safety, and good governance

Researchers and sponsors are stewards of science and the public trust. It is imperative that good governance is demonstrably shown in all phases of the research, and especially in relation to risk assessment and management. This requires compliance with applicable national and international biosafety and regulatory policies and standards. Research conducted with respect and humility for the broader ecosystem in which humans live, taking into account the potential immediate and longer-term effects through appropriate ecological risk assessment, is a hallmark of both good stewardship and good governance [(*2*), pp. 128; 170–172)].

Demonstrate transparency and accountability

Knowledge sharing is not only essential for the advancement of science, but for transparency to foster public trust in emergent technologies. The timely reporting of results and broad sharing of data shall be the norm in gene drive research, consistent with the tradition of openness established in its parent communities of genetic and genomic science. Measures of transparency and accountability that contribute to building public trust and a cohesive community of practice will be supported [(*2*), pp. 171; 177–178)].

Engage thoughtfully with affected communities, stakeholders, and publics

Meaningful engagement with communities, stakeholders, and publics is critical for ensuring the best quality science and building and sustaining public confidence in the research. Funded research shall include the resources needed to permit robust, inclusive, and culturally appropriate engagement to ensure that the perspectives of those most affected are taken into account [(*2*), pp. 142–143)].

Foster opportunities to strengthen capacity and education

Strengthening capacities in science, ethics, biosafety, and regulation is essential for enabling agile and steady progress in gene drive research globally. Opportunities to partner, educate, and train shall be supported throughout all phases of the research from the early stages to deployment. Strengthening capabilities within countries testing and deploying the technology is essential for informed decision-making [(*2*), pp. 128; 170–172)].

FROM GLOBAL TO LOCAL BY DESIGN OR CHANCE?

A. Split drives separate components of drive systems, one of which is never copied. In daisy-chain systems, capacity to spread is limited by loss of non-driving elements from one end of the chain.

B. Precision drives target unique polymorphisms. Locally fixed allele variants could serve as homing targets.

C. Threshold drives require high frequency in a population before drive will occur. For example, under-dominant systems use expression of counteracting toxins and antibodies to link to population frequency.

D. Safeguards such as drug-inducibility, nutrient dependency, traditional physical containment and other methods may limit effects

E. Resistance associated with mutation degrades efficiency. May be viewed as a localization feature rather than efficiency degrading bug.

NEED WORKSHOPS TO EVALUATE DESIGNS AND TESTING METHODS

SESSION III: FORECASTING IMPLICATIONS OF EMERGING BIOTECHNOLOGIES

THE CASE FOR PROACTIVE AND ADAPTIVE CONSIDERATION OF RISKS AND BENEFITS

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I. Lessons from the NIH Guidelines Workshop

- David Baltimore Keynote: Asilomar and NIH Guidelines
- Panel on Emerging Biotechnologies: New Stuff Undermines Premises

II. Approaches to Risk Governance

- Permissive and Precautionary Risk Governance
- Forecasting Failures: Laser, GPS, Automobile
- Proactive and Adaptive Risk Governance: Exemplary US EU Cases

III. Applications to Current Biotech: Uncertainty, Observability and Reversibility

- Business-As-Usual? SCGT human and animal, regenerative medicines
- Not sure? Opiate production
- Unique Risks? Xeno-transplantation, HGGT, gene drives

IV. Conclusions: Implications for Funders and Researchers

CONSIDERATIONS FOR RESEARCHERS AND FUNDERS

Duty

Those proposing/conducting/funding emerging technologies have a duty to evaluate actions with reference to both legal standards and ethical norms

Obligations that Follow from Duty

101 Align own work with law/norms based on existing knowledge
201 Encourage others to align their work with laws/norms
301 Identify key gaps in existing knowledge and fill gaps through research
401 Identify key gaps in legal coverage and join debate on gaps

RECOMMENDATIONS FOR NIH FROM 2017 EDITORIAL ON GUIDELINES

PROBLEM: NEW RISKS AND ACTORS

- Risks: More than listed pathogens
- Actors: More than NIH recipients

NEED: BROAD SPECTRUM RESPONSES

Proactive Engagement with Risks

- Reach non-NIH funded actors
- Foster researcher/funder guidance
- Oversight beyond Select Agents
- Source DNA from IGSC synthesizers

Adaptive Learning and Reassessment

- IBCs as eyes and ears
- Pool info via WHO BWC CBD IEGBBR
- Fund research on potential risks
- Identify and fill oversight gaps
- Use info to modify voluntary and mandatory oversight

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EDITORIAL

Revisit NIH biosafety guidelines

To celebrate the anniversary of an arcane federal guideline is a rare event. For an agency to use that moment to invite reflection on modifying policies is even rarer. Last month, the U.S. National Institutes of Health (NIH) did just that, with a workshop that marked the 40th anniversary of its Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. The meeting was an inspiring start for charting future oversight of nonclinical applications.

The guidelines, created to address research risks associated with genome engineering, affect institutions receiving NIH support for such research. Responsibilities include setting up Institutional Biosafety Committees (IBCs) to assess risks and potential hazards through standards for containment and laboratory practices. Noncompliance on any project, whatever the funding source, can result in loss of all such NIH funding. In his address to the workshop, David Baltimore—an organizer of the 1975 Asilomar Conference that motivated the safety guidelines for recombinant DNA technology—argued that research conducted under the guidelines has been safe and adequately contained, and that natural selection "took care of the rest," as genetic alterations did not confer fitness or reproductive advantages.

Today, however, three developments may necessitate modification of oversight. Easy-to-use gene-editing tools are diffusing from universities and companies to personal and community labs and across international borders. These new locales typically do not depend on NIH funding and lack IBC oversight. Gene drive systems can increase the odds of inheritance of an altered gene from 50 to 99.5%; natural selection may not limit propagation of non-Mendelian constructs. And conventional risk management practices that focus on listed pathogens may underestimate risks of new, unlisted organisms. The informality of voluntary guidelines has enabled prompt responses by funders and researchers to emerging evidence on benefits and risks of technologies. But what has worked with those receiving NIH funding with IBCs may not work with the wider range of actors who now have access to these technologies.

How might the NIH address these issues? Its participation in international forums should expand, including consultations with the International Expert Group on Biosafety and Biosecurity Regulations, World Health Organization, and United Nations Biological Weapons Convention. Research funders, publishers, insurers, and the NIH should set common benchmarks on researcher conduct and link access to funding, publication, and underwriting to adherence to common standards. The NIH should engage more directly with institutional biosafety officers, whose awareness of events on the ground should inform the guidelines and who provide a direct channel for influencing researcher behavior. Programs are needed in settings lacking IBCs, such as the Woodrow Wilson Center's "ask a biosafety officer" program. Another example is the safety committee of the International Genetically Engineered Machine competition, which provides mechanisms to reach community laboratory teams.

"...conventional risk management practices...may underestimate risks of new, unlisted organisms."

The scope of the guidelines to address biosecurity concerns also should expand. For example, NIH could require researchers to obtain synthesized DNA from firms adhering to U.S. Department of Health and Human Services' guidance on security screening of orders. And it would be wise for the NIH to require open preregistration of experiments as a condition of funding, starting in high-risk fields such as gene drives, to foster reevaluation of safeguards, benefits, and risks.

Ideally, research supported by all funding sources in all countries and research settings would be covered in the future guidelines. We call upon all stakeholders and interested parties to work creatively and expeditiously to build a system that will meet these needs.

–Kenneth A. Oye, Maureen O'Leary, Margaret F. Riley

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