Gene drives in our future: Challenges of and opportunities for using a self-sustaining technology in pest and vector management

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OECD Co-Operative Research Program Conference on Environmental release of engineered pests: Building an international governance framework

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(2003)

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Site-specific selfish genes as tools for the control and genetic engineering of natural populations

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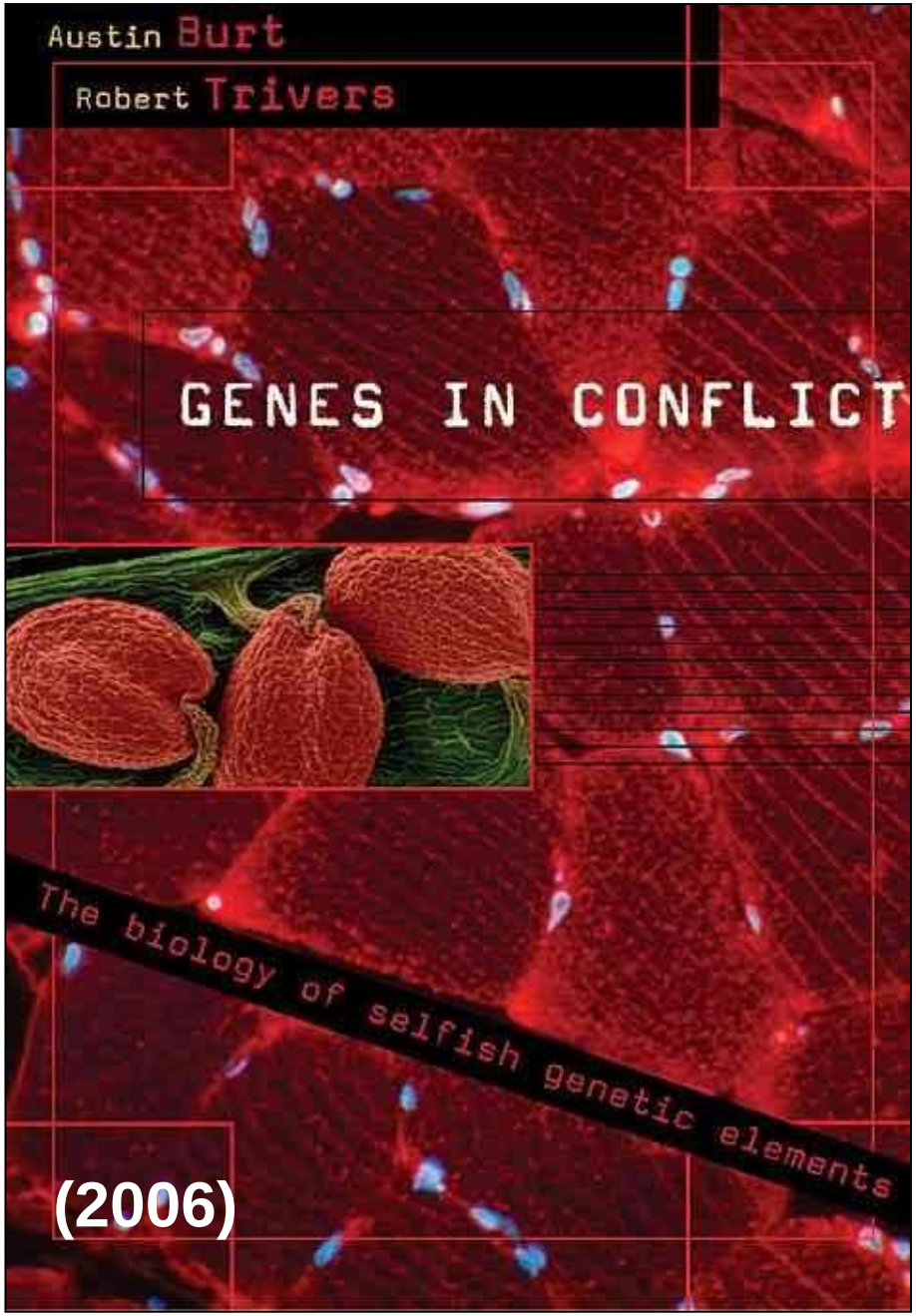
"Site-specific selfish genes exploit host functions to copy themselves into a defined target DNA sequence....<u>If such genes can be engineered</u> to target new host sequences, then they can be used to manipulate natural populations...."



A gene drive is a process of inheritance by which a gene is guaranteed to pass from one generation to the next, and ultimately throughout a population.

Gene drives are an example of a new technology with uncertain benefits and risks, raising compelling questions at the intersection of science and society.

Questions to discuss

1) Defining characteristics of gene drives?

2) Potential examples of gene drive applications?

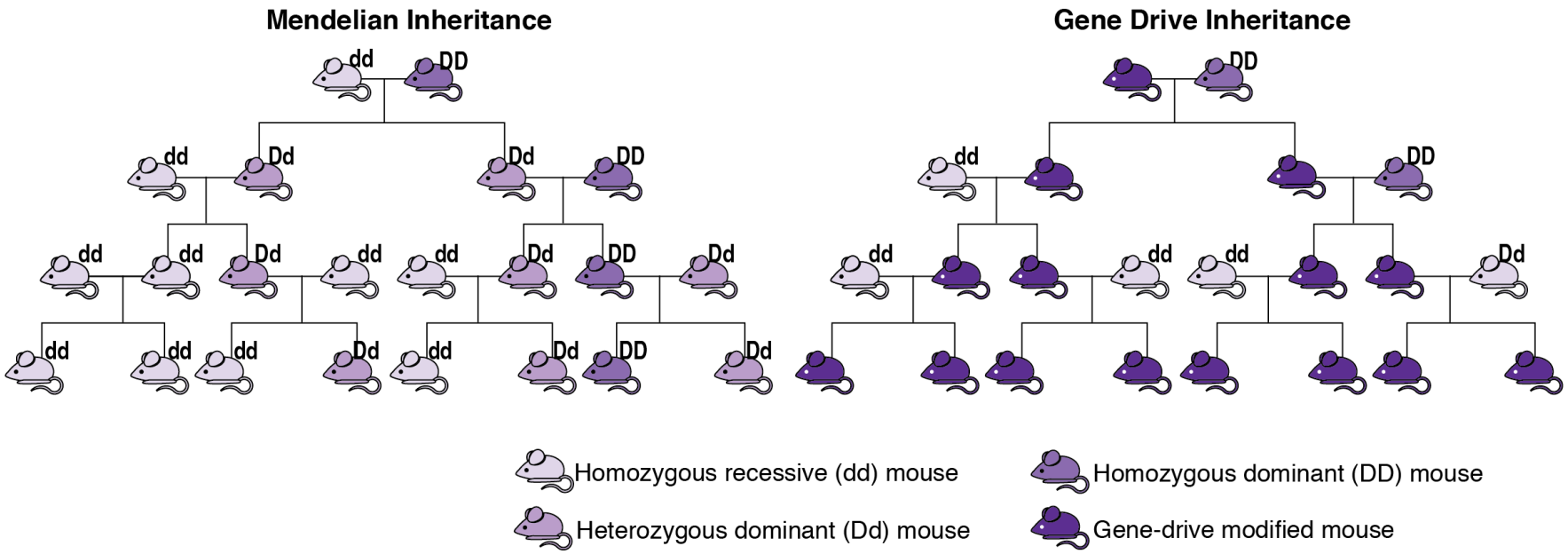
3) Task of the National Academy of Sciences committee that authored the gene drives report?

4) Major report recommendations relevant for pest control?

5) Report recommendations with implications for international coordination of regulatory and risk assessment frameworks?

What are gene drives?

Gene drives are systems of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced.



Basic facts about gene drives

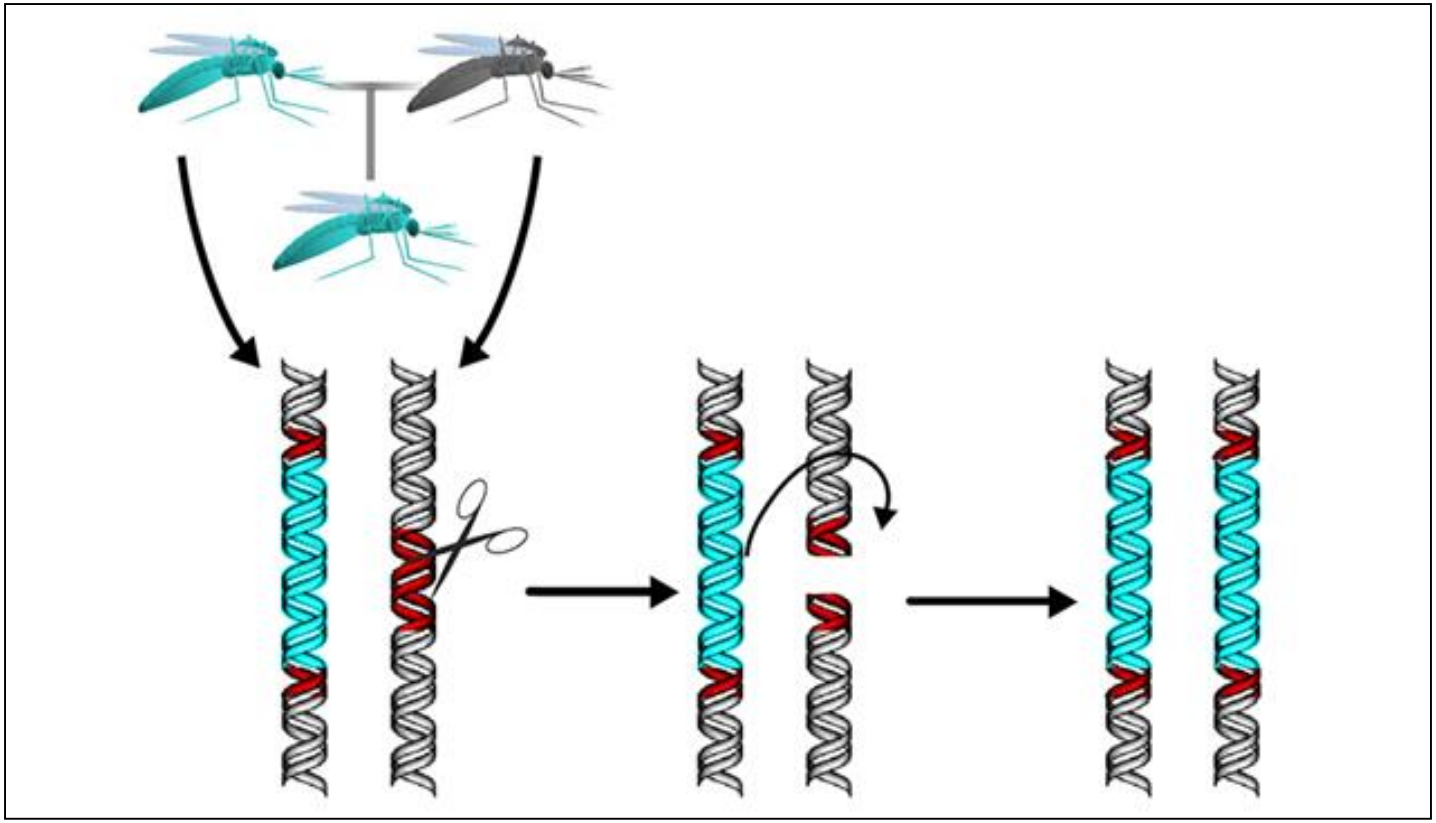
- Occur in nature in many species
- Work through various mechanisms
- Earliest proposals to develop gene drives were mid-20th century, <u>but until now the technology was unavailable</u> to design one to spread a specific trait throughout a population

Editing made easier

Gene-editing tools are improving. The CRISPR/Cas9 system is easier to program and faster to produce than other gene editors in use.

Platform	Year developed	First used in live animals	Time to do an experiment
Zinc finger nucleases	1996	2002	Months/year
TALENs	2010-2011	2011	Week(s)
CRISPR/Cas9	2012	2012-2013	Days

SOURCE: MARK OSBORN/UNIV. OF MINNESOTA



“In organisms that inherit one drive-containing and one wild-type chromosome, the drive cuts the wild-type chromosome, causing the cell to copy the drive when it uses the drive-containing chromosome as a template to repair the damage….all of the organism’s offspring will inherit a drive-containing chromosome to repeat the process (Esvelt et al. 2014).”

Criteria for choosing a species to develop a gene drive

- Sexual reproduction
- Short generation time
- Stability of the driving genetic elements
- Population structure that facilitates spread of the gene drive

eLIFE
elifesciences.org

FEATURE ARTICLE

(2014)

EMERGING TECHNOLOGY

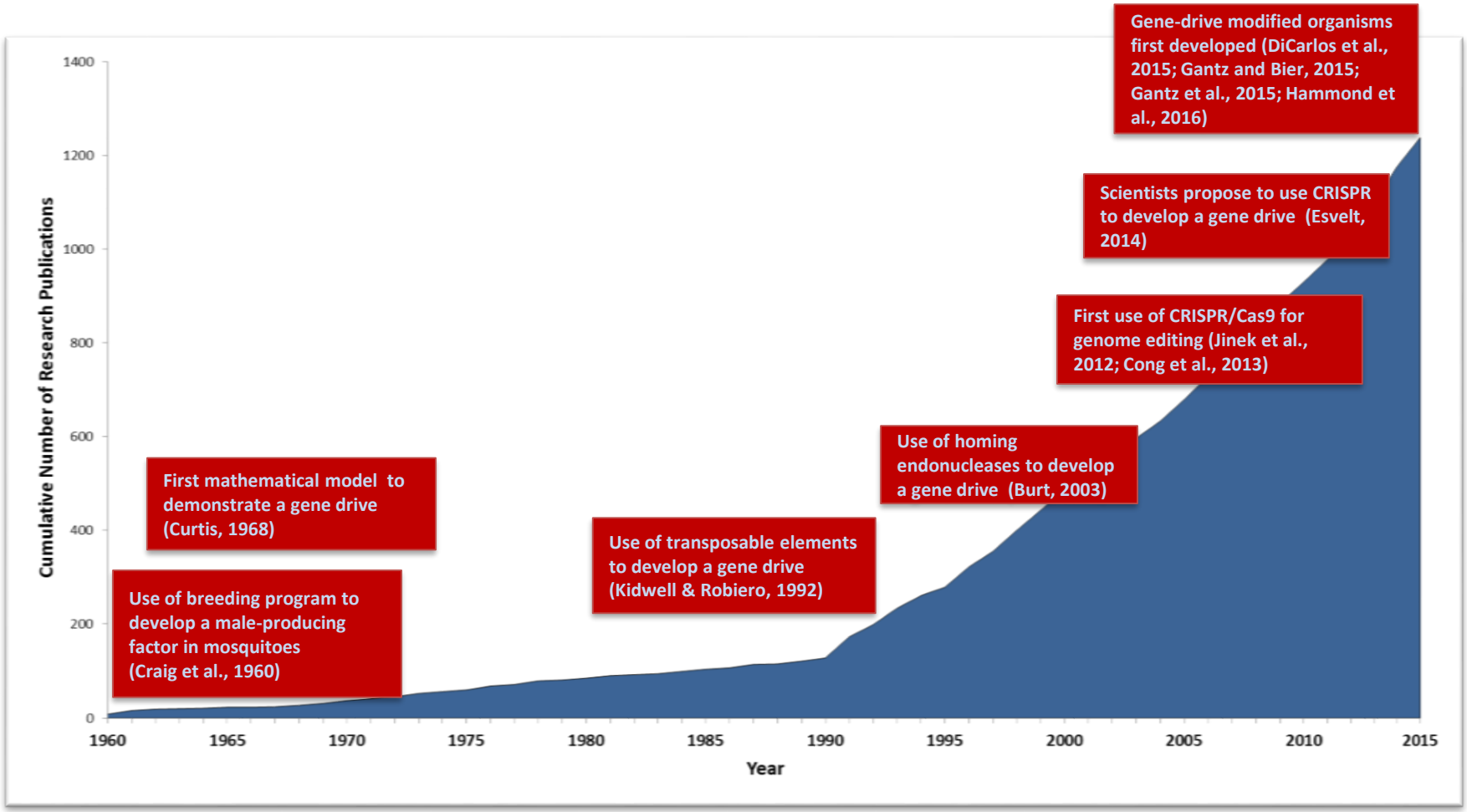
Concerning RNA-guided gene drives for the alteration of wild populations

Abstract Gene drives may be capable of addressing ecological problems by altering entire populations of wild organisms, but their use has remained largely theoretical due to technical

KEVIN M ESVELT*, ANDREA L SMIDLER, FLAMINIA CATTERUCCIA* AND GEORGE M CHURCH*

"Gene drives may be capable of addressing ecological problems by altering entire populations of wild organisms, <u>but their use has remained largely theoretical due to technical constraints</u>. Here we consider the potential for RNA-guided gene drives based on the CRISPR…nuclease Cas9 to serve as a general method for spreading altered traits through wild populations…."

Recent increase in pace of the field



Cumulative number of gene drive research publications (1960 – 2015)

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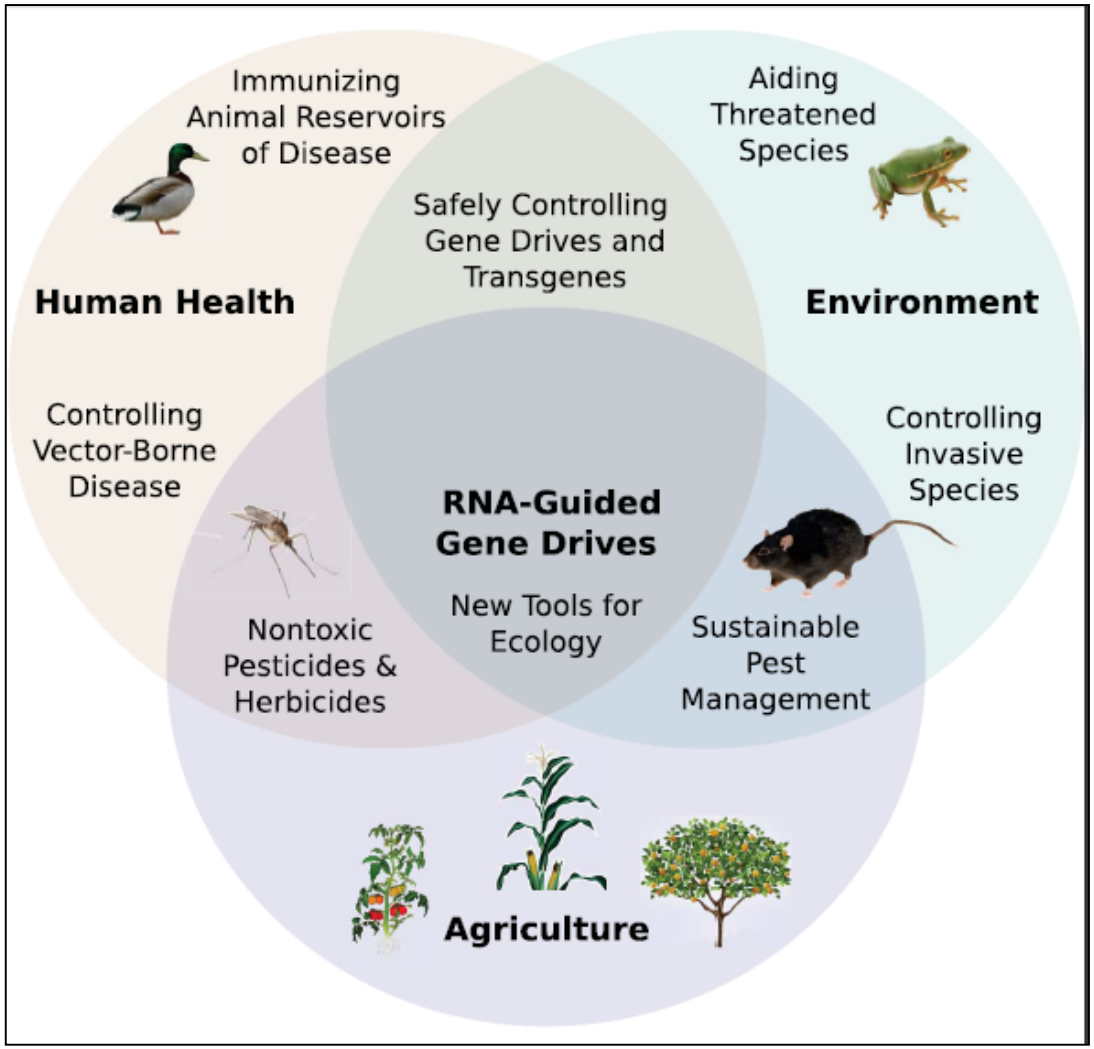
Key features and potential uses of gene drives

- Defining features:
  - Spread and persistence
  - Potential to cause irreversible ecological change
- Two potential uses:
  - Population suppression: Decrease numbers
  - Population replacement: Change genetic characteristic(s)

Many proposals to use gene drives for various challenging issues

"…RNA-guided gene drives could potentially prevent the spread of disease, support agriculture by reversing pesticide and herbicide resistance in insects and weeds, and control damaging invasive species…"



(From Esvelt et al. 2014)

The New York Times

SCIENCE

Gene Drives Offer New Hope Against Diseases and Crop Pests

By NICHOLAS WADE DEC. 21, 2015

A woman in Tanzania under a mosquito tent with a relative who was being treated for malaria.

THE NEW YORKER

DAILY COMMENT

COULD GENETICALLY MODIFIED MOSQUITOES SAVE HAWAII'S ENDANGERED BIRDS?

By Michael Specter, SEPTEMBER 9, 2016

There are now genetic technologies that, at least in theory, are environmentally benign, but could wipe out the mosquitoes that have decimated the birds of Hawaii… That has many conservation ecologists tremendously excited.

Sciencexpress (2014) 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.

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

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

"…[gene] drives may present environmental and security challenges as well as benefits."

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Motivations for the study

Many questions about science, ethics, and governance

- Could gene drives have unintended consequences for public health and the environment?
- Do we know enough to consider releasing gene-drive modified organisms into the environment?
- *Should* a gene drive be used to suppress or eliminate a pest species?
- How do we decide where gene-drive modified organisms could be released? What should be governments' role?

Anticipatory governance

Article

Social Studies of Science
2014, Vol. 44(2) 218–242

DOI: 10.1177/0306312713508669
sss.sagepub.com
SAGE

Understanding 'anticipatory governance'

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"Anticipatory governance is a broad-based capacity extended through society that can act on a variety of inputs to manage emerging knowledge-based technologies while such management is still possible."

Committee on gene drive research (by expertise)

Biosafety and Biosecurity
Stephen Higgs, Kansas State University

Developmental Biology
Lisa A. Taneyhill, University of Maryland

Ecological Risk Assessment
Wayne Landis, Western Washington University

Entomology and Vector-Borne Diseases
Nicole L. Achee, University of Notre Dame
Lynn Riddiford, Howard Hughes Medical Institute

Ethics and Scientific Integrity in Research
Elizabeth Heitman, *Co-Chair,* Vanderbilt University Medical Center
Gregory E. Kaebnick, The Hastings Center

Plant Biology and Ecology
Vicki Chandler, Minerva Schools at Keck Graduate Institute
Brandon S. Gaut, University of California, Irvine

Population Ecology
James P. Collins, *Co-Chair,* Arizona State University
Joseph Travis, Florida State University
Paul E. Turner, Yale University

Public Interfaces with Controversial Science
Jason A. Delborne, North Carolina State University

Science and Technology Policy and Law
Ann Kingiri, African Centre for Technology Studies
Joyce Tait, University of Edinburgh
David E. Winickoff, University of California, Berkeley

The National Academies of
SCIENCES · ENGINEERING · MEDICINE
BOARD ON LIFE SCIENCES

Gene Drives on the Horizon:
Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values

June 8, 2016

Public Release Event

Join the conversation:
#GeneDriveStudy

nas-sites.org/gene-drives

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Responsible science to develop gene drive technologies

A responsible science approach calls for continuous evaluation, assessment, and education relative to the social, environmental, regulatory, and ethical considerations of gene drives.

Values are important at every step

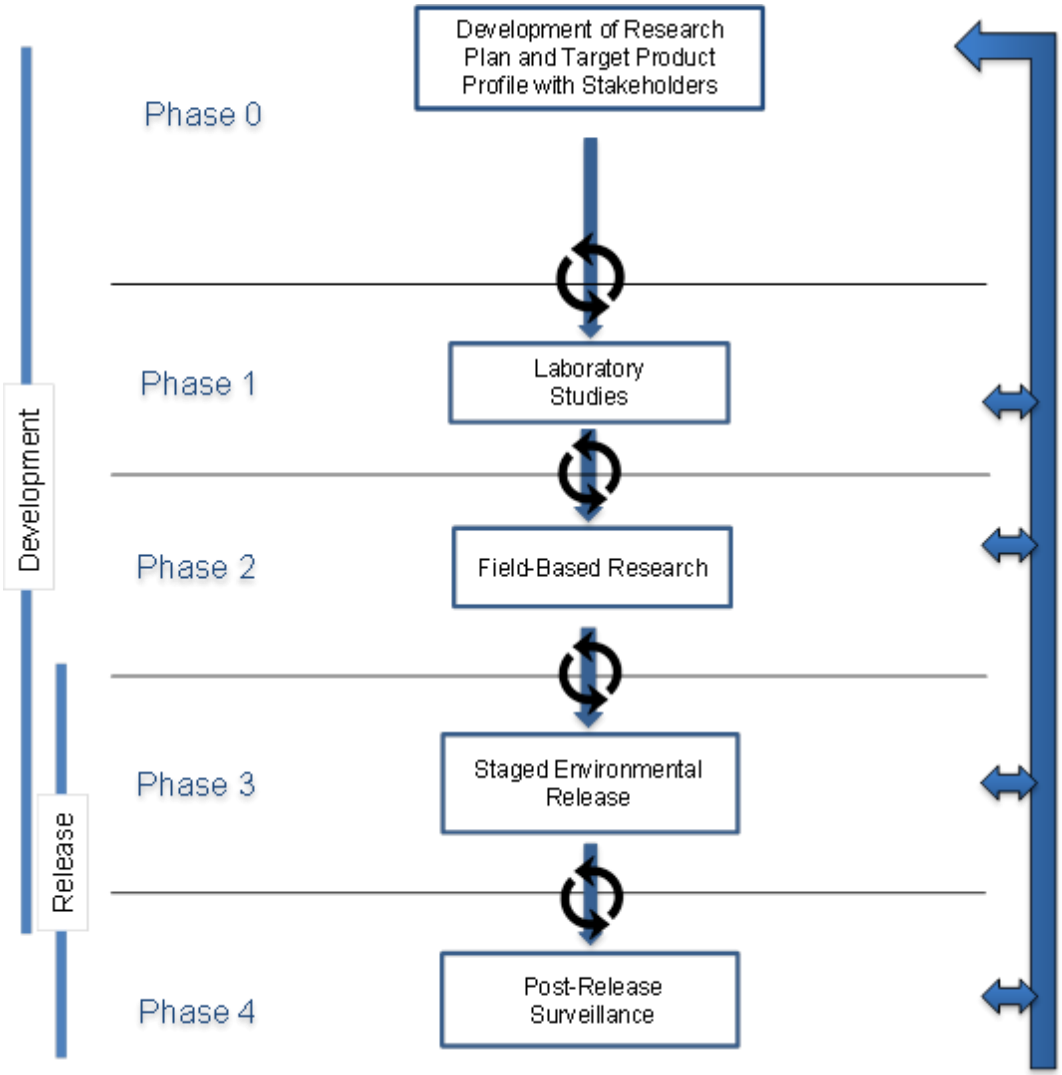
Responsible science rests on values: deeply held, complicated, sometimes evolving beliefs about what kinds of things – in humans' lives and the world at large – should be fostered, protected, or avoided.

State of the science

- Insufficient evidence to support the release of gene-drive modified organisms into the environment.
- Benefits of gene drives for basic and applied research are significant and justify proceeding with laboratory research and controlled field trials.

Recommendation: Funders should coordinate, and if feasible collaborate, to reduce gaps in knowledge.

Phased testing: A precautionary approach



Phased testing: Safety

Confinement: use ecological conditions or biological methods to prevent unintended or uncontrolled *persistence* of an organism in the environment (e.g., climatic isolation).

Containment*:* use human-made or natural physical restrictions to prevent unintended or uncontrolled *release* of an organism into the environment (e.g., large cages, greenhouses, and aquaculture pens; geographic isolation).

Recommendations:

- Researchers, regulators, and other decision-makers should not rely on a "reversal" gene drive as the sole means for mitigating the effects of another gene drive.
- Whenever possible include a gene drive that spreads a visible marker to distinguish modified organisms.

Phased testing: Selecting sites for field tests

Site selection criteria should include:

- Scientific and technical considerations (e.g., presence of the target species, methods for containment and confinement)
- Values of relevant publics
- Capabilities of local, regional, and national governance bodies
- Ability of researchers to engage with local communities

Recommendation: Give preference to locations in countries with the existing scientific capacity and governance frameworks to conduct and oversee the safe investigation of gene drives.

Risk assessment

The *probability* of an effect on one or more specific endpoints due to a specific stressor or stressors.

In other words, how often a specific change or changes in the environment will affect something of value to society, such as human health, outdoor recreation, or the survival of an endangered species.

Risk assessment: Precaution

The uncertain benefits and risks of gene drives calls for governance by a measured version of precaution. This conclusion reflects a conviction that precaution is advisable under some conditions, yet that precaution can be developed in a way that does not easily succumb to the common objections to it. Precaution can be consistent with support for science.

Ecological risk assessment

Steps to assess risk due to a gene drive:

- Trace cause-and-effect pathways
- Identify sources of uncertainty
- Quantify the probability of the outcomes
- Incorporate concerns of relevant publics
- Compare benefits and harms
- Compare alternative approaches

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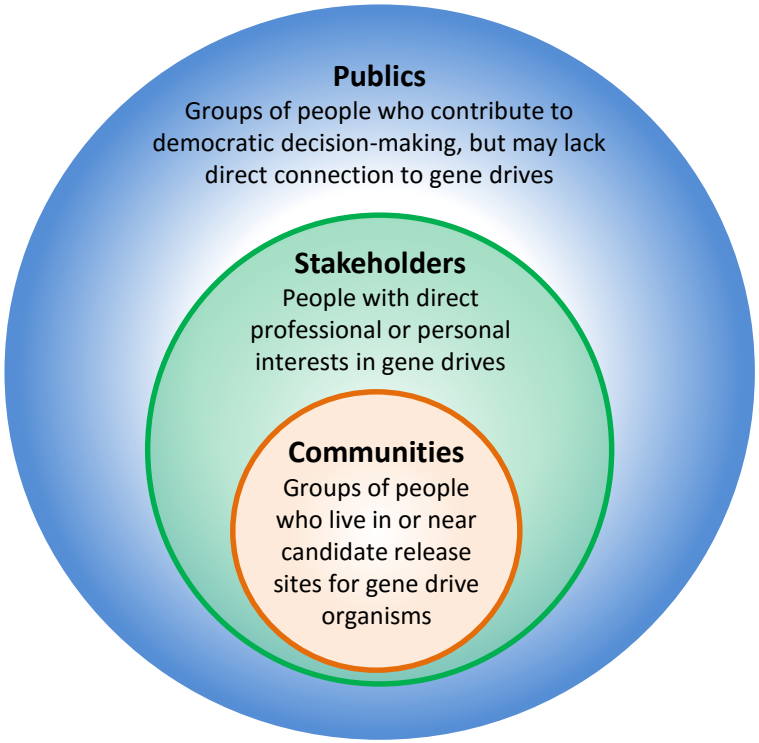
Public engagement is needed in research, risk assessment, and governance



Outcomes of engagement may be as crucial as scientific outcomes.

Recommendation: Governing authorities, including research institutions, funders, and regulators, should develop and maintain clear policies and mechanisms for how public engagement will factor into research, ecological risk assessments, and public policy.

Challenges to governance of gene drive research and development (Part 1)

Existing governance mechanisms may be inadequate because they:

- Do not consider gene drives' intentional spread and potential irreversible effects on ecosystems
- Lack clarity in jurisdiction of oversight
- Provide insufficient means for public engagement
- Do not address potential for misuse
- Lack policies for collaborating with other countries with divergent systems of governance

Challenges to governance of gene drive research and development (Part 2)

There are overlaps and gaps in U.S. regulation of organisms in which gene drives might be deployed.

Recommendation: The U.S. government should clarify the assignment of regulatory responsibilities for field releases of gene-drive modified organisms, including the roles of agencies that are not currently included in the Coordinated Framework for the Regulation of Biotechnology.

Challenges to governance of gene drive research and development (Part 3)

After release, a gene-drive modified organism *is not limited by political boundaries*, but regulation of GMOs under the US Coordinated Framework for the Regulation of Biotechnology and United Nations Convention on Biological Diversity is predicated on containment.

Recommendation: Research institutions, regulators, and funders should revisit international regulatory frameworks, national laws, non-government policy, and professional codes of conduct to determine whether and how they may be applied to gene drive research.

On the other hand….

A Call for Conservation with a Conscience: No Place for Gene Drives in Conservation

New technologies have played an important role in protecting life on earth, and we the undersigned support innovation and science in conservation. However, we believe that a powerful and potentially dangerous technology such as gene drives, which has not been tested for unintended consequences nor fully evaluated for its ethical and social impacts, should not be promoted as a conservation tool.

From the climate impact of the internal combustion engine to the synthetic chemicals that have poisoned the web of life, we have learned some lessons. We now understand the serious need for precaution when radical new technologies arise, especially with gene drives, which change the rules of genetics and inheritance and have consequences beyond our comprehension.

Gene drives have the potential to dramatically transform our natural world and even humanity's relationship to it. The invention of the CRISPR-CAS9 tool and its application to gene drives (also known as a "mutagenic chain reaction") gives technicians the ability to intervene in evolution, to engineer the fate of an entire species, to dramatically modify ecosystems, and to unleash large-scale environmental changes, in ways never thought possible before. The assumption of such power is a moral and ethical threshold that must not be crossed without great restraint.

We the undersigned leaders and practitioners in the fields of science, policy, environmental protection, conservation, and law are alarmed that some conservation organizations have accepted funding for and are promoting the release of engineered gene drive organisms into the wild. They propose to use extinction as a deliberate tool, in direct contradiction to the moral purpose of conservation organizations, which is to protect life

Founding signatories include:

Dr Jane Goodall

Dr David Suzuki

Open Letter, September, 2016
http://www.synbiowatch.org/wp-content/uploads/2016/08/ETC_letter_vs_genedrives_v5.pdf

On the other hand….

Trends in Biotechnology
(2016)

CellPress

Scientific Life

Scientists Should Oppose the Drive of Postmodern Ideology

Marcel Kuntz[1,*]

The National Academies of Sciences of the USA recently published a report entitled *Gene Drive on the Horizon*. This commentary discusses the 'Aligning Research with Public Values' aspects in this report, the topic of public engagement, and the worrying ideological shift towards postmodernism which aims to deconstruct Enlightenment values.

examples range from communication to active participation in research. Second, according to this report, PE can 'support democracy and justice', making it a moral imperative for researchers.

'Aligning Research with Public Values' is not only worrying because it potentially restricts academic freedom and because of its intrinsic relativism, but also because it illustrates a clear ideological shift. Whereas at the end of the 19th century philosopher Ernest Renan and others considered science as 'the first need of humanity', and that society must organize itself scientifically to 'improve the established order', the NAS report bows to an opposed thinking where science must organize itself according to 'public values'. While the 20th century has rightly moved away from Renan's views, this new shift is gaining ground, and it is also problematic. For example, as the report mentions, in 1982 the President's Commission stated that (on human genetics) 'the public could rely on the judgments of experts in the field', while in 2010 it insisted (regarding synthetic biology) on 'justice and fairness' and called for a principle of 'democratic deliberation'.

Box 1. What Are 'Public Values' and What Does 'Public Engagement' Mean?

Public Values

In Chapter 4 (Charting Human Values), the NAS report [1] defines 'values' as 'critical components of human

Conclusion: Questions to discuss

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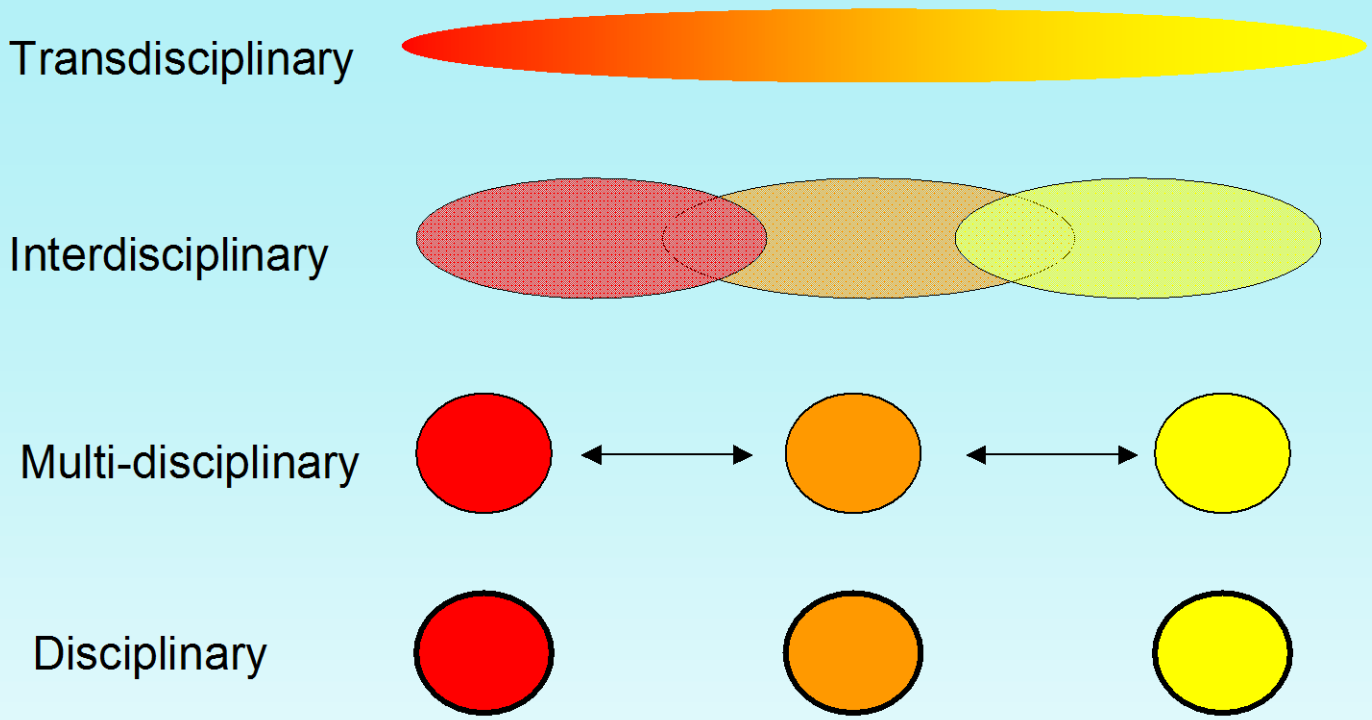

Conclusion:
Scholarship unlimited by borders—sustaining disciplines while blurring their boundaries

Conclusion:
Scientific freedom and responsibility

As we think about moving gene drive research into the future, the challenge we face is integrating the scientific freedom that

- allows research to move ahead

with acting responsibly and

- conducting research that embraces ethical, legal, and larger societal values.

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