Genetic control strategies for pests : Available guidance for responsible research

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Andy Sheppard FTSE - Research Director Biosecurity

Outline

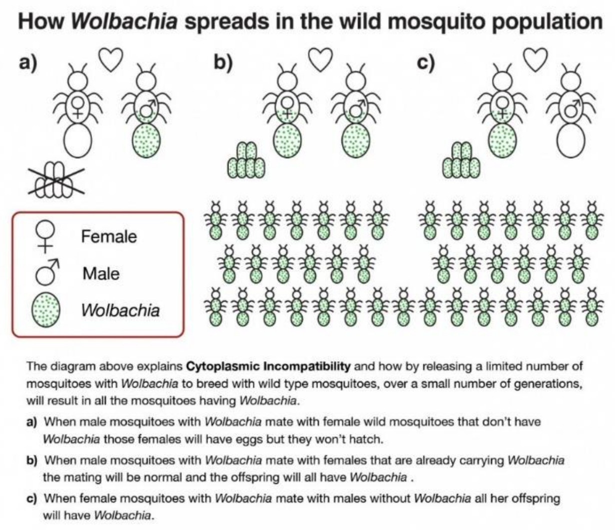
- Gene-drive global concerns
- International scientific guidance/guidelines to address concerns
- Public consultation
- Building safer gene-drive strategies
- Take home messages

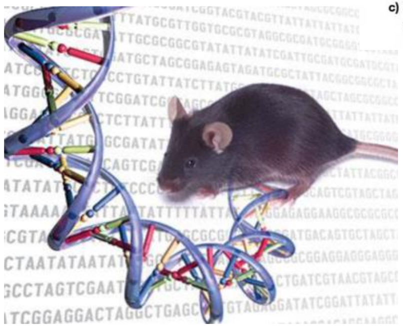
Self-sustaining meiotic gene-drive systems

Genetic mechanisms (natural or synthetic) that can propagate modified gene(s) through a target population via *super-Mendelian* inheritance

Natural selfish genetic elements (gene-drives)?

- **Wolbachia** in *Aedes* & *Culex* spp. mosquitos
  - Cytoplasmic incompatibility; infected ♂ x WT ♀ - lethal
  - Population replacement with infected lines with reduced competence
- **Y-drive** in insects e.g. *Aedes* leads to breakage of X chromosome distorting sex ratio – 80-90% heritable in wild populations
- **Medea gene element** (maternal toxin & antidote traits) in beetles, fungi & plants – all offspring without antidote gene die
- **Pre-gametic (biased meiosis) & post-gametic (gamete/pollen killers) drives** in plants
- **T-Sry mice –** male sex determining mutation in 30% of wild mice

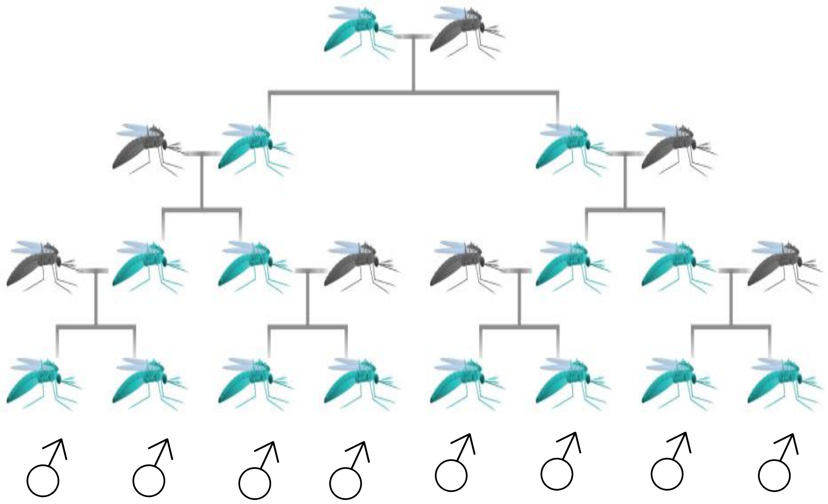




Fitness costs often lead to reduced titres of selfish genotypes in wild populations

Synthetic Gene-Drive system in pest management – drive deleterious genes into the genome of every pest individual in the population = eradication?

- 2002 an Idea
- 2009 discovery of CRISPR-Cas9 gene shears
- 2014 gene-drives a GM reality
- 2016 – public acceptability?
  - ethics questions
  - regulations for use?



1st target malaria mosquito

TARGET MALARIA

nature biotechnology

A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*

Andrew Hammond[1], Roberto Galizi[1], Kyros Kyrou[1], Alekos Simoni[1], Carla Siniscalchi[2], Dimitris Katsanos[1], Matthew Gribble[1], Dean Baker[3], Eric Marois[4], Steven Russell[3], Austin Burt[1], Nikolai Windbichler[1], Andrea Crisanti[1] & Tony Nolan[1]

Gene drive systems that enable super-Mendelian

homozygote in a process known as 'homing.' Through this mechanism,

TARGET MALARIA

WHY MALARIA MATTERS | WHO WE ARE | WHERE WE OPERATE | OUR WORK | BLOG | RESOURCES | NEWS

PNAS

Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*

Valentino M. Gantz[a,1], Nijole Jasinskiene[b,1], Olga Tatarenkova[b], Aniko Fazekas[b], Vanessa M. Macias[b], Ethan Bier[a,2], and Anthony A. James[b,c,2]

[a]Section of Cell and Developmental Biology, University of California, San Diego, La Jolla, CA 92093-0349; [b]Department of Molecular Biology and Biochemistry, University of California, Irvine, CA 92697-3900; and [c]Department of Microbiology and Molecular Genetics, School of Medicine, University of California, Irvine, CA 92697-4500

Contributed by Anthony A. James, October 26, 2015 (sent for review October 11, 2015; reviewed by Malcolm Fraser and Marcelo Jacobs-Lorena)

Genetic engineering technologies can be used both to create transgenic mosquitoes carrying antipathogen effector genes targeting human malaria parasites and to generate gene-drive systems capable of introgressing the genes throughout wild vector populations. We developed a highly effective autonomous Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated protein 9 (Cas9)-mediated gene-drive system in the Asian malaria vector *Anopheles stephensi*, adapted from the mutagenic chain re-

directed to new sites while providing confidence that treated areas will remain malaria-free (5, 7).

We and others are pursuing a population-modification approach that involves the introduction of genes that confer a parasite-resistance phenotype to mosquitoes that otherwise would be fully capable of transmitting the pathogens (8–13). The expectation is that the introgression of such an effector gene at a high enough frequency in a vector population would decrease or

2nd target mice

Paul Thomas

THE UNIVERSITY of ADELAIDE

NEWS IN FOCUS

NATURE July 2018

GENE EDITING

Gene drives tested in mammals for first time

Technology worked inconsistently in mice.

BY EWEN CALLAWAY

A controversial technology that can alter the genomes of entire species has been applied to mammals for the first time. In a preprint published on 4 July, researchers and researchers have suggested that the technology could help to kill off rodent pests. The technique has attracted controversy — and even a failed attempt to ban its global use — because, if released in the wild, organisms carrying gene drives might be hard to contain.

Science

1K

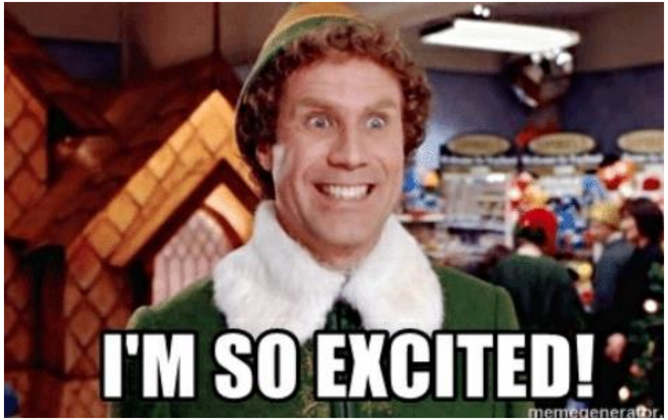
28

The genome editor CRISPR can be used to engineer female lab mice that have increased odds of passing down a specific gene to offspring. ISTOCK.COM/GORKEMDEMIR

'Gene drive' passes first test in mammals, speeding up inheritance in mice

By Jon Cohen | Jul. 10, 2018 , 1:50 PM

Researchers have used CRISPR, the genome editing tool, to speed the inheritance of specific genes in mammals for the first time. Demonstrated in lab-reared insects several years ago, this controversial "gene-drive" strategy promises the ability to quickly spread a gene throughout an entire species. It has sparked dreams of deploying lethal genes to eradicate pests such as malaria-carrying mosquitoes—and now, perhaps, crop-damaging, disease-causing mammals such as rabbits, mice, and rats.



Everything an ideal control tool should be:

- Humane
- Species specific
- Self-disseminating
- NOT CONTAGIOUS (spreads by sexual reproduction)
- Not repeated release of many animals
- Hope ?

Should be banned

- Uncontrollable
- Irresponsible
- GM
- Won't work anyway
- Regulatory nightmare
- International implications
- Ecological and trade risk?
- Humans playing god

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Science

Gene drives: Feral science or feral solution?

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ABC Science By Natasha Mitchell for Science Friction

Updated 24 June 2018 at 8:47 am
First posted 24 June 2018 at 8:08 am

Rodents can cause havoc on remote islands, but there may now be a gene drive to render female mice sterile. (Getty Images: DEA/A. Calegari)

A new genetic technology bankrolled by the United States military has the potential to wipe out feral mice and malaria — but scientists are treading carefully, warning it could have unintended consequences.

BIOSAFETY

Safeguarding gene drive experiments in the laboratory

Multiple stringent confinement strategies s... whenever possible

By Omar S. Akbari[1,2], Hugo J. Bellen[3,4], Ethan Bier[5,*], Simon L... George M. Church[8,9], Kevin R. Cook[10], Peter Duchek[11], Owain I... Esvelt[8,*], Valentino M. Gantz[5], Kent G. Golic[13], Scott J. Gratz[14], ... Keith R. Hayes[16], Anthony A. James[17], Thomas C. Kaufman[10], J... Harmit S. Malik[18,19], Kathy A. Matthews[10], Kate M. O'Connor-(... Norbert Perrimon[9,21], Fillip Port[6], Steven Russell[22], Ryu Ueda[2...

WE NEED AN **URGENT REVIEW** OF BIOSAFETY PROTOCOLS FOR CRISPR AND GENE-DRIVE EXPERIMENTS IN **WILD ORGANISMS.**

HIJACKING EVOLUTION

Gene-drive technology could alter the genome of an entire species. Researchers need to answer these key questions before deploying it in the wild.

BY MEGAN SCUDELLARI

Austin Burt and Andrea Crisanti had been trying for eight years to hijack the mosquito genome. They wanted to bypass natural selection and plug in a gene that would mushroom through the population faster than a mutation handed down by the usual process of inheritance. In the back of their minds was a way to prevent malaria by spreading a gene to knock out mosquito populations so that they cannot transmit the disease.

Crisanti remembers failing over and over. But finally, in 2011, the two geneticists at Imperial College London got back the DNA results they'd been hoping for: a gene they had inserted into the mosquito ...

that the genome no longer has the natural version of the chosen gene, and instead has two copies of the gene drive. In this way, the change is passed on to up to 100% of offspring, rather than around 50% (see 'How gene drives work').

Since 2014, scientists have engineered CRISPR-based gene-drive systems in mosquitoes, fruit flies and fungi, and are currently developing them in mice. But that's just the beginning of the story. Questions about whether a gene drive is possible have been supplanted by other unknowns: how well they will work, how to test them and who should regulate the technology. Gene drives have been proposed as a way to reduce or eliminate ...

ILLUSTRATION BY ANA KOVA

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NGOs organised & mobilized - Calls for R&D moratoria through IUCN (2016) and CBD (2018)

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NEWS · 29 NOVEMBER 2018 · CORRECTION 30 NOVEMBER 2018

UN treaty agrees to limit gene drives but rejects a moratorium

Treaty's vague language on how researchers can release engineered organisms has both opponents and supporters of the technology claiming victory.

Ewen Callaway

nature International weekly journal of science

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News & Comment > News > 2018 > September > Article

NATURE | NEWS

'Gene drive' moratorium shot down at UN biodiversity meeting

Freeze on genetic technology would have been a disaster, say scientists, but activists plan to renew the fight.

Ewen Callaway

Outline

- Gene-drive global concerns
- International scientific guidance/guidelines to address concerns
  - Networks & Forums
  - Principles, Guidelines, Core Commitments
  - Peer-reviews
  - Codes of Ethics
- Public consultation
- Building safer gene-drive strategies
- Take home messages

Science

Risk assessment

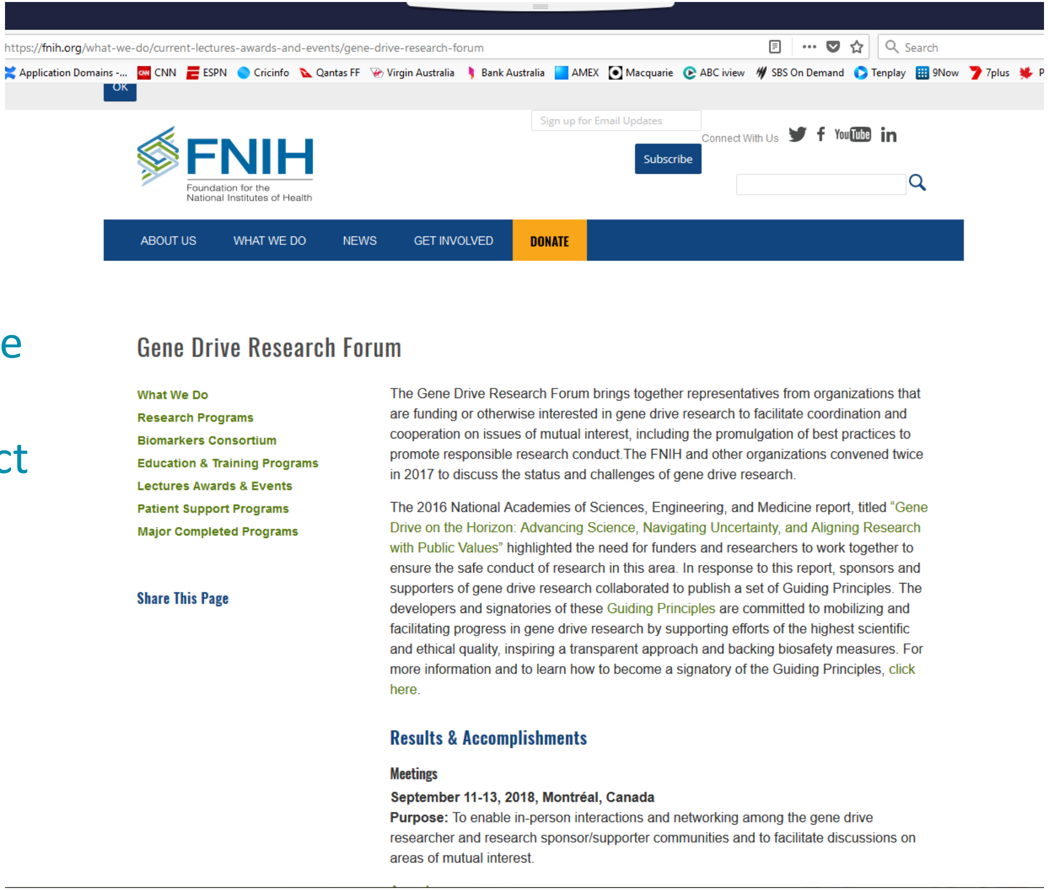
Social License, Liaison

Frameworks, underpinning science

OUTREACH NETWORK FOR
GENE DRIVE RESEARCH

Gene drive forums

- Promulgation of best practice
- Responsible research conduct
- Safe conduct



BIOETHICS

Principles for gene drive research

Sponsors and supporters of gene drive research respond to a National Academies report

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 dis-

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

RESPONDING TO THE NASEM REPORT

Sponsors of scientific research have a responsibility to support innovation that promotes and sustains the public good (*11*). They share the common goal of advancing knowledge and human well-being, while protecting and promoting societal values that underpin the responsible conduct of science. The 2010 report from The Presidential Commission for the Study of Bioethical Issues, "New Directions: The Ethics of Synthetic Biology and Emerging Technologies," highlights the important point that the responsibility for ensuring the conduct of quality science is not the exclusive domain of scientists, but is a shared responsibility among research sponsors and policy-makers alike (*11*). In this Policy Forum, we use the term "science" in its broadest sense, referring inclusively to the life and physical sciences as well as social science, and the humanities, i.e. ethics. Moreover, researchers, sponsors, and policy-makers also share the responsibility of monitoring the progress of science and communicating it effectively to the public

Guiding principles for the sponsors and supporters of gene drive research

Advance quality science to promote the public good

The purs … note, the public g… quality science and ethic… et by the research community and relevant decision-making bodies [(*2*), p. 106)].

Public good/Societal value

Promote stewardship, safety, and good governance

Researchers and sponsors are stewards of science and the public trust. It is imperative that g… especi… iance with a… standa… ystem in whic… erm effects through appropriate ecological risk assessment, is a hallmark of both good stewardship and good governance [(*2*), pp. 128; 170–172)].

Good governance to maintain public trust

Demonstrate transparency and accountability

Know… transp… of result… ent with the tra… omic 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)].

Transparency & accountability

Engag…s

Mean… for ensur… in the re… ust, inclus… s of those most affected are taken into account [(*2*), pp. 142–143)].

Stakeholder communities engagement

Foster opportunities to strengthen capacity and education

Streng… for enabli… to partne… rch, from t… for testing… [(*2*), pp. 128; 170–172)].

Foster global best practice through education

The National Academies of SCIENCES ENGINEERING MEDICINE THE NATIONAL ACADEMIES PRESS

http://nap.edu/23405

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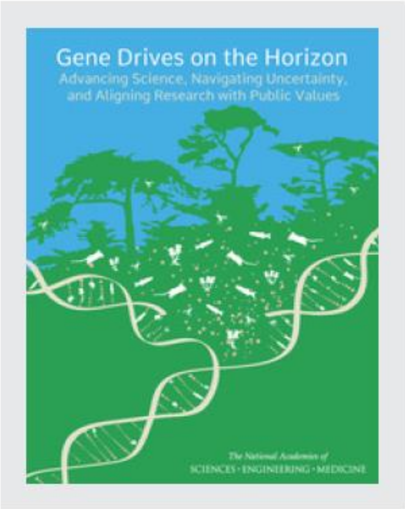


Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values

DETAILS

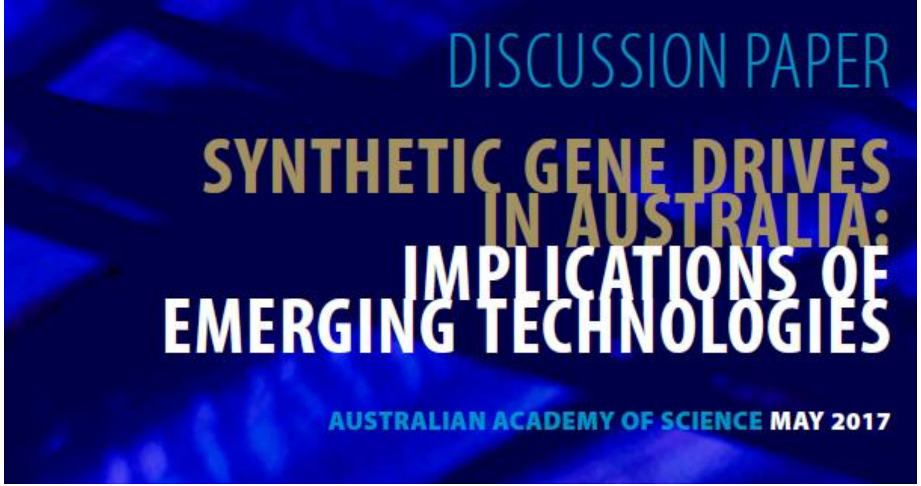
230 pages | 7 x 10 | PAPERBACK
ISBN 978-0-309-43787-5 | DOI 10.17226/23405

2016

"Research institutions, regulators, and funders should revisit international regulatory frameworks, national laws, non-governmental policy, and ***professional codes of conduct on research and the release of genetically modified organisms*** *to determine whether and how they may be applied to the specific context of gene drive research, particularly with regard to the site selection issues, capacity building for responsible and inclusive governance systems, scientific and post release surveillance, and stakeholder engagement. (Emphasis added)*[5]"

Guiding Principles for the Sponsors of Gene Drive Research

- **Advance quality science to promote the public good**
- **Promote stewardship and good governance**
- **Demonstrate transparency and accountability**
- **Engage thoughtfully with communities, stakeholders and publics**
- **Foster opportunities to strengthen capacity and education**



Australian Academy of Science

www.science.org.au/gene-drives

2017

The Australian Academy of Science recommends that:

Communication/Governance

communication of governance arrangements regarding regulation of synthetic gene drives.

2. Resources be provided to study synthetic gene drives in isolated laboratory populations with sample sizes and time frames that are large enough and/or long

Quality & duration of science

transmission distortion, together with the intended and potentially unintended consequences that these process may lead to.

3 **Stringent containment** taken

4. Any decision to release a synthetic gene drive con **Risk assessment** basis follo l risk assessment which includes ecological and evolutionary modelling.

5. T **Communication/ Consultation** on with t the e arly w

6. The wider implications of synthetic gene drives (e.g **Consideration of wider implications**

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Core commitments for field trials of gene drive organisms

Kanya C. Long et al. Science 2020;370:1417-1419

Core commitments for field trials of gene drive organisms

Fair partnership and transparency

- Partner with collaborating communities, local experts, and stakeholders to increase qual-

Community partnerships/data transparency

possible considerations of trial redesign or termination
- Present timely data on open platforms and work toward a global registry for GDOs

Product efficacy and safety

- Support the establishment of acceptable performance parameters of a GDO in collabora-
tion with partner

Measure efficacy & safety

- Identify sources … safety
and efficacy
- Make efficacy and safety data publicly available

Regulatory evaluation and risk/benefit assessment

- Engage early and often with regulators, following national regulatory procedures and
regional and

Risks/benefits with regulators

- Develop me… ution
- Expand risk… dge and
expertise through engagement with local communities and other stakeholders

Monitoring and mitigation

- Engage and partner with community members, regulators, and experts to prepare
monitoring and mitigation plans

Monitoring & mitigation

- Define cond… ed and prepare
local infrast
- Openly report field, modeling, and laboratory data on GDO safety and effectiveness
in field conditions

Science AAAS

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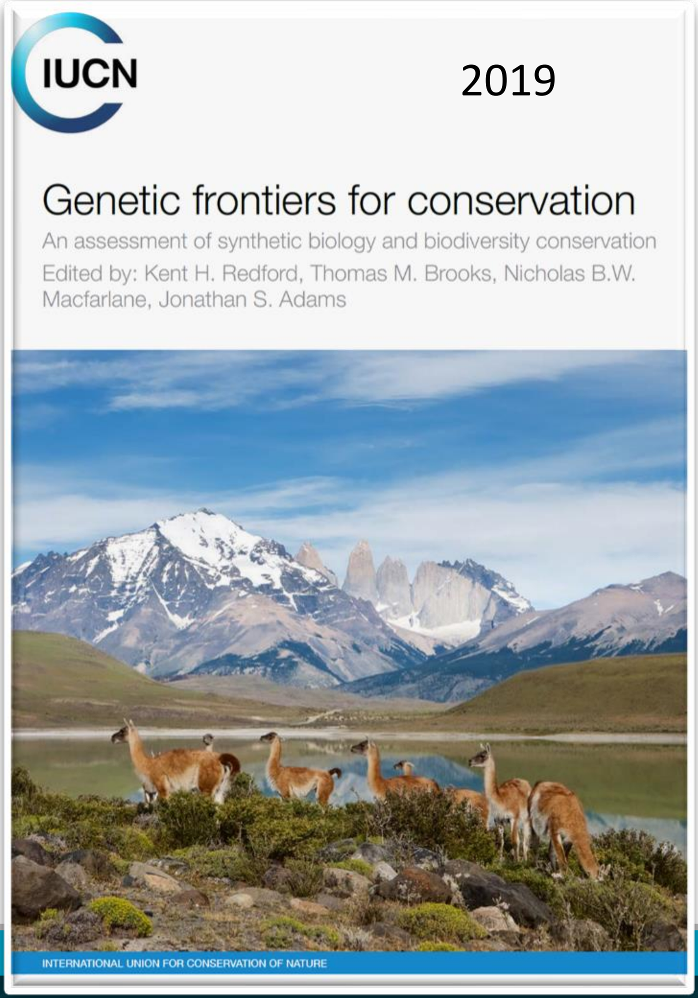
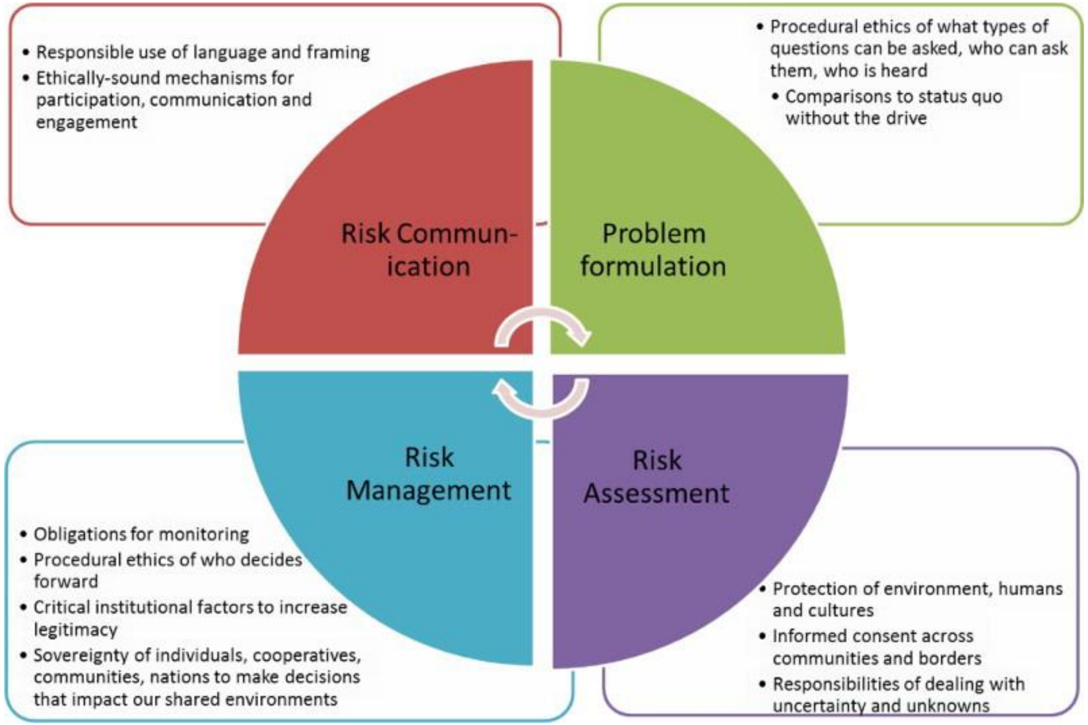
Assessments



Gene-drive roadmap - risk governance and ethics



Kuzma, J., Gould, F., Brown, Z., Collins, J., Delborne, J., Frow, E., Esvelt, K., Guston, D., Leitschuh, C., Oye, K. and Stauffer, S., 2018. **A roadmap for gene drives: using institutional analysis and development to frame research needs and governance in a systems context**. *Journal of Responsible Innovation*, *5*(sup1), pp.S13-S39.

Code of Ethics for Gene Drive Research – *The CRISPR Journal* 2021

Annas, G.J., Beisel, C.L., Clement, K., Crisanti, A., Francis, S., Galardini, M., Galizi, R., Grünewald, J., Immobile, G., Khalil, A.S. and Müller, R., 2021. A Code of Ethics for Gene Drive Research. *The CRISPR Journal*, *4*(1), pp.19-24.

Conduct transparent gene-drive research consistent with societal needs respecting human rights, public safety, and ecological stewardship.

Scientific responsibility:

1. minimize the risk of research misappropriation (e.g. in the context of the Biological Weapons Convention;
2. prevent development, production, or acquisition of biological agents or toxins; and
3. continuously assess risks before and after release, ensuring full timely disclosure of risk factors for society and environment.

Ecological stewardship: identify, minimize, and justify any adverse effects on the public's health and the natural environment.

Public engagement and benefit sharing (using best practice):

1. integrate ecological risk assessment to inform decision-making for any proposed field test or environmental releases.
2. proactively include wide-ranging discussions with all relevant stakeholder communities during planning using
   i. scenarios,
   ii. unforeseeable risks,
   iii. containment and reversal options
   iv. effectiveness likelihood

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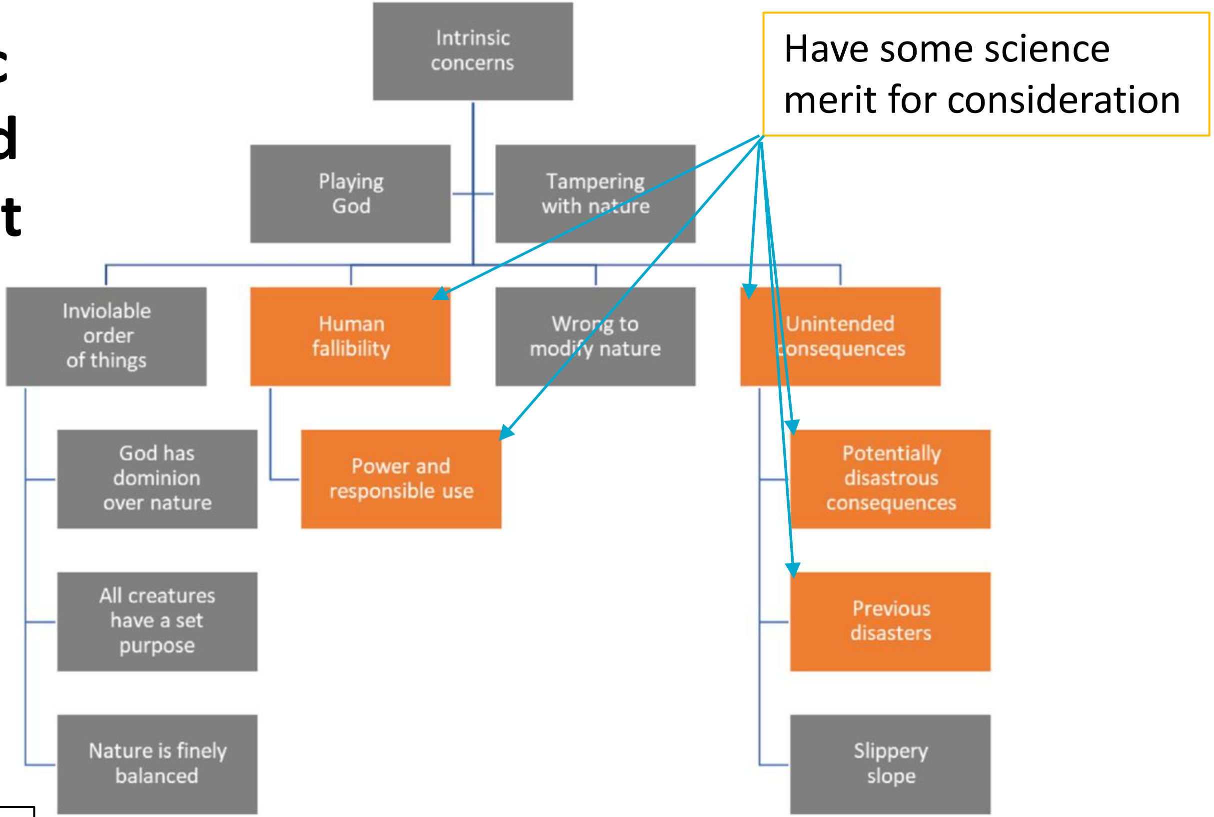
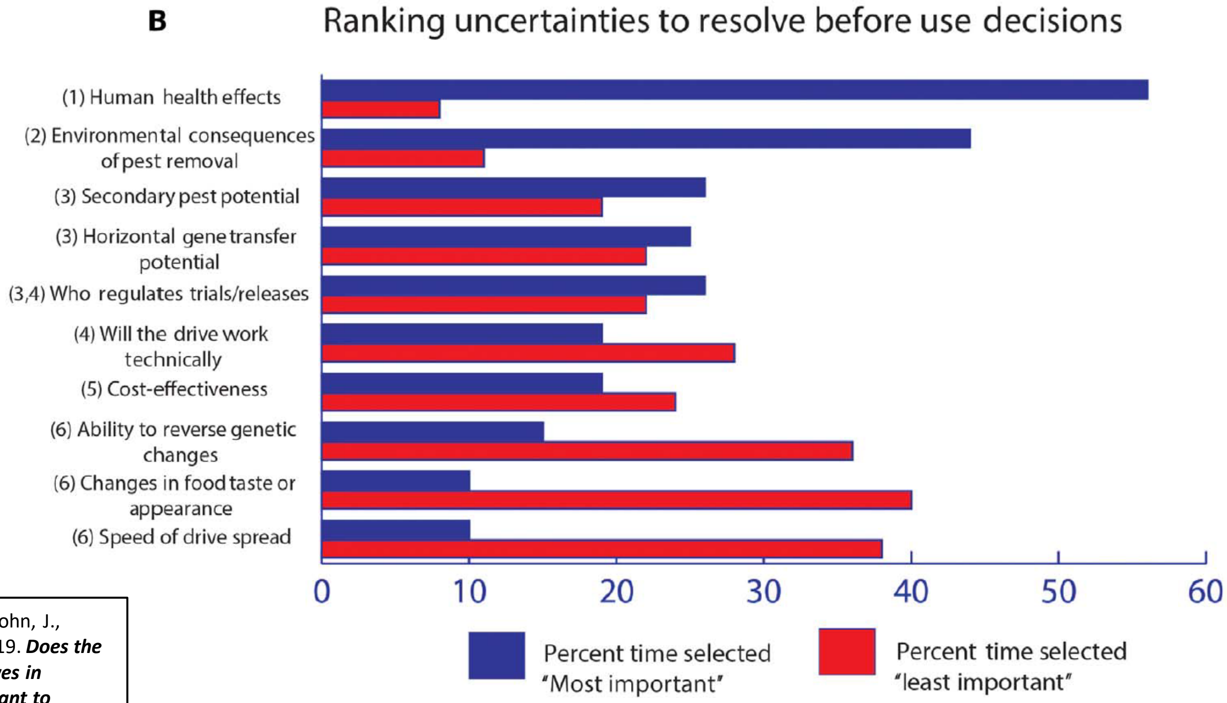
Typologies of intrinsic societal claims around human interventionist approaches



Carter, L., Mankad, A., Hobman, E.V. and Porter, N.B., 2021. Playing God and tampering with nature: popular labels for real concerns in synthetic biology. *Transgenic Research*, *30*(2), pp.155-167.

What does the US public want to know?



Jones, M.S., Delborne, J.A., Elsensohn, J., Mitchell, P.D. and Brown, Z.S., 2019. ***Does the US public support using gene drives in agriculture? And what do they want to know***?. *Science advances*, *5*(9), p.eaau8462

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GBIRd

Genetic Biocontrol of Invasive Rodents

GENETICS & MODELLING

RODENT ECOLOGY & BEHAVIOR

RISK ASSESSMENT/ REGULATORY/ POLICY & IP

STAKEHOLDER ENGAGEMENT & FIELD TRAIL SITE ASSESSMENT

POPULATION GENOMICS & SPATIAL CONTROL

MACQUARIE University

New Zealand's Biological Heritage – National Science Challenges

ISLAND CONSERVATION – Preventing Extinctions

NC STATE UNIVERSITY

CSIRO

CENTRE FOR INVASIVE SPECIES SOLUTIONS

USDA

A&M

THE UNIVERSITY of ADELAIDE

ISLAND CONSERVATION

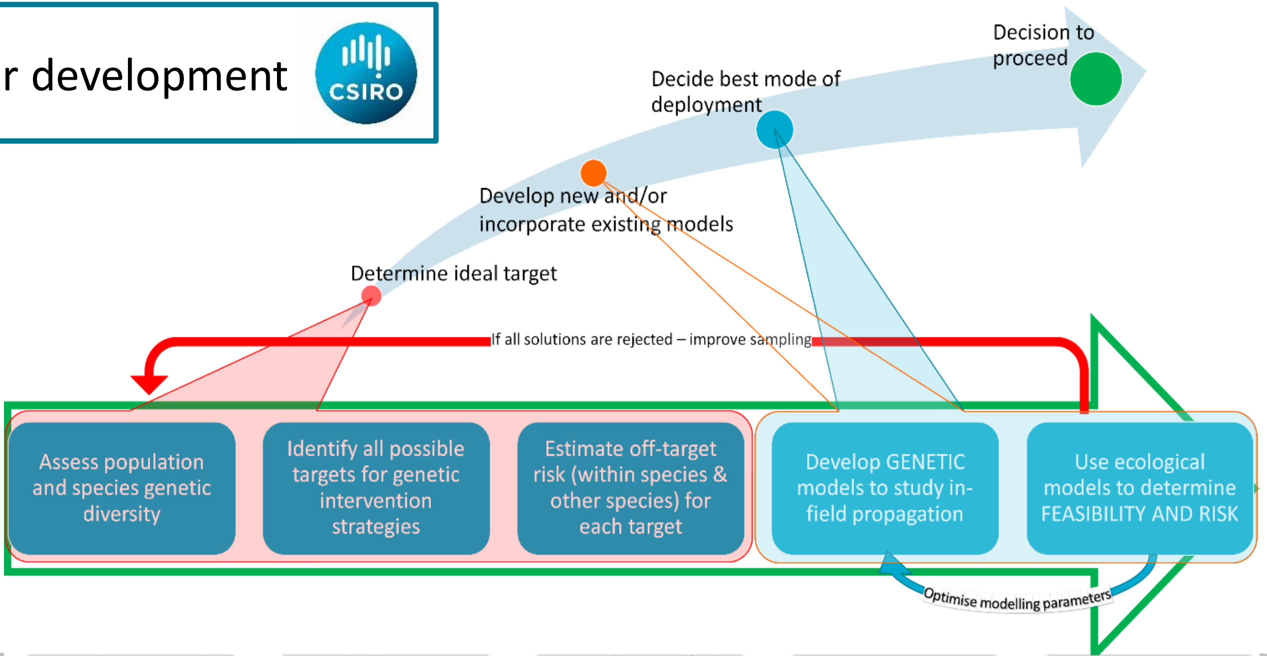
Preventing Extinctions

GBIRd

Gene drive Utility And Risk Determination pipeline (GUARD)

In silico evaluation of feasibility and risk of gene drive options against target and non-target populations/species, based on population genomic data

Under development



Take home messages

- **Potential genetic control strategies are diversifying, based on a precautionary approach** away from the widely criticised "uncontrollable gene-drive approach", which no well informed institutions see as acceptable
-
- **Majority of relevant government agencies, reputable R&D providers and many NGOs have signed up to collectively agreed guidelines** for undertaking open & transparent research, supported by *national academies* and *regulators* - mostly still early stage research without field-ready systems

- **The research community working on** such genetic control solutions is putting priority and equal resourcing in to **independent public and stakeholder community engagement** research
  - to objectively address societal views and concerns ensuring each jurisdiction considers application from its unique values and ethics perspectives

Plenty of available guidance for responsible research !

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Luke Barrett – CSIRO
Mathieu Legros – CSIRO
Kumaran Nagalingam - CSIRO
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Royden Saah - Island Conservation
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John Eisemann – USDA APHIS
John Goodwin NCSU USA
Jason Delbourne NCSU USA
Andrea Byron Landcare Research NZ

Thank you

US *Intended Consequences* Workshop participants recognise the need for/to:

- Conservationists and other stakeholders to codesign conservation interventions for intended consequences for biodiversity benefits
- New risk assessment tools during intervention planning and implementation.
- Consider risks of “no intervention”
- Be transparent about social and cultural values
- Strong Inclusive engagement with relevant stakeholder communities (including indigenous)
- A dynamic *code of practice* for genetic interventions that weighs ecological and social risks, and potential benefits evolving with new knowledge, additional experience, and further deliberation via an inclusive process
- Monitoring to help design successful interventions, manage uncertainty, and codify lessons learned along the way.

Phelan et al. 2021. Intended Consequences Statement. *Conservation Science and Practice* 3 e371