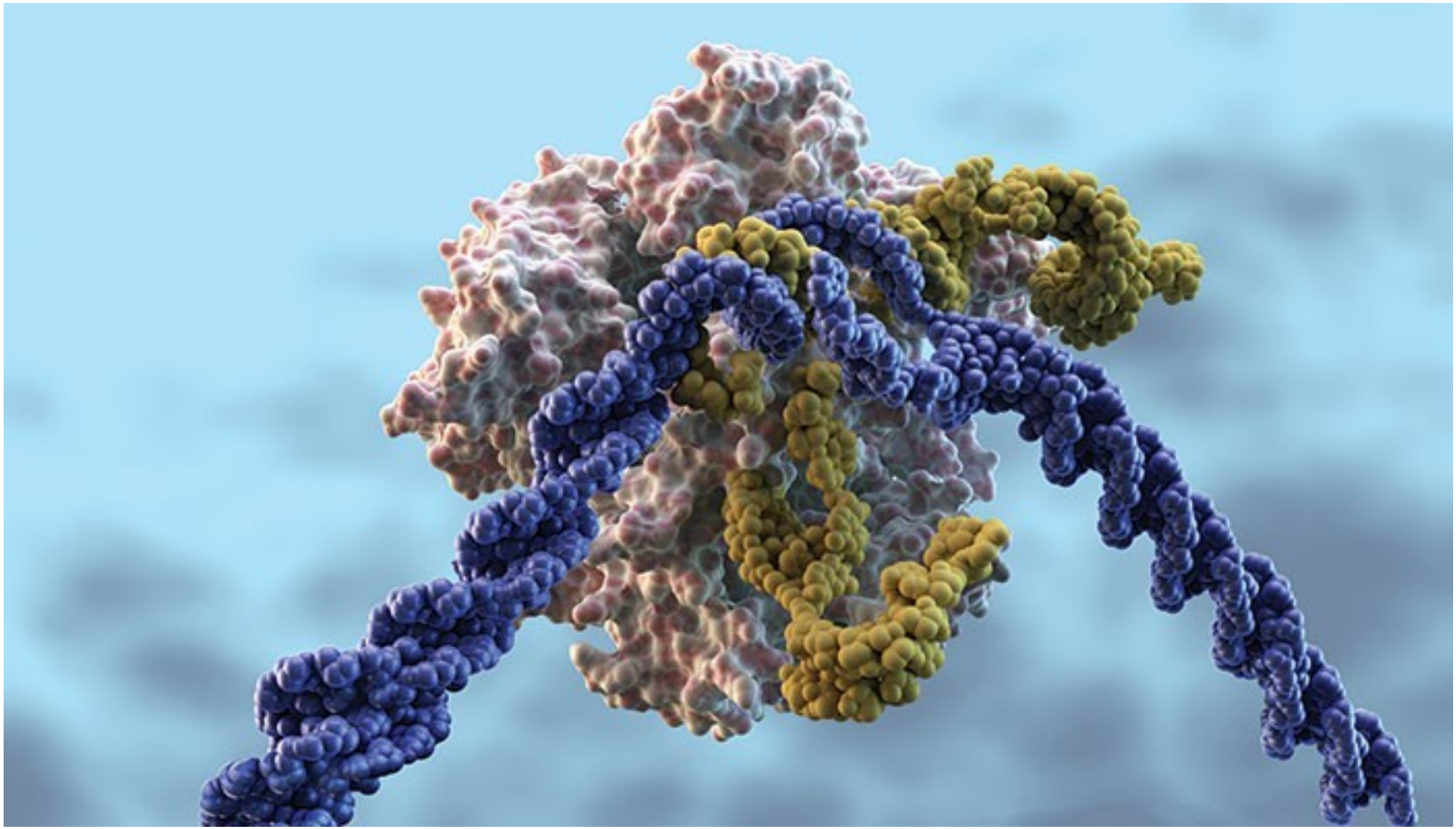
CRISPR-based gene drive



What is gene drive?

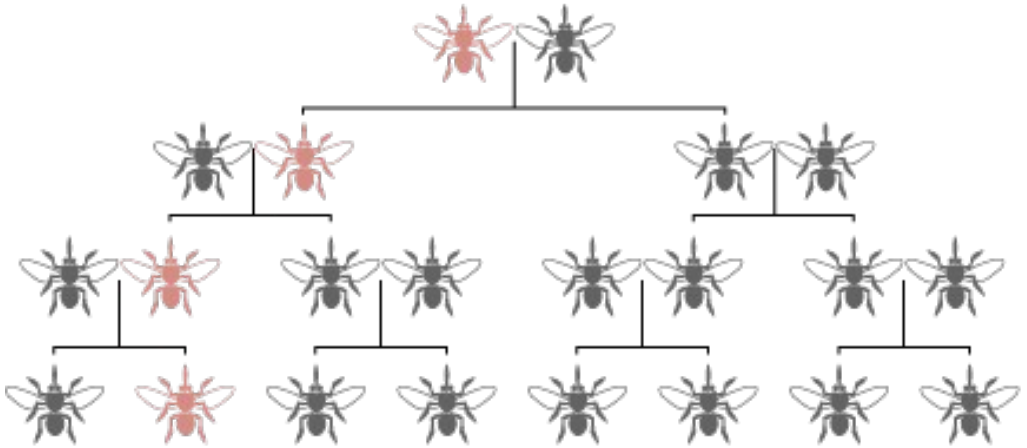
A novel biotechnology under development which aims to bias inheritance and control disease vectors, invasive species and other pests.

Public health, agriculture, conservation biology

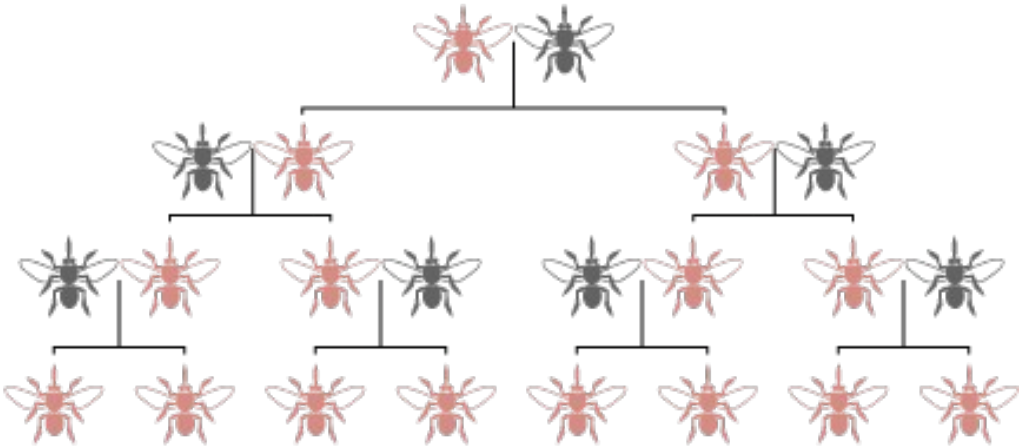
"*A natural phenomenon in several species*"

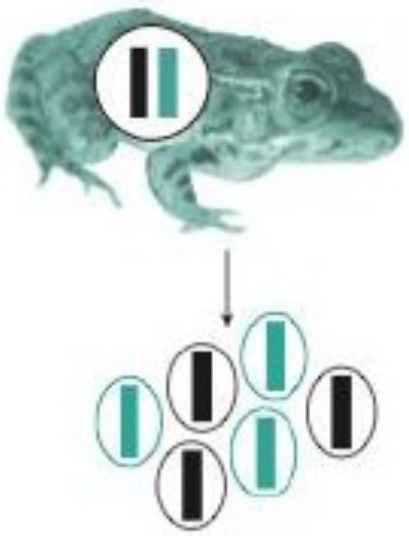
(Austin Burt, 2020)

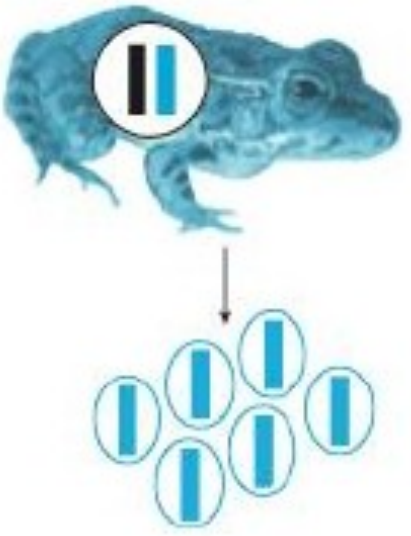
Normal reproduction



Reproduction with gene drive

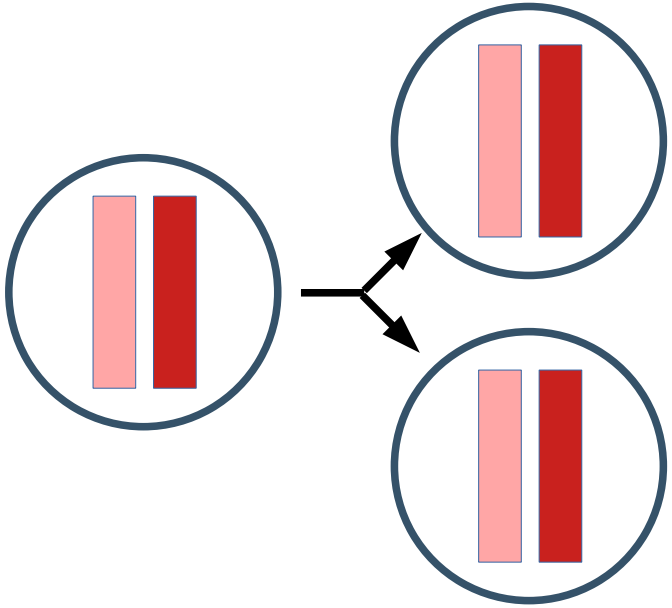




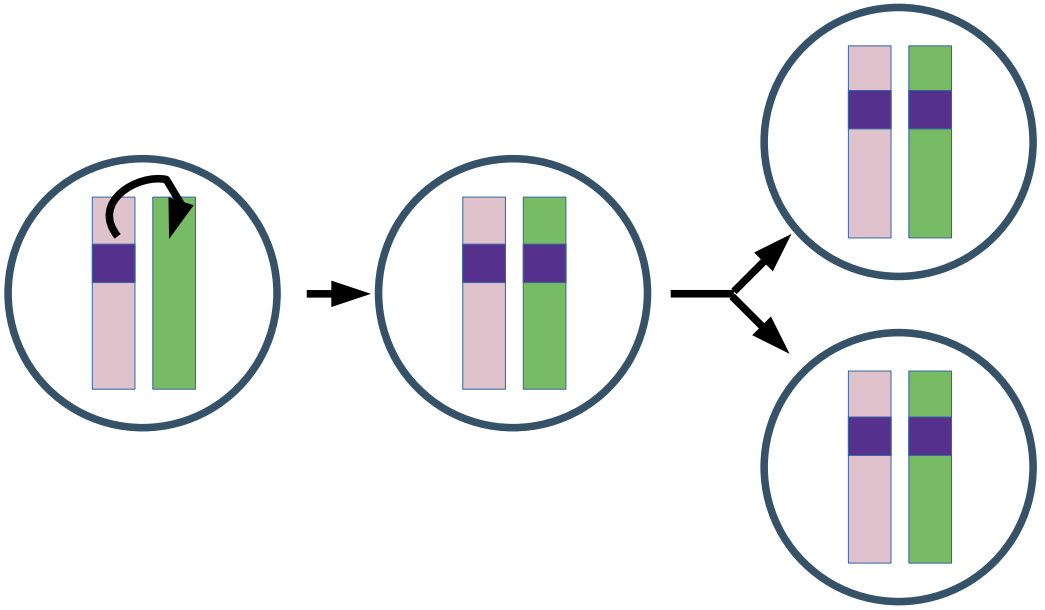


Rode et al. 2019

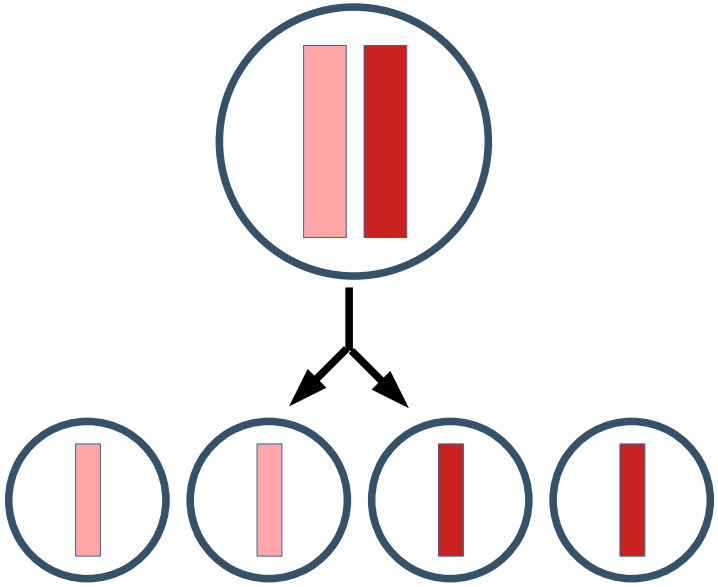
Cell division (mitosis)



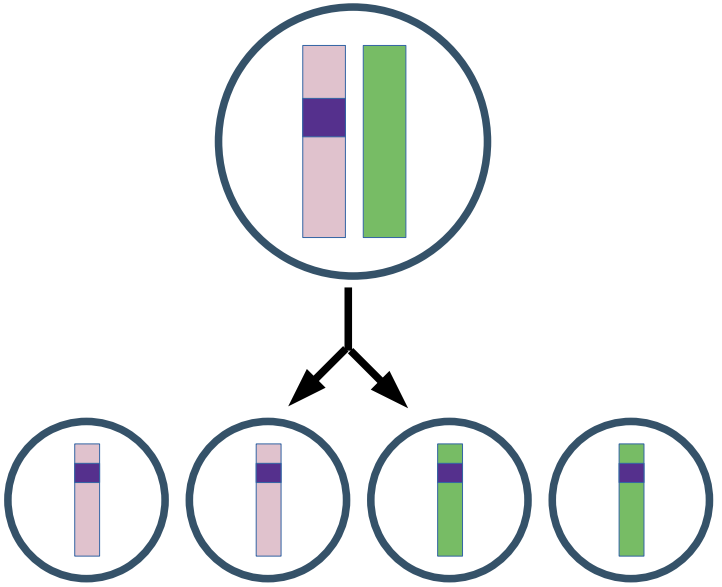
Gene drive



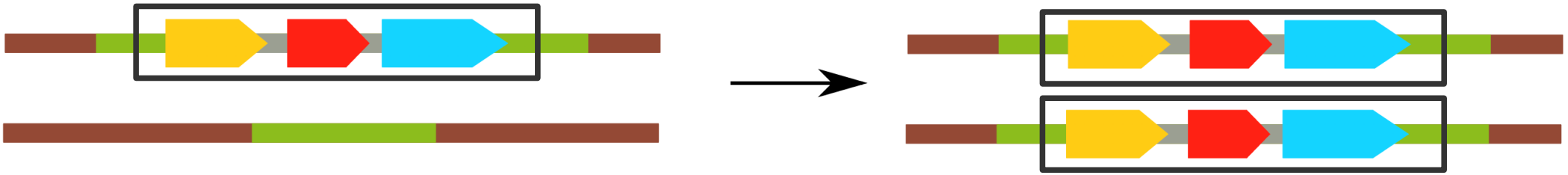
Normal reproduction

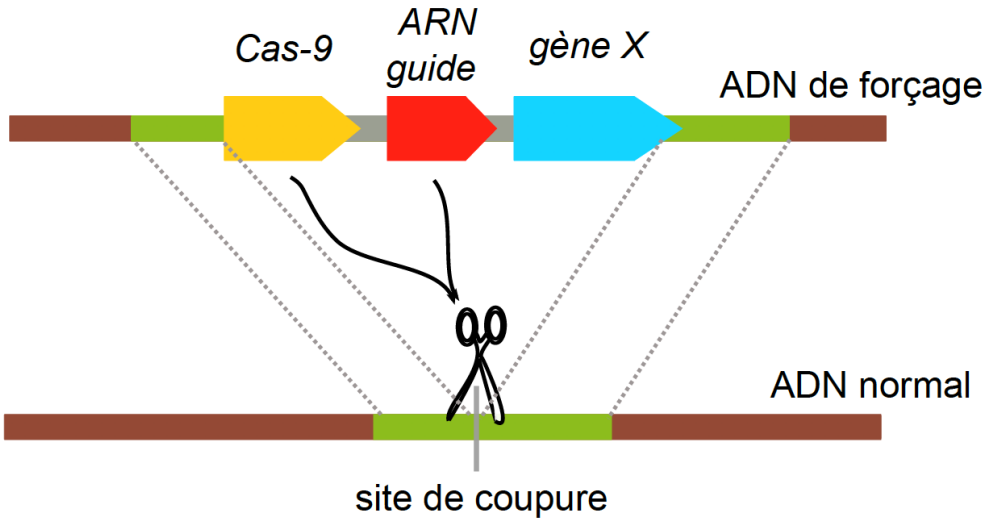


Gene drive



How a gene drive construct copies itself





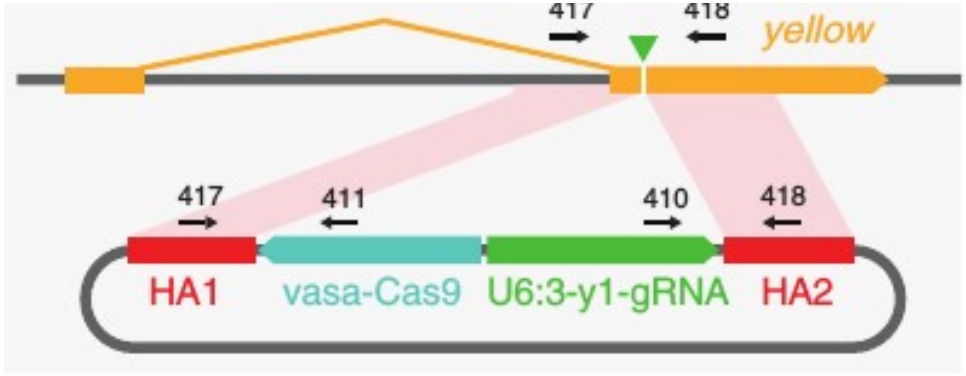
1rst gene drive organisms

GENOME EDITING

Science, April 2015

The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations

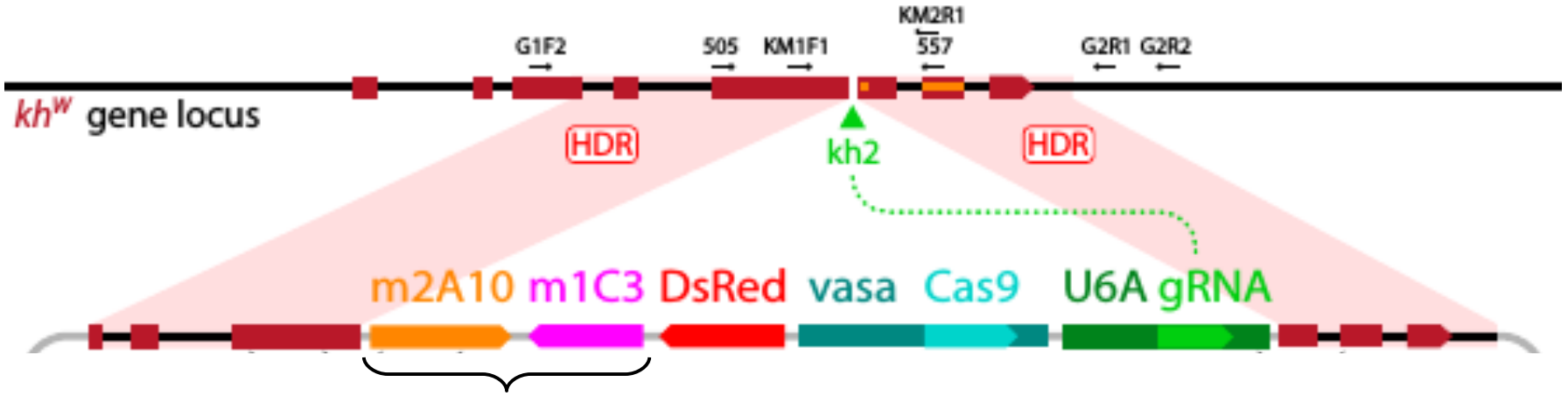
Valentino M. Gantz* and Ethan Bier*



E

	y^- ♂	y^- ♀	mosaic ♀	y^+ ♂	y^+ ♀	total
y^{MCR} ♂ x y^+ ♀	0	40	0	50	1	91
y^{MCR} ♀ x y^+ ♂	214	203	11	2	6	436

Mosquitoes without parasites



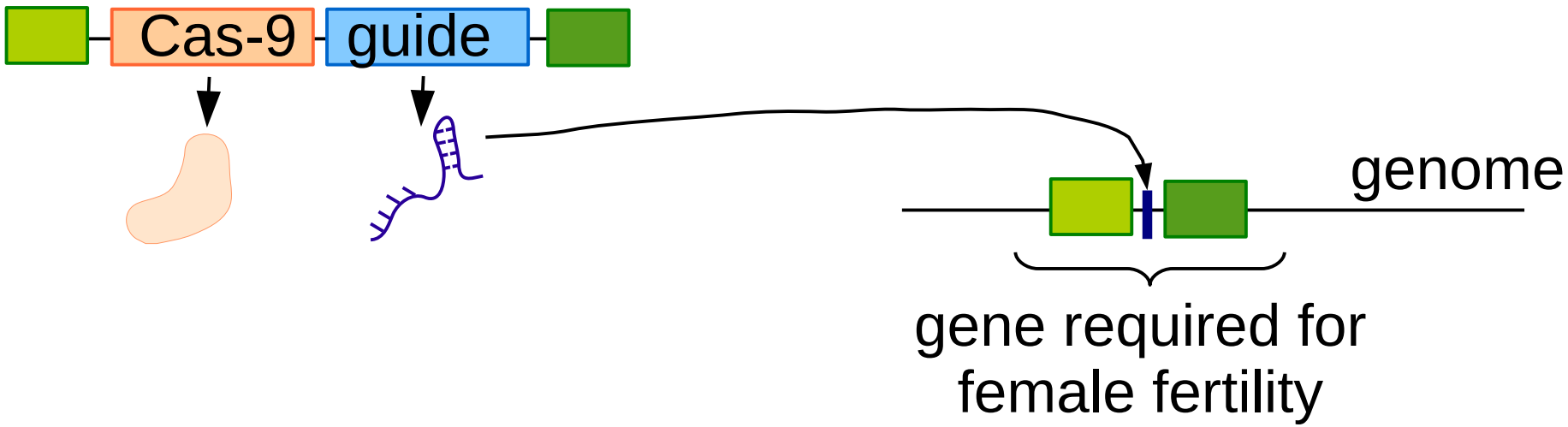
antibodies
anti-parasites

PNAS, November 2015

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]

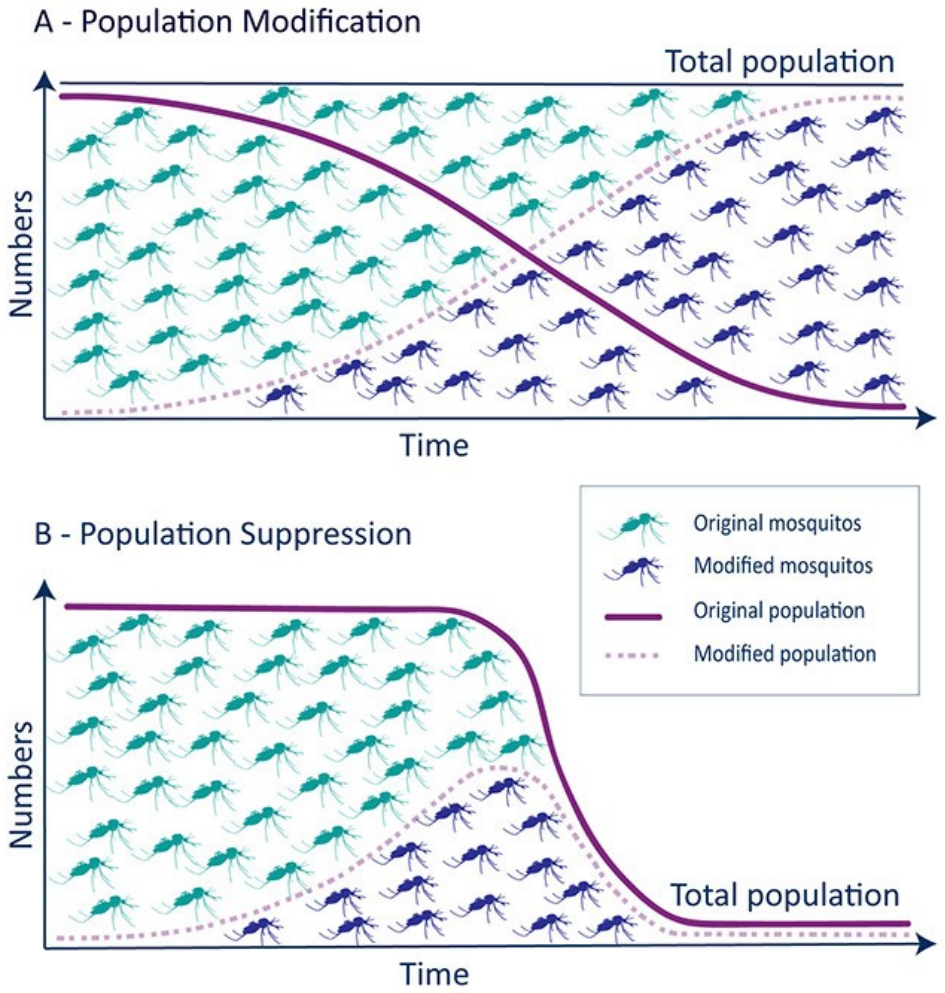
Sterile mosquitoes



Nature Biotechnology, décembre 2015

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]



"*Outcome conceptually similar to "vaccinating" pest populations*"
(Luke Alphey, 2020)

"*Agronomic science has been modifying **crops** to increase productivity or resistance to pests or pathogens.*

*Gene drive now allows manipulating **pests**.*"

Agricultural pest control with CRISPR-based gene drive: time for public debate

Should we use gene drive for pest control?

Virginie Courtier-Orgogozo[1], Baptiste Morizot[2] & Christophe Boëte[3]

EMBO J. 2017

Various applications of Gene Drive

(A) ERADICATION DRIVES

spreading strongly deleterious mutations in invasive populations

Eradicating invasive pest species

Eradicating invasive black rats that threaten the kereru (New Zealand pigeon) and other endemic species in New Zealand (NASEM 2016)
Image: David Mudge; Ngā Manu Nature Images

Eradicating invasive disease vectors

Eradicating invasive mosquitos, vector of avian malaria in Hawaiian honeycreeper birds (NASEM 2016)
Image: Sean McCann; Flickr

(B) SUPPRESSION DRIVES

spreading mildly deleterious mutations in invasive populations

Reducing the height of invasive common ragweed to decrease its competitive pressure on native plants (Neve 2018)
Image: Ashley Bradford; inaturalist.org

(C) RESCUE DRIVES

spreading beneficial mutations in endangered populations

Protecting lowland leopard frogs from highly pathogenic fungus (Esvelt et al 2014)
Image: Brian Gratwicke; Flickr

Rode et al. 2019

Two advanced gene drives

Drosophila suzukii
Invasive pest species

Scott et al. 2018

***Anopheles* mosquitoes**
Vector of malaria

TARGET MALARIA

https://targetmalaria.org

Risks and ethical issues associated with gene drives

What is novel about gene drive?

Several DNA pieces assembled together
Eukaryote cis-regulatory regions with bacteria coding regions

Manipulates the 2 pillars of evolution
- mutation
- transmission
-> can bypass selection and spread deleterious alleles

Potentially more effective than other biotechnologies
- ease of use
- speed of change
- unprepared regulatory environment

Classical Darwinian Evolution

1

Variation

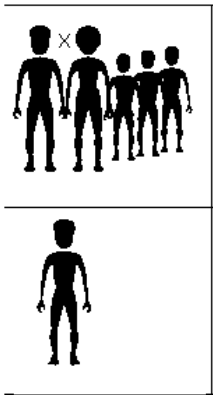
Mutations in DNA

2

Transmission to the next generation

3

Reproduction
Variability between individuals



Selection

Genetic Drift

http://evolution.berkeley.edu

What are the risks?

Molecular off-targets

Propagation to non-target populations

Propagation to non-target species

Consequences for ecosystems

Failure of counter-measures

What are the risks?

Molecular off-targets

Propagation to non-target populations

Propagation to non-target species

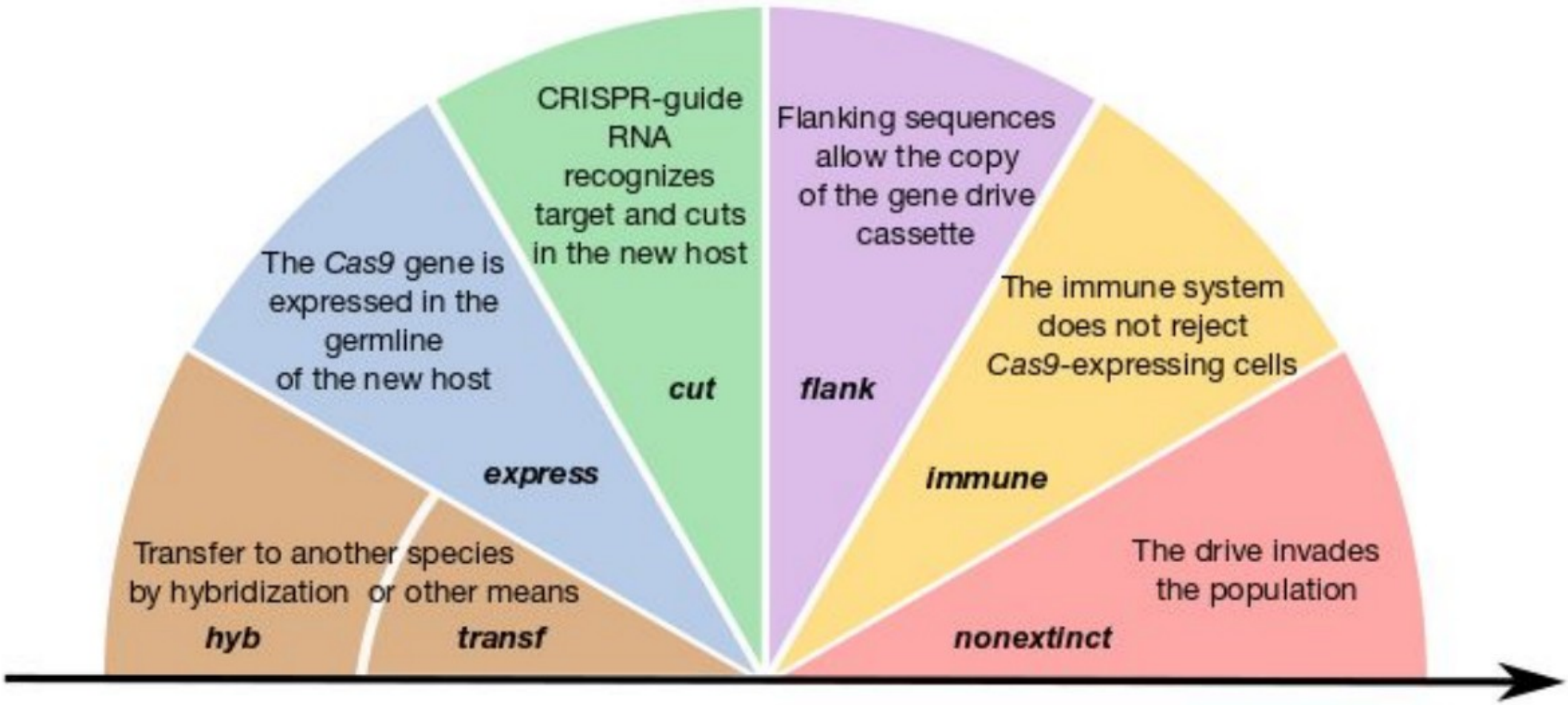
Consequences for ecosystems

Failure of counter-measures

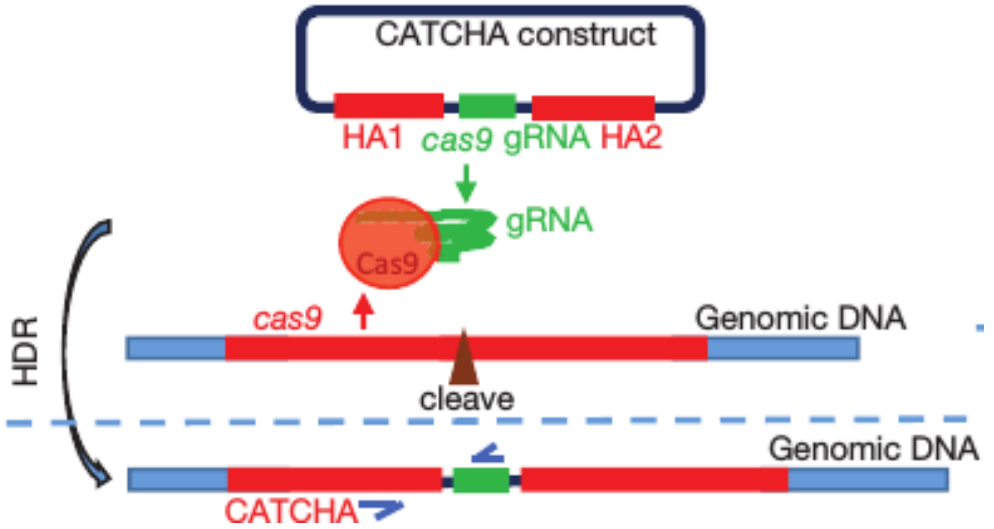
Evaluating the probability of CRISPR-based gene drive contaminating another species

2019

Virginie Courtier-Orgogozo[1] | Antoine Danchin[2] | Pierre-Henri Gouyon[3] | Christophe Boëte[4]



Need to stop a drive? Use another one!

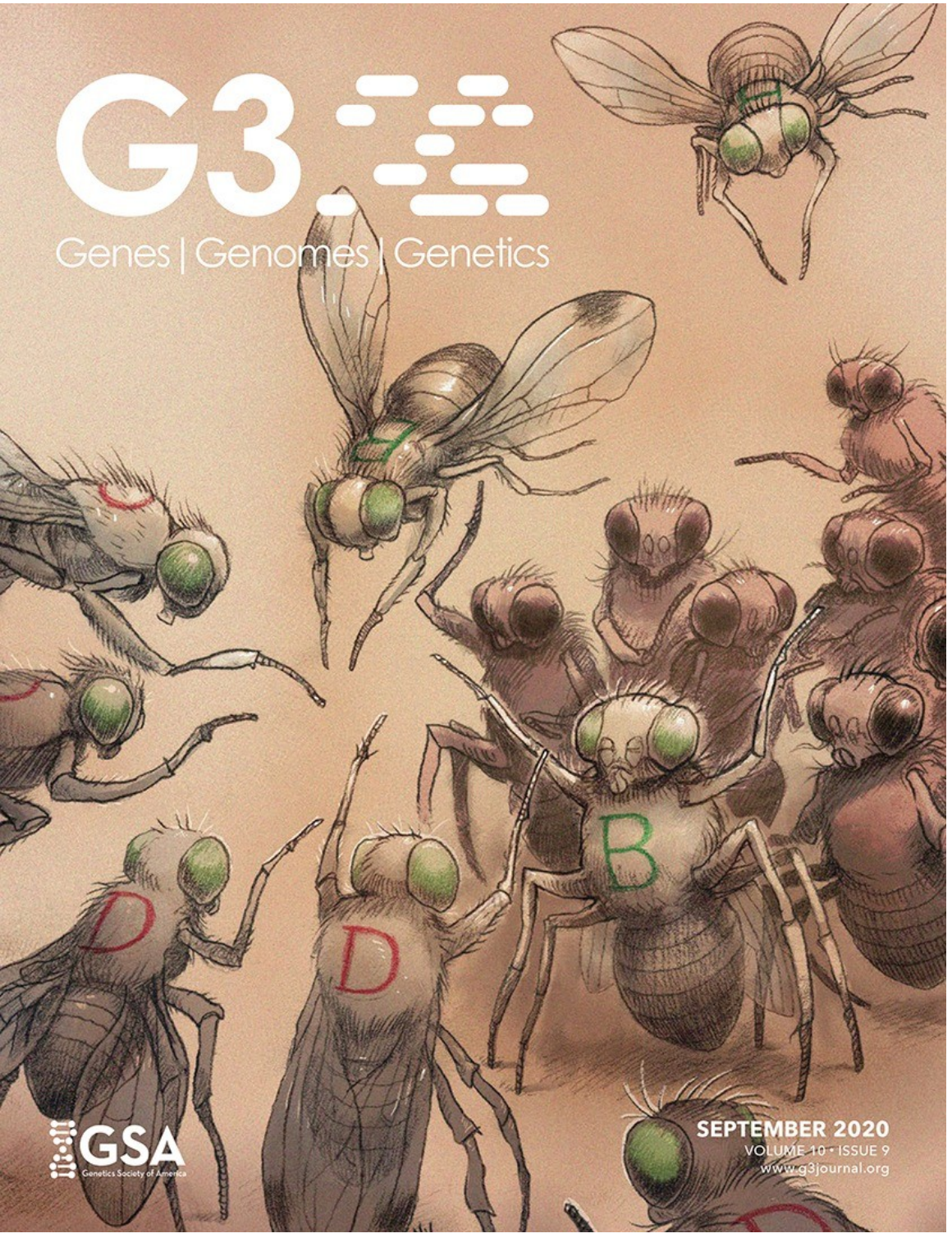


CORRESPONDENCE

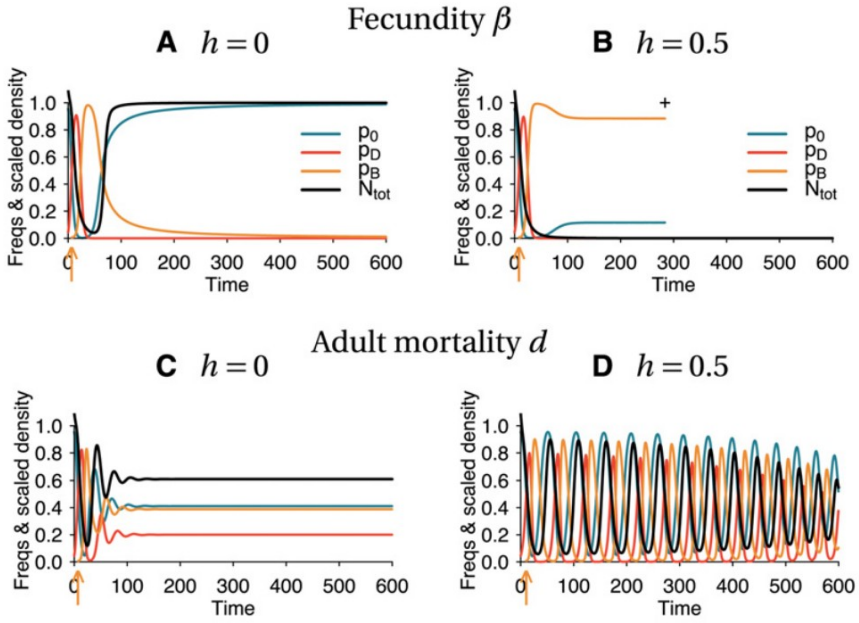
Nature Biotechnologies, Feb 2016

Bing Wu[1,2], Liqun Luo[1] & Xiaojing J Gao[1–3]

Cas9-triggered chain ablation of *cas9* as a gene drive brake



A brake is not guaranteed to stop an eradication drive



Rode et al., G3 2020

Gene drives: good or bad?

May eradicate diseases and pest species

Less expensive than other methods

Potentially faster than other methods

Potentially more powerful than other methods

Potentially less efficient than expected (resistance via mutations in the target site, cryptic species)

An uncontrolled system released in the wild

Impact on other species and ecosystems not quantified

Gene drives

Biases:

Living
in malaria area

Developing
gene drives

etc.

Regulation

Falls under the GMO regulation

Cartagena Protocol: international agreement, established as a supplement to the Convention on Biological Diversity (CBD), which aims to protect biological diversity from the potential risks imposed by LMOs (*Living Modified Organisms=any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology*)

Researchers added extra safety rules in their laboratories

What to do if it goes wrong?

International regulation?