Can New Technologies Really Turn the Tide?

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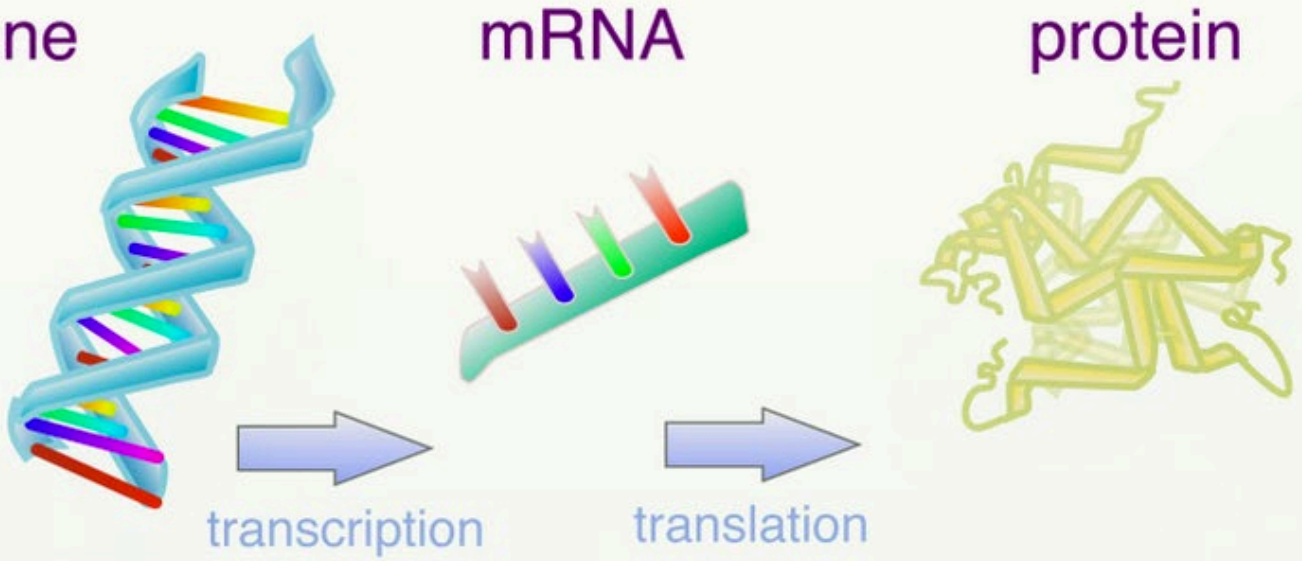
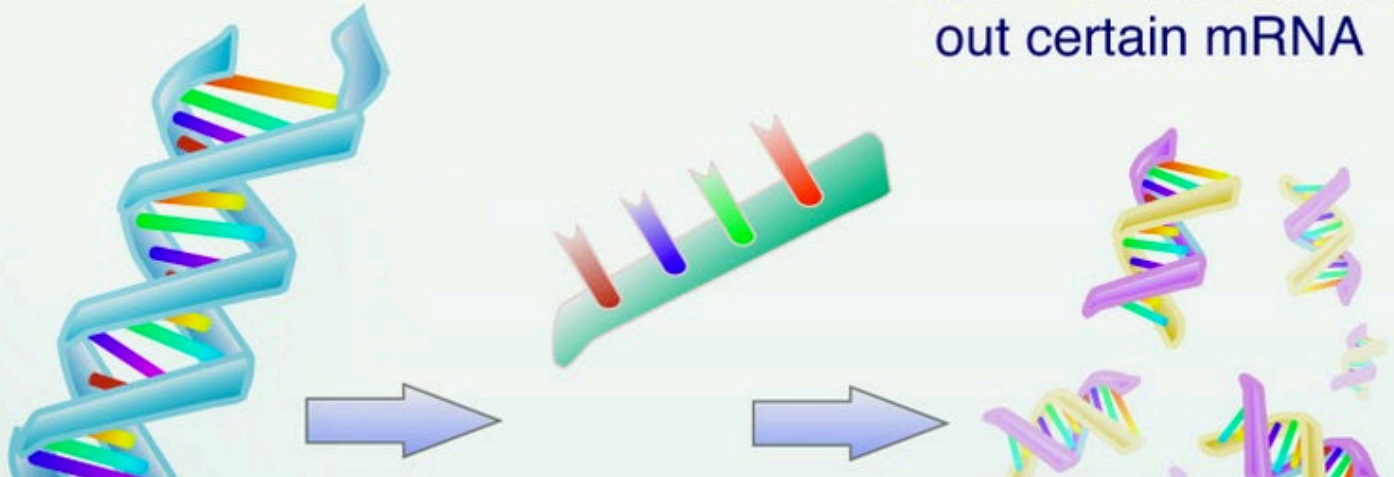
normal protein production



gene silencing

molecules that censor out certain mRNA

(usually dsRNA = double-stranded RNA)



prevents

gene-silencing

Pest Management Science 72:801-809. 2016

The next generation of insecticides: dsRNA is stable as a foliar-applied insecticide

Keri San Miguel and Jeffrey G Scott*

Abstract

BACKGROUND: RNAi is a powerful tool used to study gene function. It also has been hypothesized to be a promising new method for control of insect pests on crops, although the perceived instability of dsRNA in the environment has constrained thinking about the options for this new type of pest control.

RESULTS: We confirmed that foliar application of Colorado potato beetle dsRNA actin is highly effective for control, demonstrated that treatment with actin-dsRNA protects potato plants for at least 28 days under greenhouse conditions and found that the dsRNA is not readily removed by water once dried on the leaves.

CONCLUSION: These new results suggest that foliar application of dsRNA could be a valuable control strategy for some pests. Technological aspects of spraying dsRNA that need to be considered in the future are discussed.

Keywords: Colorado potato beetle (*Leptinotarsa decemlineata*); crop protection; RNAi; double-stranded RNA

The EPA Quietly Approved Monsanto's New Genetic-Engineering Technology

It's the first time RNA interference will be used to kill insect pests.

SARAH ZHANG | JUN 23, 2017 | SCIENCE

(IMPORTANT: this is heritable, since they inserted a transgene to do this.)

EPA United States Environmental Protection Agency

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Pesticide Registration

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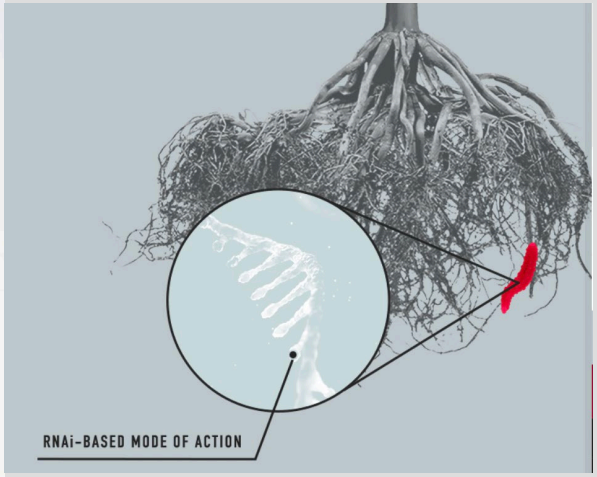
EPA Registers Innovative Tool to Control Corn Rootworm

In June 2017, EPA registered four products containing the Ribonucleic acid interference (RNAi) based Plant-Incorporated Protectant (PIP) called SMARTSTAX PRO. This product will help U.S. farmers control corn rootworm, a devastating corn pest that has developed resistance to several other pesticides.

Related Information

- Overview of Plant-Incorporated

SmartStax® PRO With RNAi TECHNOLOGY



SMARTSTAX® PRO WITH RNAi TECHNOLOGY*

Available in 2022

SmartStax® PRO Technology is the next generation of protection against an ongoing threat: corn rootworm. Built on the strong foundation of SmartStax® Technology, SmartStax® PRO Technology introduces a third mode of action that offers improved corn rootworm control over a range of pressures for the strongest biotech defense** available in 2022.

SmartStax PRO Technology contains the two proven Bt traits found in SmartStax Technology to target corn rootworm. In addition, the introduction of RNAi Technology adds an entirely new mode of action against this insect. RNAi works by interfering in a naturally occurring process within the corn rootworm to stop the production of a specific protein vital to their life cycle. Together, these three modes of action form a powerful combination against this top threat to corn.

The Advantage of RNAi Technology

Bayer is the first to develop RNAi technology to combat corn rootworm, which offers a new and unique third mode of action against the pest. By interfering with a corn rootworm's ability to create a specific protein critical to its own survival, RNAi technology effectively causes mortality after ingestion.

Because RNAi technology works differently than a soil-applied insecticide or Bt-traits to control corn rootworm, it can increase your corn's ability to defend itself against the billion-dollar bug.

Leonard *et al.*, *Science* **367**, 573–576 (2020) 31 January 2020

BEE HEALTH

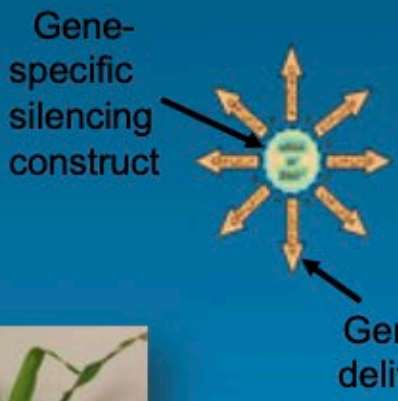
Engineered symbionts activate honey bee immunity and limit pathogens

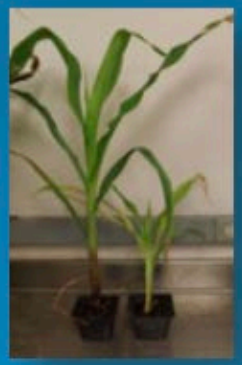
Sean P. Leonard[1,2], J. Elijah Powell[1], Jiri Perutka[2], Peng Geng[2], Luke C. Heckmann[1], Richard D. Horak[1], Bryan W. Davies[2], Andrew D. Ellington[2], Jeffrey E. Barrick[2]*, Nancy A. Moran[1]*

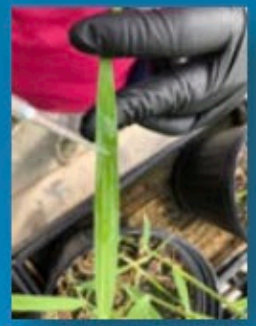
varroa mite

Gene Silencing

- Sequenced the *Phragmites* transcriptome (road map)
  - Developed numerous gene targets
- Tested many silencing vectors in model species and in *Phragmites*
- Developing cutting-edge delivery system for *Phragmites*







Demonstrated in:

Tobacco (Lakshmanan et al., 2013)
Rockcress (Ng et al., 2016)

USGS
US Army Corps of Engineers
WAYNE STATE UNIVERSITY

Gene Silencing

Next Steps

- Optimize delivery system
- Explore new targets
- Scale up to field trials
- Continue outreach and regulatory groundwork

Tulane University LSU

USGS

R. Thresher et al. Biological Invasions 16:1201-1216 2014

Table 1 Recombinant methods considered to date

Method	Description	Reference(s)
Lethal construct	Construct induces embryonic death of offspring. When homozygous results in sterility and is equivalent to a sterile male/female release	Thomas et al. (2000), Horn and Wimmer (2003), Phuc et al. (2007), Thresher et al. (2009), Harris et al. (2012)
Sex-specific lethality	As above, but male or female-specific; transmitted through male or female line	Heinrich and Scott (2000), Schliekelman and Gould (2000a), Fu et al. (2007, 2010), Ant et al. (2012)
Sex-specific sterility	Construct causes offspring of one sex to be sterile; transmitted through male or female line	Schliekelman et al. (2005), Thresher (2008)
Gender distortion ("daughterless" or "sonless")	Construct causes offspring to develop as specified sex irrespective of sexual genotype	Hamilton (1967), Schliekelman et al. (2005), Thresher et al. (2005)
Inducible mortality	Construct causes death when externally triggered by, e.g., extreme environmental variability or artificial trigger; construct maintained in population by further stocking	Grewe (1997), Schliekelman and Gould (2000b)
"Trojan gene"	Construct pleiotropically has positive effect on one or more fitness components, and negative effects on others, e.g., increases mating advantage while decreasing viability of genetically modified offspring	Muir and Howard (2004)
Mutual incompatibility	Construct is lethal when present in 2 or more copies (unless genes are identical)	
Engineered under-dominance	Construct is lethal when only 1 copy present (or more than one copy but genes are identical)	Davis et al. (2001), Magori and Gould (2006)

Extraordinary Sex Ratios

Science 156:477-488 1967

A sex-ratio theory for sex linkage and inbreeding has new implications in cytogenetics and entomology.

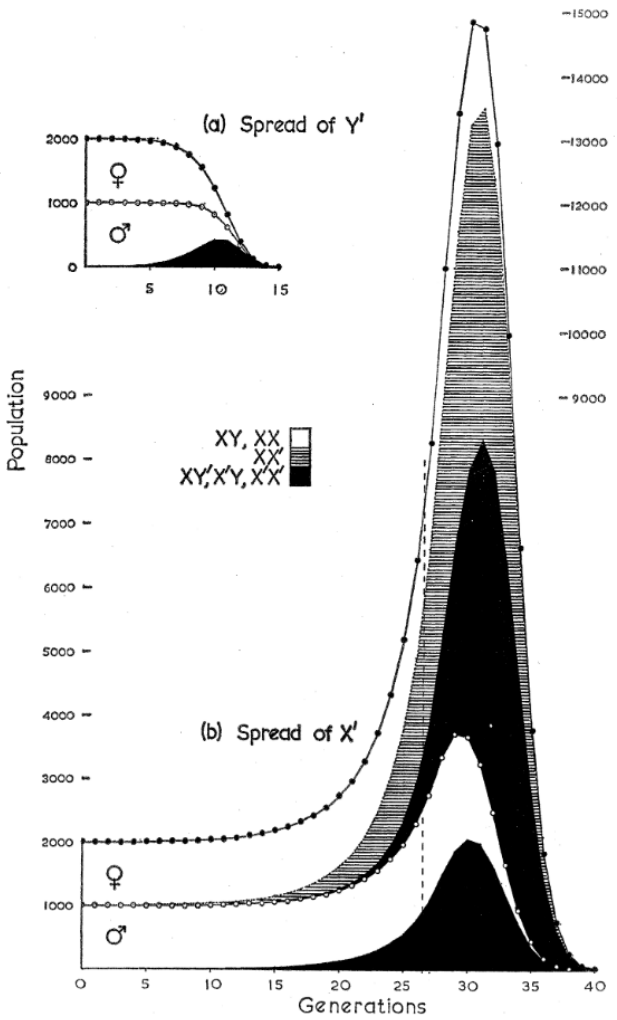
W. D. Hamilton

heritable

distorter gene
Aedes aegypti

T/t alleles in house mouse

Fig. 1. Population and its distribution by sex and genotype in the course of natural selection of (a) a Y chromosome and (b) an X chromosome, having complete drive in spermatogenesis. Mating is random, and normal males give a sex ratio of ½. It is assumed (i) that mated females have two offspring each, so that, before mutation produces the driving chromosome, the population is stationary, and (ii) that males can fertilize only two females each, so that, in (b), from the first generation in which the sex ratio is less than ⅓ (generation 27), some females have no offspring because they are unmated. Both populations start with one chromosome of the driving type in 1000 chromosomes. Extinction is considered to occur after the first generation in which the expected number of females is less than one.



Journal of Theoretical Biology
Volume 241, Issue 2, 21 July 2006, Pages 333-341

2006

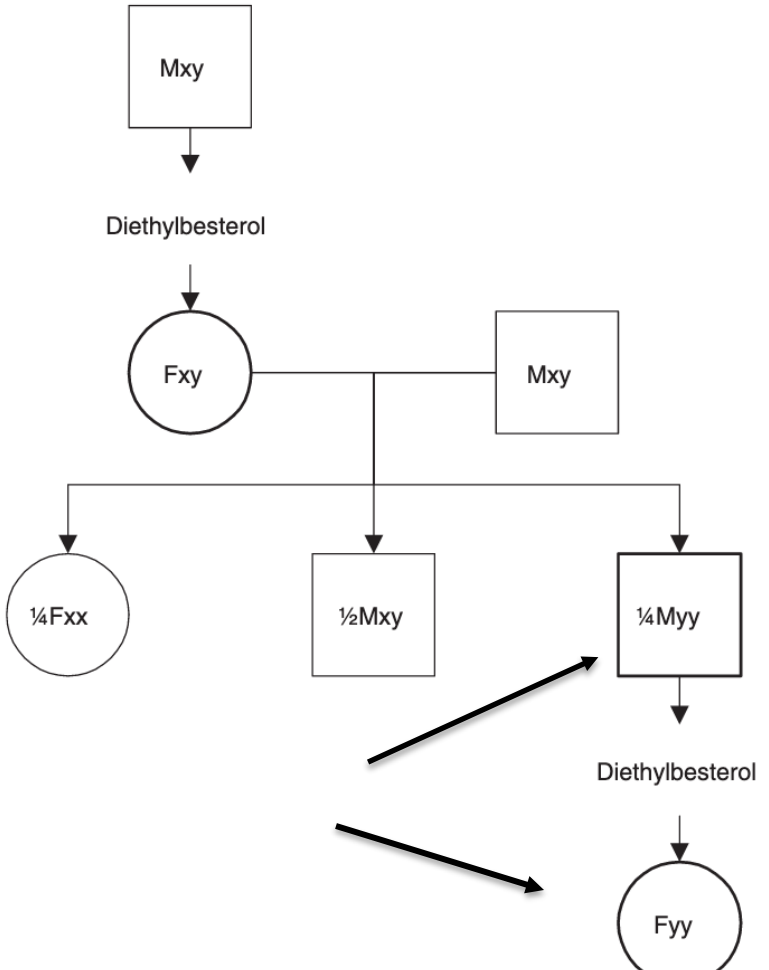
Not heritable,

unlike Hamilton suggestion

A model describing the effect of sex-reversed YY fish in an established wild population: The use of a Trojan Y chromosome to cause extinction of an introduced exotic species

Juan B. Gutierrez [a], John L. Teem [b]

Fig. 1. Tilapia feminization. *Fyy* fish are produced as a result of two rounds of exposure of juvenile fish with diethylbesterol (DES), a steroid hormone of the family of estrogens. Normal male juveniles (*Mxy*) are first exposed to diethylstilbestrol (DES) resulting in conversion to phenotypic females (Fxy). Fxy females are then mated to normal males producing 25% *Myy* males. Exposure of the *Myy* progeny to DES as juveniles results in conversion to *Fyy*. Symbols with thin borders represent wild-type genotypes.



2016

North American Journal of Aquaculture 78:72–83, 2016

ISSN: 1522-2055 print / 1548-8454 online
DOI: 10.1080/15222055.2015.1100149

ARTICLE

Production of a YY Male Brook Trout Broodstock for Potential Eradication of Undesired Brook Trout Populations

Daniel J. Schill* and Jeff A. Heindel
Idaho Department of Fish and Game, 600 South Walnut Street, Post Office Box 25, Boise, Idaho 83707, USA

Matthew R. Campbell
Idaho Department of Fish and Game, 1800 Trout Road, Eagle, Idaho 83616, USA

Kevin A. Meyer and Elizabeth R. J. M. Mamer
Idaho Department of Fish and Game, 1414 East Locust Lane, Nampa, Idaho 83686, USA

feminized males in several fish species

tilapia

common carp

trout

Non-hereditary, even if operate by doing something to the genetic machinery:

a) gene-silencing by itself
b) feminizing male fish, releasing supermales

Hereditary:

a) transgenes, including transgenes that lead to gene-silencing
b) gene-editing

transgene

OXITEC

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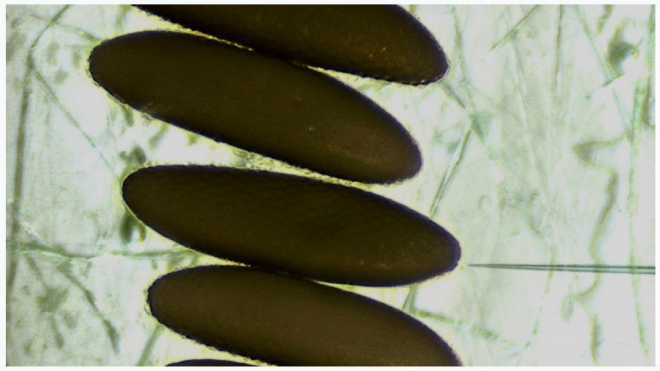


We're applying advanced science to develop new and better pest control

Oxitec's approach uses advanced genetics to develop solutions for controlling dangerous disease-carrying mosquitoes, and harmful agricultural pests.

Haedes, Aegypta and the Oxitec approach

Oxitec's vector control solution – A paradigm shift in mosquito control

TED Talk: Re-engineering mosquitos to fight disease

CORRESPONDENCE

International law should govern release of GM mosquitoes

SIR — Your News story 'Sterile mosquitoes near take-off' (*Nature* **453**, 435; 2008) discusses the likely release of genetically engineered mosquitoes to help contain dengue fever. It demonstrates just how close we are to a radically new set of strategies for managing a whole range of diseases and wildlife using genetically modified organisms (GMOs). But after assessing the risks and benefits, nations may reach different conclusions about their use. And that's quite a problem, considering that genetically modified bugs won't recognize national borders.

Malaysia may successfully avoid spreading the sterile

politics, and appropriately so. The potential for conflict over

Biological Station, CSIC, Apdo. 153, 41080 Sevilla, Spain

Dengue fever and the Aedes aegypti mosquito – an Oxitec film

What is Dengue Fever? Why are people and governments so worried about it? What's it got to do with mosquitoes, and how can we control it?

NEWS OF THE WEEK

SCIENCE AND SOCIETY

GM Mosquito Trial Alarms Opponents, Strains Ties in Gates-Funded Project

For about a decade, scientists have debated how and when to carry out the first test release of transgenic mosquitoes designed to fight human disease—a landmark study they imagined might trigger fierce resistance from opponents of genetic engineering. A stream of papers and reports has argued that a release of any genetically modified (GM) mosquito should be preceded by years of careful groundwork, including an exhaustive public debate to win the hearts and minds of the local population.

But now, it turns out that with little public debate, a company released such mosquitoes a year ago in a fiscal paradise in the Caribbean, where they have been flying under the world's radar screen until last week. At a press conference in London on 11 November, British company Oxitec announced that it carried out the world's first small trial with transgenic *Aedes aegypti* mosquitoes in Grand Cayman in the fall of

"I would completely reject any notion that this was done secretively."

—LUKE ALPHEY, CHIEF SCIENTIFIC OFFICER, OXITEC

says Bart Knols, a medical entomologist at the University of Amsterdam in the Netherlands. "This could well trigger a backlash."

Nor does the trial sit well with the collaborators in a big international project, in which Oxitec is a key member, to develop and test GM mosquitoes. The program, funded by a $19.7 million grant from the Bill & Melinda Gates Foundation and led by Anthony James of the University of Cali-

difficult situation," he says. "I would completely reject any notion that this was done secretively," says Alphey, who notes that the trial was well-known within the island's population of 50,000, "but just not picked up internationally."

Few deny that in the race to develop disease-fighting mosquitoes, Oxitec has an impressive lead. Its key idea, pioneered by Alphey while at the University of Oxford in the 1990s, is to release massive numbers of lab-bred male mosquitoes equipped with a gene that kills any offspring in the larval or pupal stage. When the males mate with females of a natural population, there are no progeny—and if the transgenic males mate more often than the natural ones, the mosquito population will dwindle or even collapse. (And because male mosquitoes don't bite, their release does not increase the risk of disease transmission to humans.)

Oxitec sees a key market in *Ae. aegypti*, the vector for dengue, a painful and sometimes fatal viral infection for which no drugs or vaccines exist. Many middle- and high-income countries already invest heavily in traditional mosquito-control measures to fight dengue, but the results are

WINGED WARRIORS

Brazil plans to release billions of designer mosquitoes to stop the spread of infectious diseases. Will it work?

By **Kelly Servick**, *in Brazil*

Every Saturday morning, Maria do Carmo Tunussi goes door to door asking her neighbors to scour their houses and yards for flowerpots, buckets, clogged gutters—anything that could collect water and offer mosquitoes a place to breed. For 17 years, Tunussi has been a community health agent at the local clinic in CECAP/Eldorado, a district of about 5000 people in the small city of Piracicaba, 2 hours northwest of São Paulo, Brazil. She has seen many surges of the mosquito-borne dengue virus, which causes fever, nausea, and agonizing joint pain. The task sometimes feels futile. "You remove the breeding site one day, and the next day, it's back," she says. "It never ends."

Last April, CECAP became the first

that effective against *A. aegypti*, and breeding site removal, which, despite Tunussi's efforts, is hard to keep up year after year. So it's not surprising that, 7 years after releasing the world's first genetically modified (GM) mosquito, Oxitec has chosen Brazil as the site of a major scale-up. It is moving from small-scale pilot projects like the one in CECAP to planned releases covering tens of thousands of people.

Indeed, Brazil is becoming a proving ground for tailored mosquitoes. About 600 kilometers to the east, in the coastal cities of Niterói and Rio de Janeiro, another lab strain of mosquitoes is on the wing. Bred by a nonprofit organization called Eliminate Dengue, this one is infected with a bacterium called *Wolbachia pipientis* that protects it from infection with dengue, Zika, and

Oxitec's transgenic mosquitoes swarm out of a container in Piracicaba, Brazil.

bouncing around in plastic tubs the size of take-out containers.

Oxitec mosquitoes bearing the lethal gene grow up feeding on tetracycline, an antibiotic that blocks *tTAV* activity and keeps

company in 2002, backed by private venture capital firms and Oxford. Last year, the U.S. synthetic biology behemoth Intrexon Corpo-

in three neighb
state of Bahia. I
lation reductio

Science 354:164-167; Oct. 14, 2016

2019

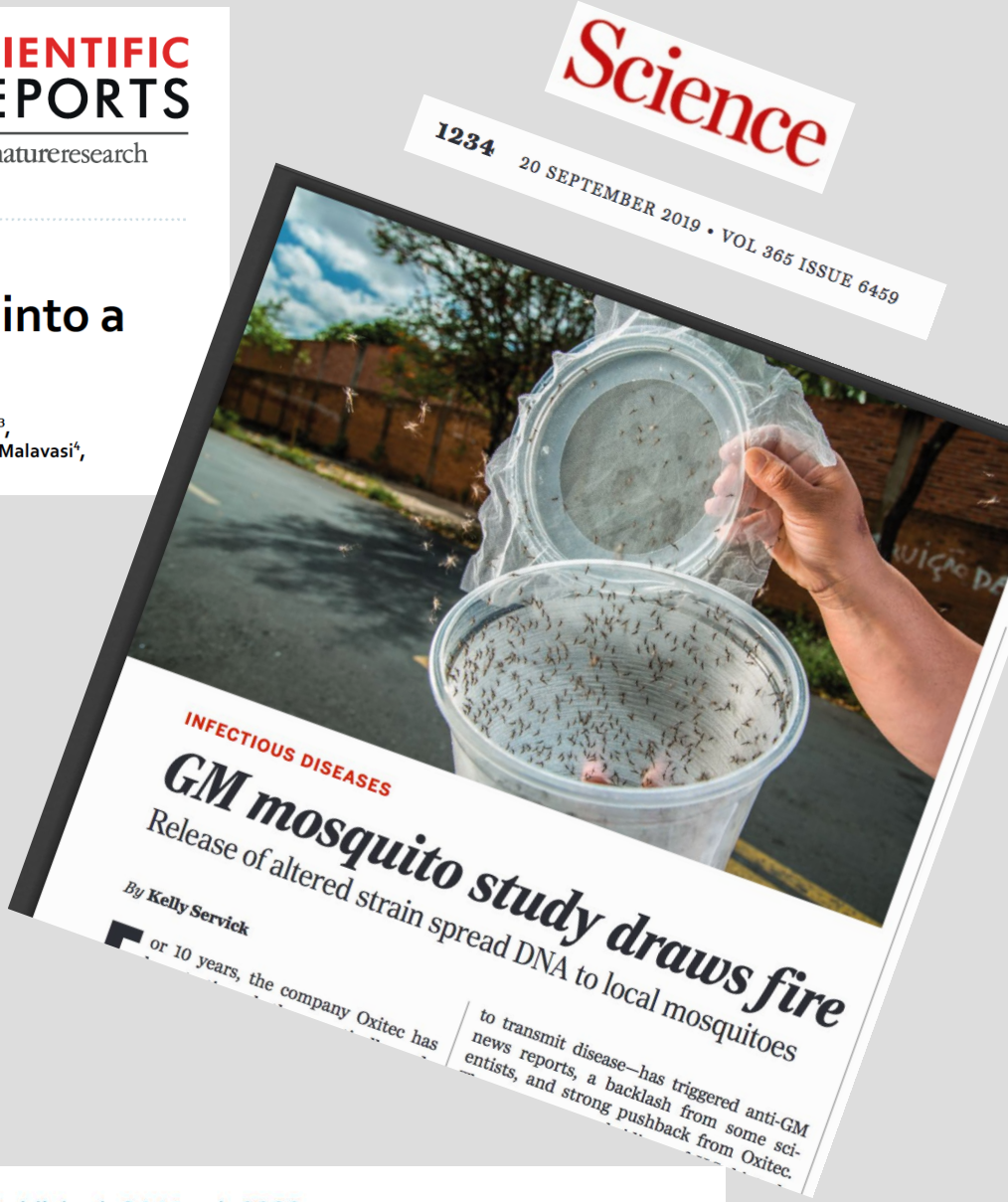
SCIENTIFIC REPORTS
nature research

OPEN

Transgenic *Aedes aegypti* Mosquitoes Transfer Genes into a Natural Population

Received: 11 February 2019
Accepted: 29 August 2019
Published online: 10 September 2019

Benjamin R. Evans[1], Panayiota Kotsakiozi[1], Andre Luis Costa-da-Silva[2,3], Rafaella Sayuri Ioshino[2,3], Luiza Garziera[3], Michele C. Pedrosa[2,3,4], Aldo Malavasi[4], Jair F. Virginio[4], Margareth L. Capurro[2,3] & Jeffrey R. Powell[1]



Oxitec response, 9/18/2019:

but:

2020

Addendum | Open Access | Published: 24 March 2020

Editorial Expression of Concern: Transgenic *Aedes aegypti* Mosquitoes Transfer Genes into a Natural Population

Oxitec projects in development using same approach as Oxitec mosquito

medfly

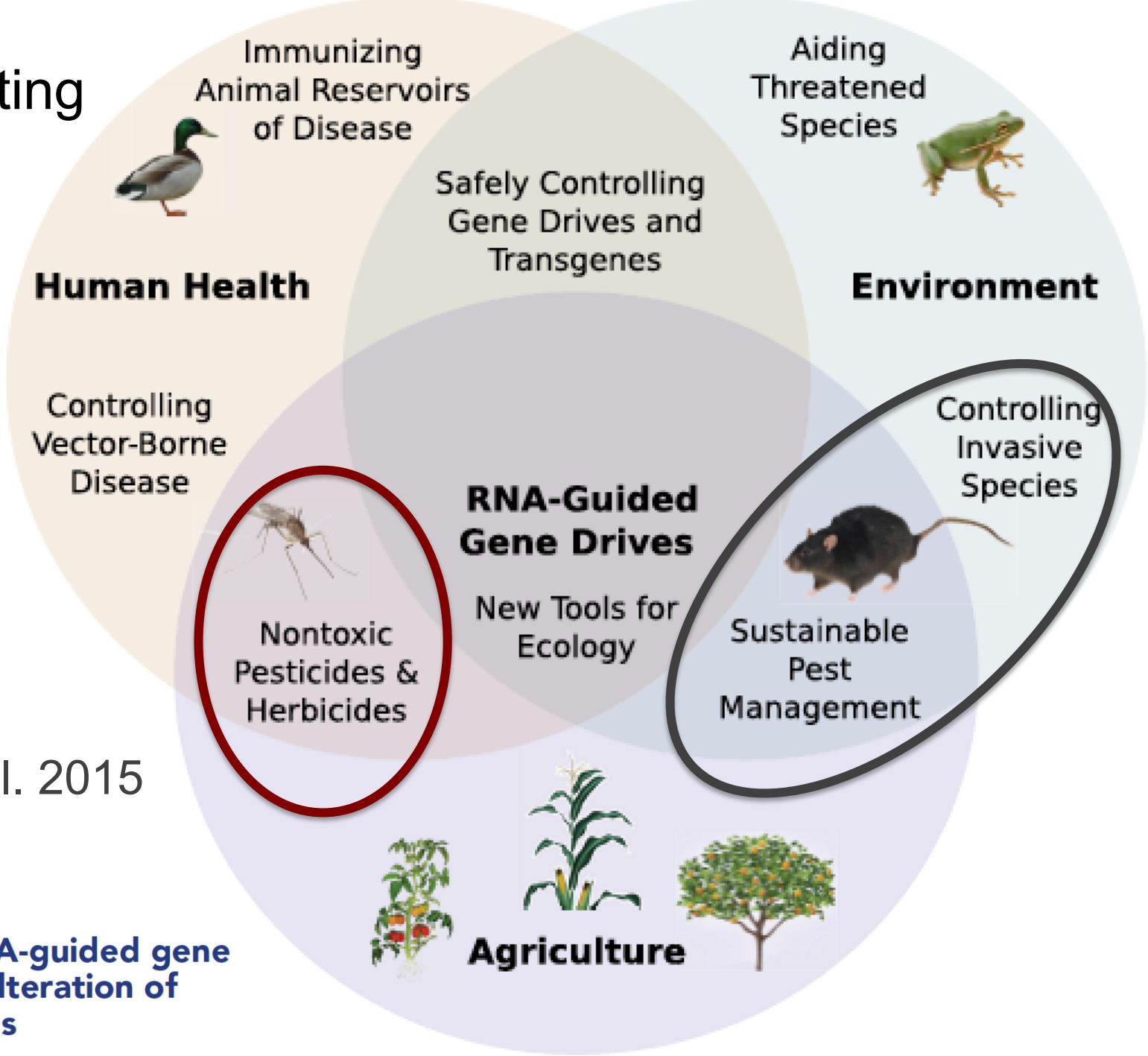
spotted wing Drosophila (*D. suzukii*)

diamondback moth

soybean looper

fall armyworm

gene-editing



Esvelt et al. 2015

EMERGING TECHNOLOGY

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

Los Angeles Times

SUBSCR

Column: The U.S. wants to air-drop poison on Farallon Islands mice. Not everybody hates the idea

A researcher is one of the only people living on the Farallon Islands about 30 miles off San Francisco. (Josh Edelson / For The Times)

BY STEVE LOPEZ | COLUMNIST

DEC. 15, 2021 5 AM PT

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NEWS

Cannibalistic House Mice Destroying the Ecosystem of California Islands

BY MARK WAGHORN, ZENGER NEWS ON 9/28/22 AT 12:50 PM EDT

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A plague of house mice is wrecking the ecosystem of the Farallon Islands of California, according to research.

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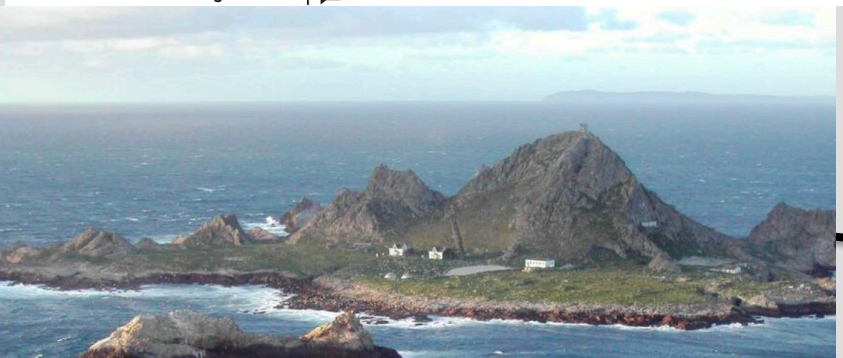
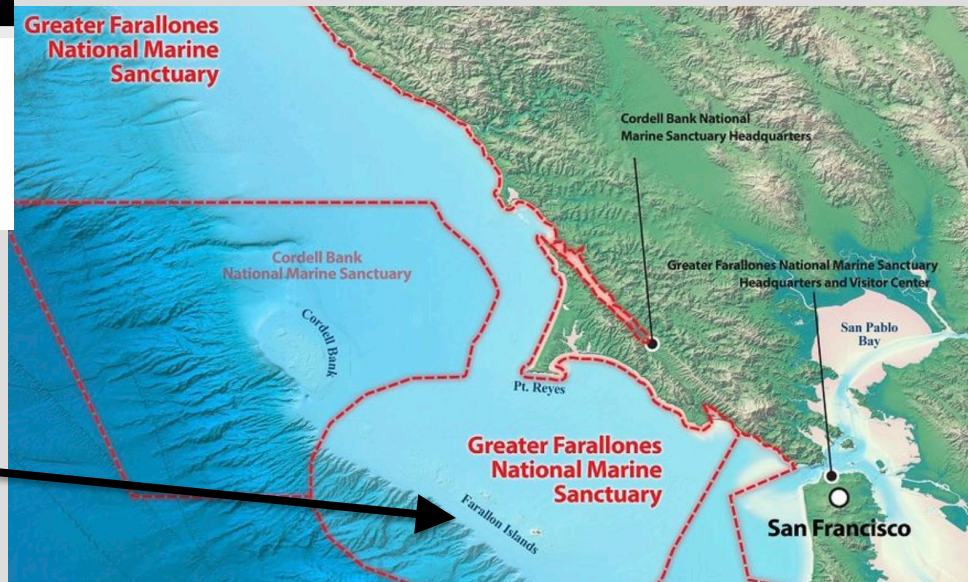
03:05

eEdition 46° The Press Democrat

Farallon Islands mouse poisoning plan divides conservation community

The California Coastal Commission will weigh in on the U.S. Fish & Wildlife Service plan at what's expected to be a marathon meeting Dec. 16. | 6





from A. Hawkes, Bay Nature, 2016

Science & Society

Trends in Biotechnology May 2

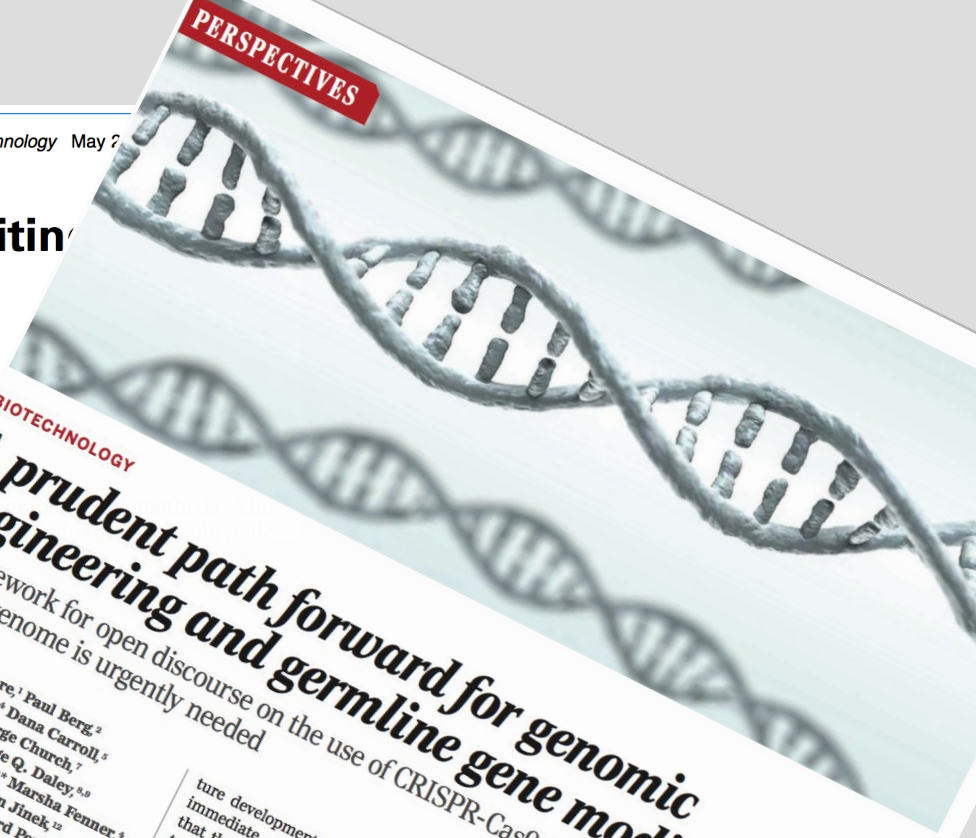
Caution required for handling genome editin technology

Motoko Araki[1], Kumie Nojima[2], and Tetsuya Ishii[1]

[1] Office of Health and Safety, Hokkaido University, Sapporo 060-0808, Japan
[2] Molecular Imaging Center, National Institute of Radiological Sciences, Chiba 263-8555, Japan

Genome-editing technology, although a robust tool for genetic engineering, is creating indistinct regulatory

ism using physical, che
modified cells, such as



BIOTECHNOLOGY

A prudent path forward for genomic engineering and germline gene modification

A framework for open discourse on the use of CRISPR-Cas9 technology to manipulate the human genome is urgently needed

By David Baltimore,[1] Paul Berg,[2] Michael Botchan,[3,4] Dana Carroll,[5] R. Alta Charo,[6] George Church,[7] George Q. Daley,[8,9] Jacob E. Corn,[4] Marsha Fenner,[4] Jennifer A. Doudna,[4,10,*] Martin Jinek,[12] Henry T. Greely,[11] Edward Penhoet,[14] G. Steven Martin,[15] Jennifer Puck,[15] Samuel H. Sternberg[16]

ture developments. The meeting identified immediate steps to take toward ensuring that the application of genome engineering technology is performed safely and ethically. The promise of so-called "precision medicine" is promised in part by synergies between powerful technologies:

CURRENT APPLICATIONS. The simplicity of the CRISPR-Cas9 system allows any researcher with knowledge of molecular biology to modify genomes, making feasible experiments that were previously difficult or impossible to conduct. For example, the CRISPR-Cas9 system enables introduc-

ScienceExpress

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]

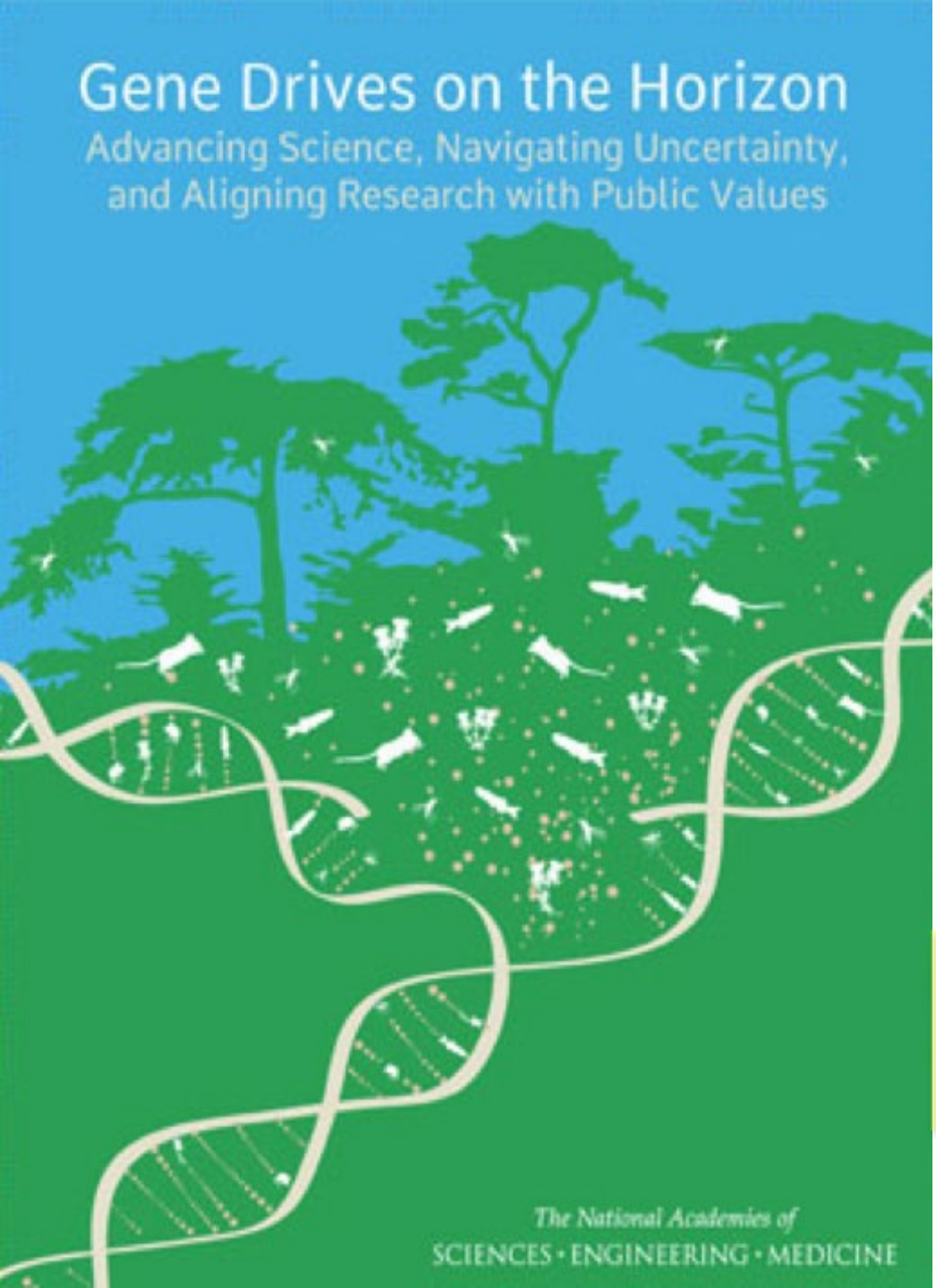
[1]Political Science Department, Massachusetts Institute of Technology. [2]Engineering Systems Division, Massachusetts Institute of Technology. [3]Wyss Institute, Harvard University. [4]Bioinformatics, Boston University. [5]Harvard School of Public Health. [6]University of Perugia, Italy. [7]Woodrow 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

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

nome engineering that uses
nuclease Cas9 to cut seq
fied by guide RNA mole
This technique is in wides
has already engineered th
more than a dozen specie
enable "RNA-guided ger
edit nearly any gene in se
ducing populations (1).

To reduce potential ne
in advance of construction
Esvelt et al. have proposed
el types of drives (1). Pre
could exclusively affect p
cies or subpopulations
sequences



2016 National Academy of Sciences

"There is insufficient evidence available at this time to support the release of gene-drive modified organisms into the environment. However, the potential benefits of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly controlled field trials."

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.

2016

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

Founding signatories include:

Dr Jane Goodall

Scientists and environmental experts and organizations from around the globe have advocated for a halt to proposals for the use of gene drive technologies in conservation. Announced today, a long list of environmental leaders, including **Dr. Jane Goodall, DBE**, genetics professor and broadcaster **Dr. David Suzuki**, **Dr. Fritjof Capra**, entomologist **Dr. Angelika Hilbeck**, Indian environmental activist **Dr. Vandana Shiva** and organic pioneer and biologist **Nell Newman**, have lent their support to the

PLOS | BIOLOGY

2017

PERSPECTIVE

Conservation demands safe gene drive

Kevin M. Esvelt[1]*, **Neil J. Gemmell**[2]*

1 MIT Media Lab, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America, **2** Department of Anatomy, University of Otago, Dunedin, New Zealand

* esvelt@media.mit.edu (KME); neil.gemmell@otago.ac.nz (NJG)

Abstract

Interest in developing gene drive systems to control invasive species is growing, with New Zealand reportedly considering the nascent technology as a way to locally eliminate the mammalian pests that threaten its unique flora and fauna. If gene drives successfully eradicated these invasive populations, many would rejoice, but what are the possible consequences? Here, we explore the risk of accidental spread posed by self-propagating gene drive technologies, highlight new gene drive designs that might achieve better outcomes, and explain why we need open and international discussions concerning a technology that could have global ramifications.

Check for updates

OPEN ACCESS

Citation: Esvelt KM, Gemmell NJ (2017) Conservation demands safe gene drive. PLoS Biol 15(11): e2003850. https://doi.org/10.1371/journal.pbio.2003850

Latest News

Letting Gene Drives Loose Outside Labs is Too Risky, says Scientist Who Promoted Idea

BY PAUL KOBERSTEIN – DECEMBER 21, 2017

But other advocates of controversial genetic engineering technology are moving ahead with plans to conduct field trials in a few years

ABSTRACTIONS BLOG

New Model Warns About CRISPR Gene Drives in the Wild

3

Two new papers urge caution in using powerful genome-editing technology against invasive species: Models show that evolving resistance won't stop aggressive standard gene drives from spreading.

A **race** between the spread of a gene drive and natural selection of genes on other chromosomes that will resist it: evolution of resistance?

As the driven gene causes the chromosome that carries it to be included in gametes at meiosis, this will cause all other genes on that chromosome and other chromosomes in those gametes to be carried along with it. Because the zygote produced by that gamete will be selected against (this is the whole point of the gene drive!), there will automatically be natural selection for genes on any other chromosomes that hinder the driven gene from being driven.

Will the gene drive wipe out the population before natural selection neutralizes the gene drive?????

TARGET MALARIA

https://targetmalaria.org/our-work/

Our Goal

How it Works

Biasing the Sex Ratio

Focus on Mosquito Female Fertility

The New York Times Sept. 25, 2018

Giving Malaria a Deadline

With a new genetic tool, scientists move a step closer to eradicating mosquitoes and the deadly diseases they carry.

gene drives

1) sterile males
2) fertile males that produce only male offspring
3) fertile males whose female offspring are sterile

TEST BIOTECH

Institute for Independent Impact Assessment of Biotechnology

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NEWSLETTER

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DATABASE

Gene Drives: Target Malaria is underestimating the risks

Plans for releases of transgenic mosquitoes are based on flawed data

17 March 2023 / The Target Malaria consortium has for several years been planning to conduct field trials using genetically engineered mosquitoes in Burkina Faso. The aim is to transfer artificial gene constructs, i. e. the so-called 'X-shredder', into wild populations of the mosquitoes. This gene construct is meant to reduce the number of female offspring, and thus bring about a decline in the overall population of mosquitoes (*Anopheles gambiae*) known to transmit malaria. However, as recent research shows, the planned releases are based on flawed data and incorrect assumptions.

Gene-editing on autopilot: What could go wrong?

By Matt Field | March 5, 2019

Illustration by Matt Field.

The headline in *The Economist* called the genetic engineering tool known as gene drive "extinction on demand." *The Guardian* referred to it as "genetic extinction" technology.

Matt Field

Matt Field is editor, biosecurity at the Bulletin of the Atomic Scientists. Before joining the Bulletin, he covered the White House, Congress, and... Read More

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Rodent genetic biocontrol - laboratory development

Gene Drive Strategies

1. CRISPR “homing” gene drive (female fertility)
2. X-shredder (male bias)
3. T-allele + CRISPR (female fertility/embryonic viability)

PNAS 2022 Vol. 119 No. 46 e2213308119 https://doi.org/10.1073/pnas.2213308119

modified t-allele in house mouse

PNAS RESEARCH ARTICLE | GENETICS OPEN ACCESS

Leveraging a natural murine meiotic drive to suppress invasive populations

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Edited by James Bull, University of Idaho, Moscow, ID; received August 3, 2022; accepted October 4, 2022

Invasive rodents are a major cause of environmental damage and biodiversity loss, particularly on islands. Unlike insects, genetic biocontrol strategies including population-suppressing gene drives with biased inheritance have not been developed in mice. Here, we demonstrate a gene drive strategy (t_{CRISPR}) that leverages super-Mendelian transmission of the *t* haplotype to spread inactivating mutations in a haplosufficient female fertility gene (*Prl*). Using spatially explicit individual-based in silico modeling, we show that t_{CRISPR} can eradicate island populations under a range of realistic field-based parameter values. We also engineer transgenic t_{CRISPR} mice that, crucially, exhibit biased transmission of the modified *t* haplotype and *Prl* mutations at levels our modeling predicts would be sufficient for eradication. This is an example of a feasible gene drive system for invasive alien rodent population control.

Significance

Invasive rodents pose a significant threat to global biodiversity, contributing to countless extinctions, particularly on islands. Genetic biocontrol has considerable potential to control invasive populations but has not been developed in mice. Here, we

Eradication of Invasive Quagga and Zebra Mussels using Engineered Disseminated Neoplasia

Steve Suhr and Marie-Claude Senut

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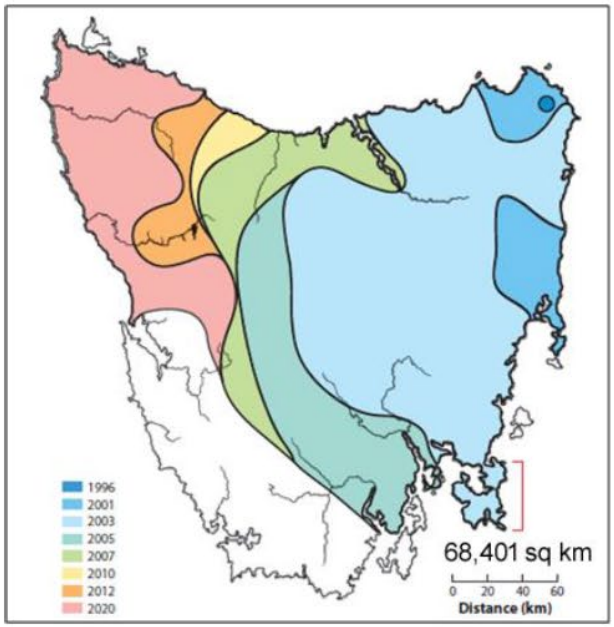
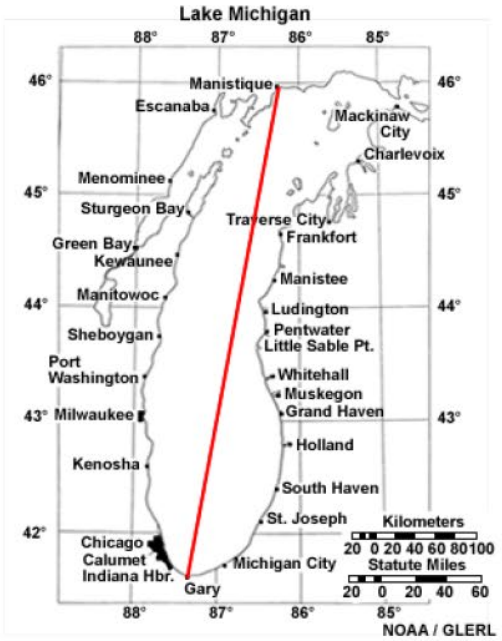
Devil Facial Tumor Disease



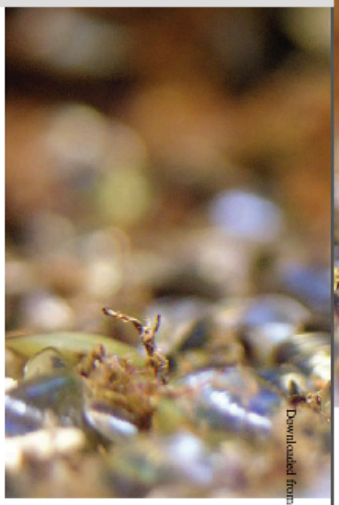


>90% decline in devil population since 1996 and extinction by 2026.

Tasmanian devil

Stammnitz et al. (2018) Cancer Cell 33, 607–619 April 9, 2018
Bender et al. (2014) Ann. Rev. Anim. Biosci. 2014; 2: 165-187.

2021



NEWS

Golden mussels (shown as newborns on top of an adult, right) grow in reeflike structures that cover underwater surfaces and clog pipes in hydroelectric power plants (left).

FEATURES

A GOLDEN MENACE

An invasive mussel is devastating ecosystems

Months after Mansur first spotted them, the animals had taken over Lake Guaíba, plugging the pipes that supplied the city with water. Masses of dark, thumb-size adults mixed with golden pinkie nail–size newborns encrusted bedrock, boats, piers, and bridges, forming dense reeflike structures with more than 200,000 individuals per square meter. Without any local predator to control them, they choked and rotted the roots of plants along the shore, and even grew on top of other animals such as native mollusk species and crabs, suffocating them. "In 2 years, the golden mussel transformed the lake's sandy

flows into the Amazon basin and connects to the Tapajós River, a tributary of the Amazon.

"It only takes one boat encrusted with the mussel to cross the wetlands for the invader to make a new home in an Amazon river," says biologist Marcia Divina at the state-owned Brazilian Agricultural Research Corporation. If the invader spreads in the Amazon, it could wipe out native species that scientists have not even studied yet, she adds. "We can't even calculate the size of the impact."

Despite a late and anemic government response, researchers funded largely by affected hydroelectric companies have developed new tools to track the mussels' relentless advance. And some are looking to an aggressive form of genetic engineering to eradicate it. That untested strategy is still likely years from being ready to deploy, but scientists see

than 15°C (as most Brazilian rivers are year-round), they spew thousands of eggs and sperm. These unite to form microscopic, free-floating larvae that attach to a new surface and grow. At 1 year old, the sesame seed–size mollusk starts to reproduce.

The population Darrigran observed in the La Plata eventually stabilized at 85,000 per square meter in 2019, the last count before the pandemic. But by then, everything around it looked different. Golden mussels are "ecosystem engineers," Darrigran explains, "altering the interactions between the local fauna and flora forever." As mussels build up on a riverbed, they impede water flow, which allows organic matter to accumulate, nourishing a new set of insect larvae, snails, and small gastropods. On average, the mussels attract 10 to 15 new species when

they take over, while crowding out previous occupants. "You always find the same species in invaded areas," Darrigran says, "and the local diversity is lost."

The mussels eat by filtering plankton, monopolizing nutrients that would otherwise feed other river-dwelling species or flow into the ocean. A single adult filters, on average, half a liter of water per hour—about 10 times more than the zebra mussels infesting the U.S. Great Lakes. The water gradually becomes clearer and lets in more light, which encourages blooms of toxic cyanobacteria. A 2008 assessment of Southern Brazil's Alto Paraná River found the mussels had completely wiped out colonies of freshwater sponges—species endangered in Brazil that act as nurseries for larvae of several types of aquatic insects.

Rebelo's group aims to spread genetic modifications that interfere with fertility. The technique relies on the gene-editing tool CRISPR-Cas9, which uses molecular "scissors" to make precise changes to DNA. The researchers will use these scissors to cut DNA in golden mussel sperm. They'll insert both a sequence that disrupts fertility genes and a sequence encoding the scissors themselves. When mutant sperm fertilize eggs in the lab, the offspring will have the fertility-blocking mutations—and the genetic instructions for the scissors—in their germ cells, which give rise to gametes (sperm and eggs).

That's where the gene drive steps in to turn these offspring into superspreaders of infertility: When they reach adulthood and produce gametes, the scissors, which are designed to only be active in germ cells, will cut out and replace the normal fertility genes inherited from the mother so that all the

[redacted]

Science 374: 390-393

The New York Times

As D.I.Y. Gene Editing Gains Popularity, 'Someone Is Going to Get Hurt'

After a virus was created from mail-order DNA, scientists are sounding the alarm about the genetic tinkering carried out in garages and living rooms.

Science 354:541
2016

A reporter does CRISPR

By **Jon Cohen**

I speak biology fluently, but the molecular complexities of the novel genome-editing tool called CRISPR left me as befuddled as when I peruse descriptions of the inflationary universe. So I decided to test what one investigator told me: CRISPR (for "clustered regularly interspaced short palindromic repeats") may sound intimidating, but it is so simple to use that "any idiot" could do it.

I would give it a try.

Biologist Roland Wagner (left) watches as Jon Cohen attempts a key pipetting step in creating a CRISPR construct.

I've already learned that any idiot cannot do CRISPR: It takes, at least, basic laboratory skills.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