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Gene drives are not all the same

Alekos Simoni

Polo of Genomics, Genetics, Biology

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Polo GGB and Target Malaria

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- Company providing services and research
- Three facilities: the Diagnostic and Genomics; the Genetics & Ecology laboratory and the Immunology.
- Partner of international reserach consortia and networks e.g. **Target Malaria** (BMFG), SafeGenes (DARPA), InfraVec2 (EU), Scenarios (EU), ISIDORe (EU)

Mosquito facility equipped with large cages for semi-field testing

Target Malaria

A not-for-profit research consortium, including:

- **Scientists**: protein engineers, molecular biologists, medical entomologists, population biologists, and social scientists
- Risk, regulatory and community engagement **advisors**
- Teams from **Africa, Europe**, and **North America**

Mission

We will develop and share new, cost-effective and sustainable genetic technologies to modify mosquitoes and reduce malaria transmission

What is a gene drive?

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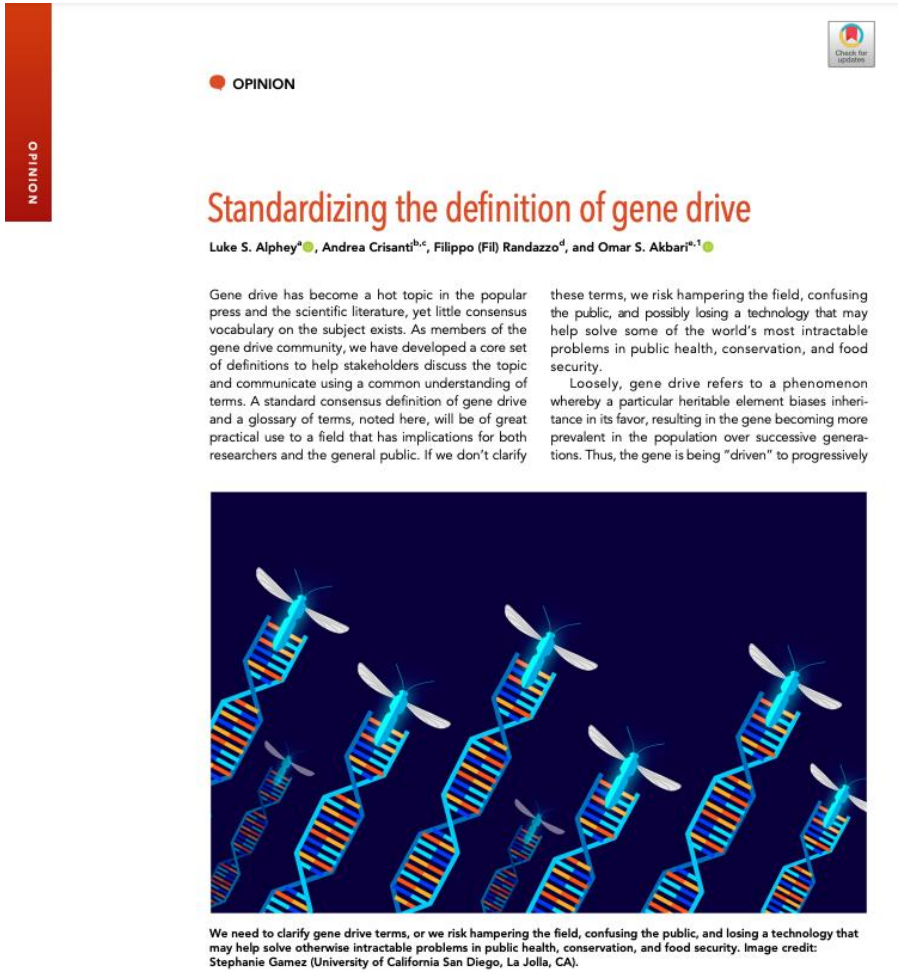

OPINION

OPINION

Standardizing the definition of gene drive

Luke S. Alphey[a], Andrea Crisanti[b,c], Filippo (Fil) Randazzo[d], and Omar S. Akbari[e,1]

Gene drive has become a hot topic in the popular press and the scientific literature, yet little consensus vocabulary on the subject exists. As members of the gene drive community, we have developed a core set of definitions to help stakeholders discuss the topic and communicate using a common understanding of terms. A standard consensus definition of gene drive and a glossary of terms, noted here, will be of great practical use to a field that has implications for both researchers and the general public. If we don't clarify these terms, we risk hampering the field, confusing the public, and possibly losing a technology that may help solve some of the world's most intractable problems in public health, conservation, and food security.

Loosely, gene drive refers to a phenomenon whereby a particular heritable element biases inheritance in its favor, resulting in the gene becoming more prevalent in the population over successive generations. Thus, the gene is being "driven" to progressively

We need to clarify gene drive terms, or we risk hampering the field, confusing the public, and losing a technology that may help solve otherwise intractable problems in public health, conservation, and food security. Image credit: Stephanie Gamez (University of California San Diego, La Jolla, CA).

PNAS, 2020

1. A **phenomenon of biased inheritance** of a genetic element (a gene) over the rest of the genome, leading the the increase of frequency over time, even in the presence of a fitness costs.

2. The **genetic element** (the construct) that cause the process of biased inheritance

3. The **tool** to achieve a goal, for instance changing the population of a target organism

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Mendelian vs Gene Drive inheritance

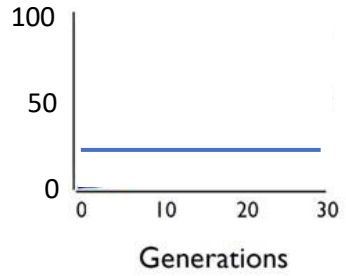
Without GENE DRIVE

Generation 1

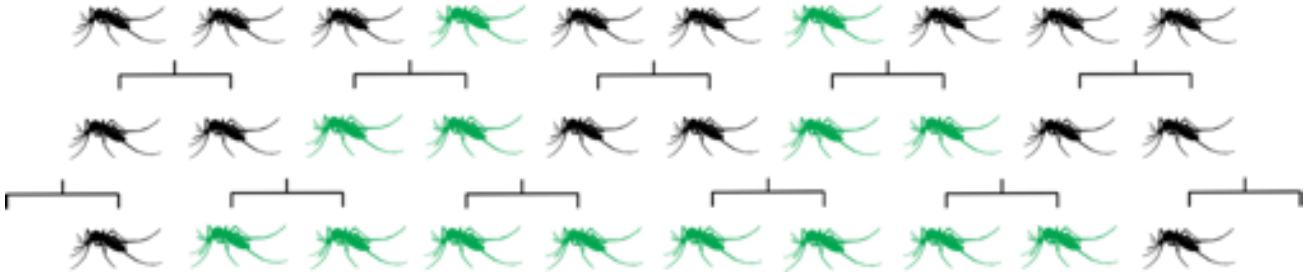
Generation 2

Generation 3

Frequency of gene remains constant



With GENE DRIVE

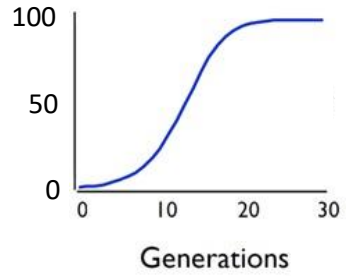


Generation 1

Generation 2

Generation 3

Frequency of gene increases



Gene drive spreads through the population even if it imposes a fitness cost

Quinn & Nolan, Current Opinion in Insect Science, 2020

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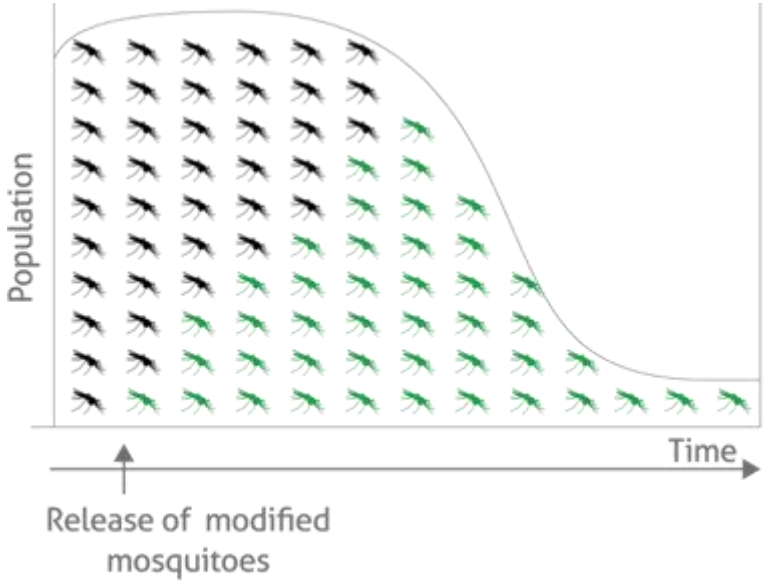
Main applications for gene drives: suppression or replacement

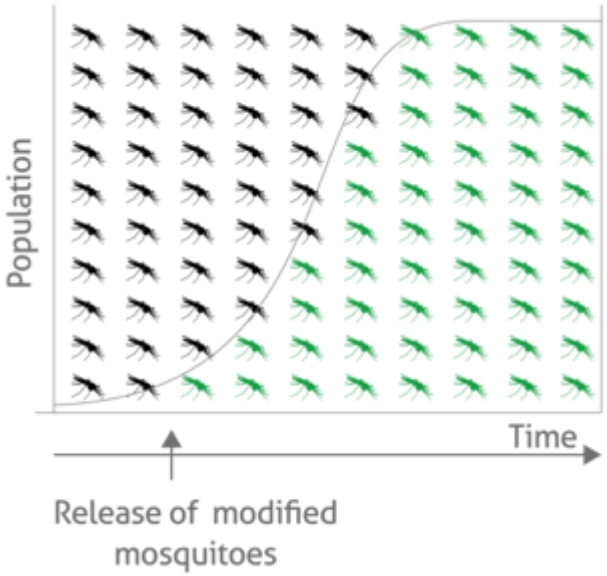
Population suppression

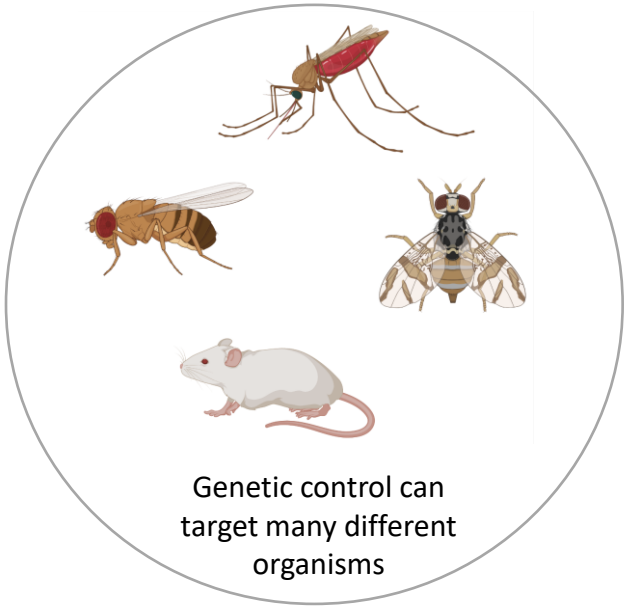
Releasing modified mosquitoes into the population can cause transient or permanent population suppression



Population replacement

Releasing modified mosquitoes into the population can lead to the spread of a gene that blocks malaria transmission



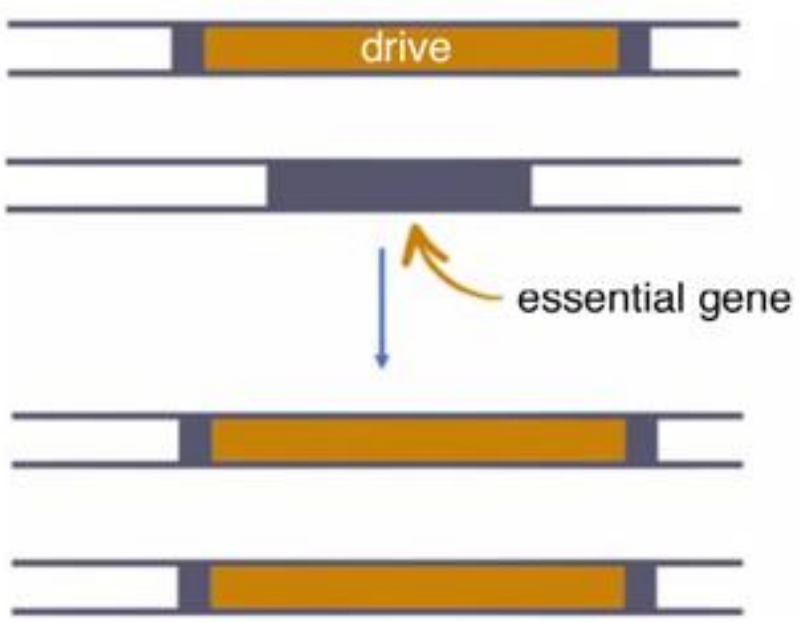


Genetic control can target many different organisms

Gene drive can be used for **both approaches**. It allows the genetic modification to spread through a population in an efficient way.

Gene drive to impose a load or to drive a cargo

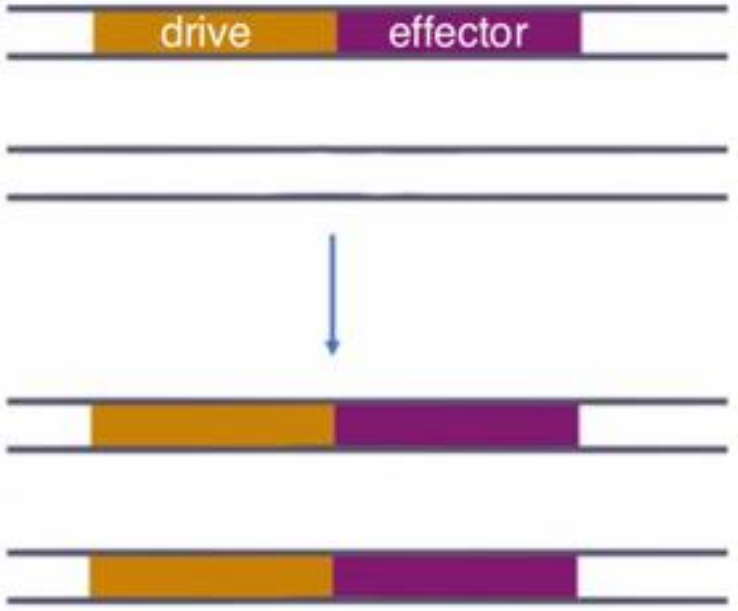
Disrupt an essential gene



e.g.

- female fertility gene
- recessive lethal gene
- mosquito receptor for parasite

Carry an effector gene as 'cargo'



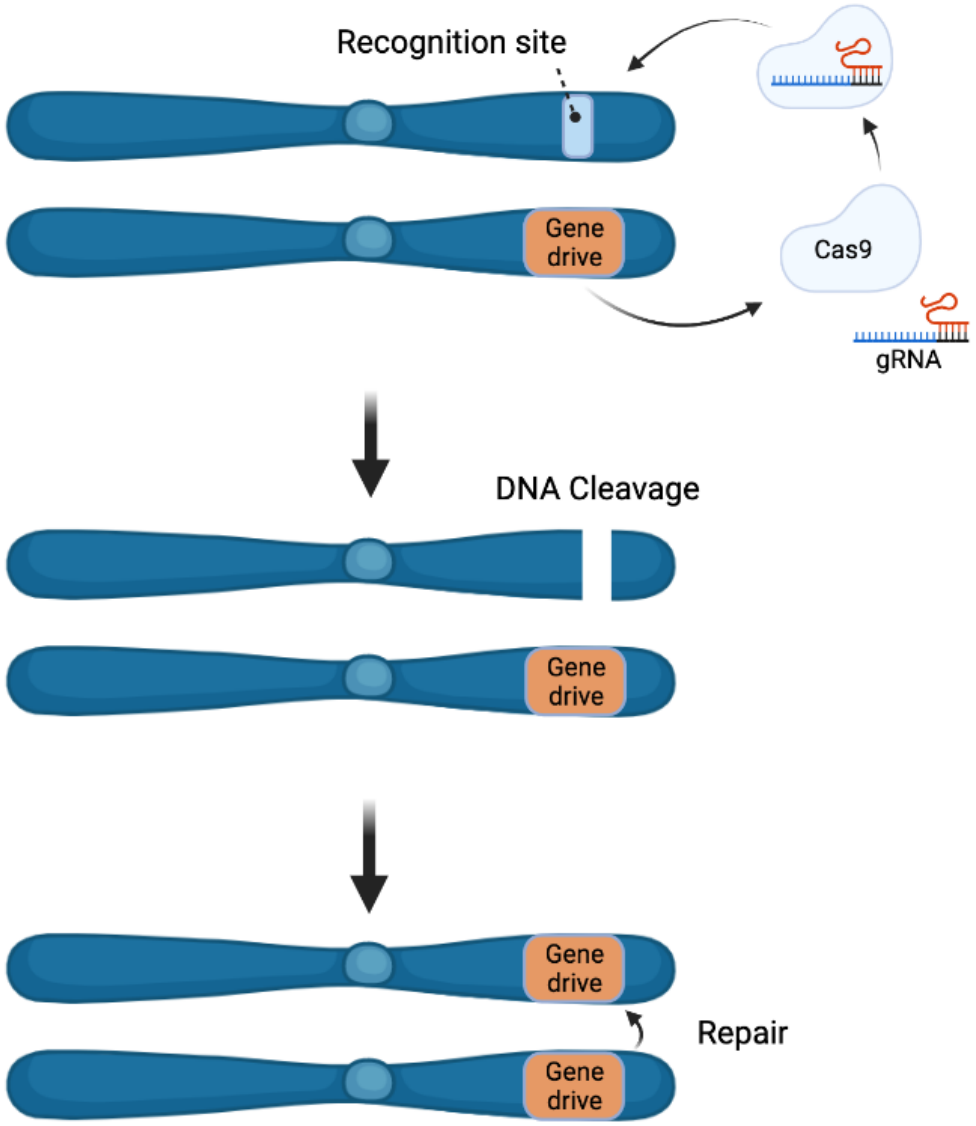
e.g.

- Anti-parasite immune gene
- single chain antibody against parasite

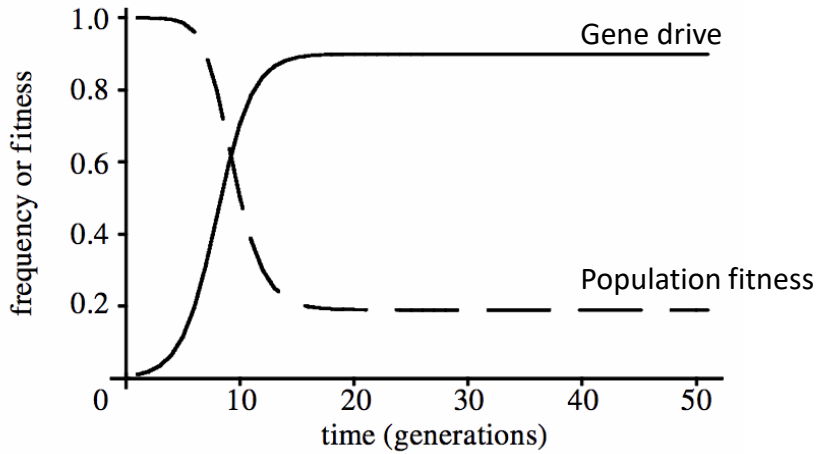
Current Opinion in Insect Science

Different types of gene drives

Homing-based gene drives



'**homing**': the process of homologous recombination repair followed by DNA cleavage*



Burt, *Proc R Soc Lond B,* 2003

- Any specific nuclease can be used for cleavage
- Can be used to target essential genes (**population suppression**) or to drive a cargo (**population replacement**)
- Developed for mosquito control with promising results in the lab
- Low-threshold drive
- Unlimited spread (dependent on fitness costs). 'Local' or 'private' drive proposed (genetically isolated)

* Homing restricted to germline formation

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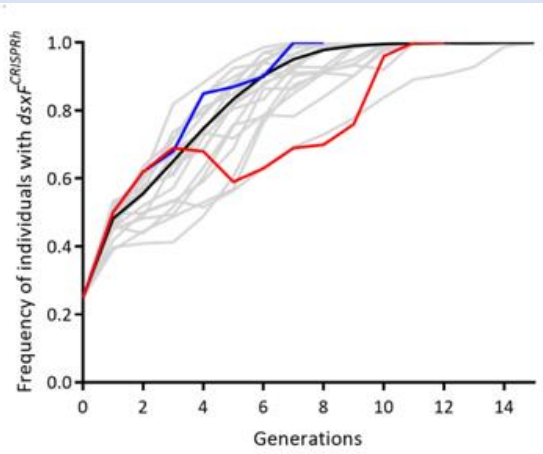
Gene drive targeting a female fertility leads to mosquito populations suppression

A CRISPR–Cas9 gene drive targeting *doublesex* causes complete population suppression in caged *Anopheles gambiae* mosquitoes

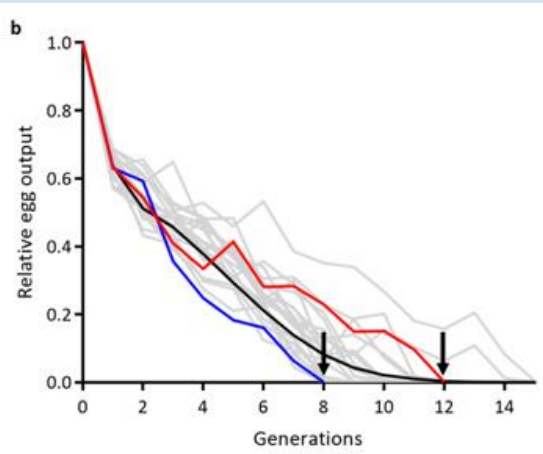
Kyros Kyrou[1,2], Andrew M Hammond[1,2], Roberto Galizi[1], Nace Kranjc[1], Austin Burt[1], Andrea K Beaghton[1], Tony Nolan[1] & Andrea Crisanti[1]

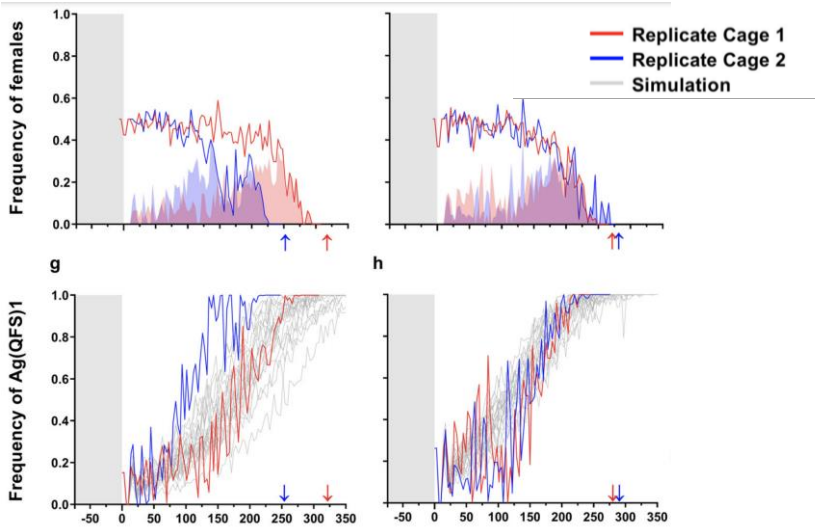
Small cage experiment

Frequency of Drive



Egg Output





nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-24790-6 OPEN

Gene-drive suppression of mosquito populations in large cages as a bridge between lab and field

Andrew Hammond[1,2,9], Paola Pollegioni[3,4,9], Tania Persampieri[3,9], Ace North[5], Roxana Minuz[3], Alessandro Trusso[3], Alessandro Bucci[3], Kyros Kyrou[1], Ioanna Morianou[1], Alekos Simoni[1,3], Tony Nolan[1,6,10✉], Ruth Müller[3,7,8,10✉] & Andrea Crisanti[1,10✉]

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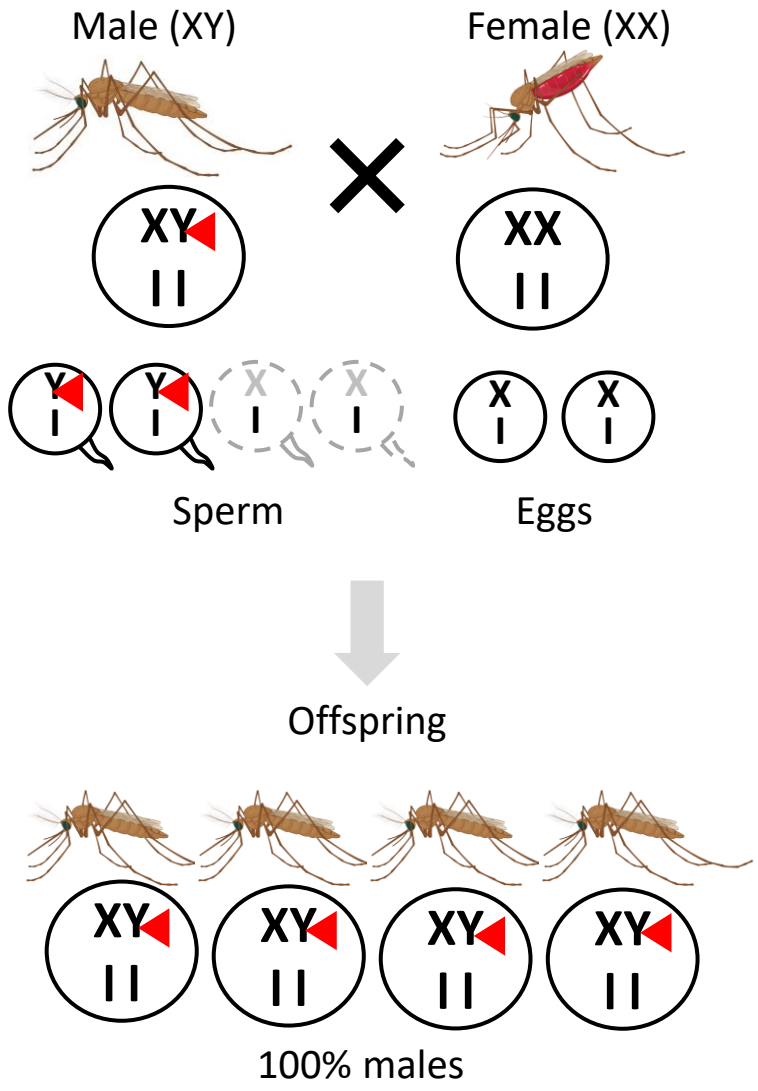
Sex distorter drives (or Y-drive)

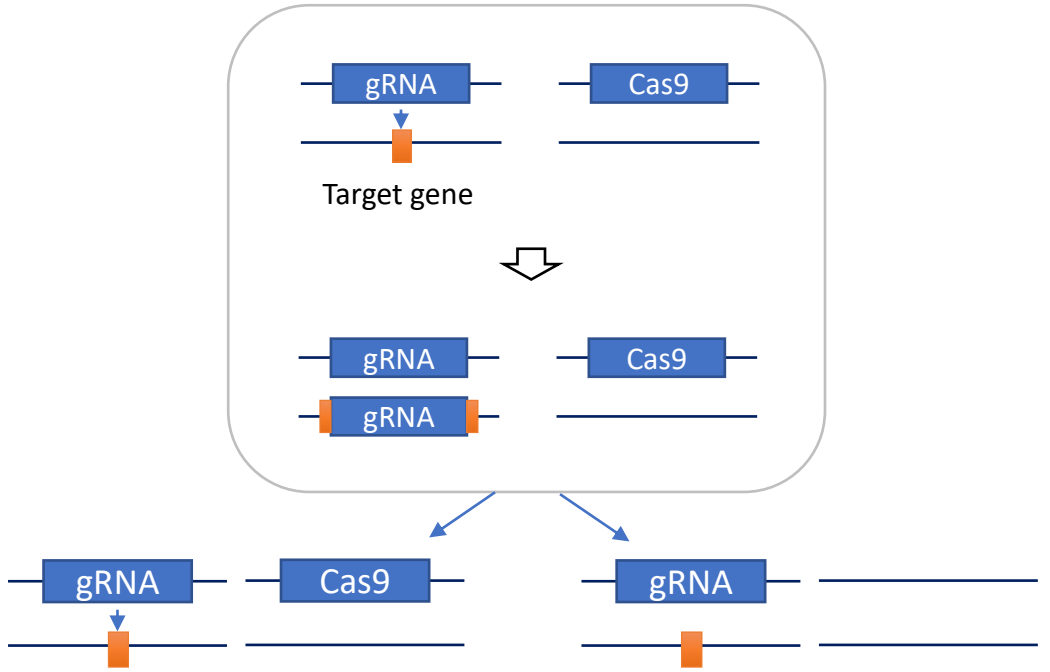
- Efficient way to control a population is to bias the sex towards males
- Targeting the X-chromosome during male gametogenesis generate male bias
- If effector is on male sex chromosome it drives to fixation (without ‘homing’)

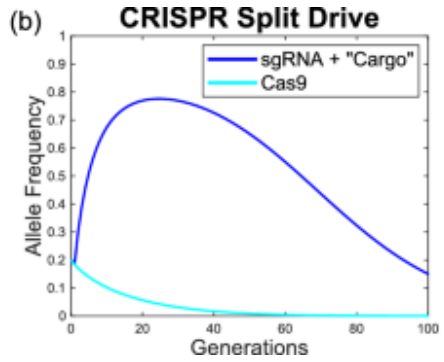
- Low threshold drive
- Unlimited spread (dependent on fitness and male bias rate
- Biological limitation to express nucleases from the Y chromosome



Split drives

- Drive elements are split into two locus
- When together, one component spreads, while the second is mendelian inherited
- The spread is limited in time (it decline overtime)
- Spread is spatially limited and threshold dependent





Edgington et al, Sci Reports 2020

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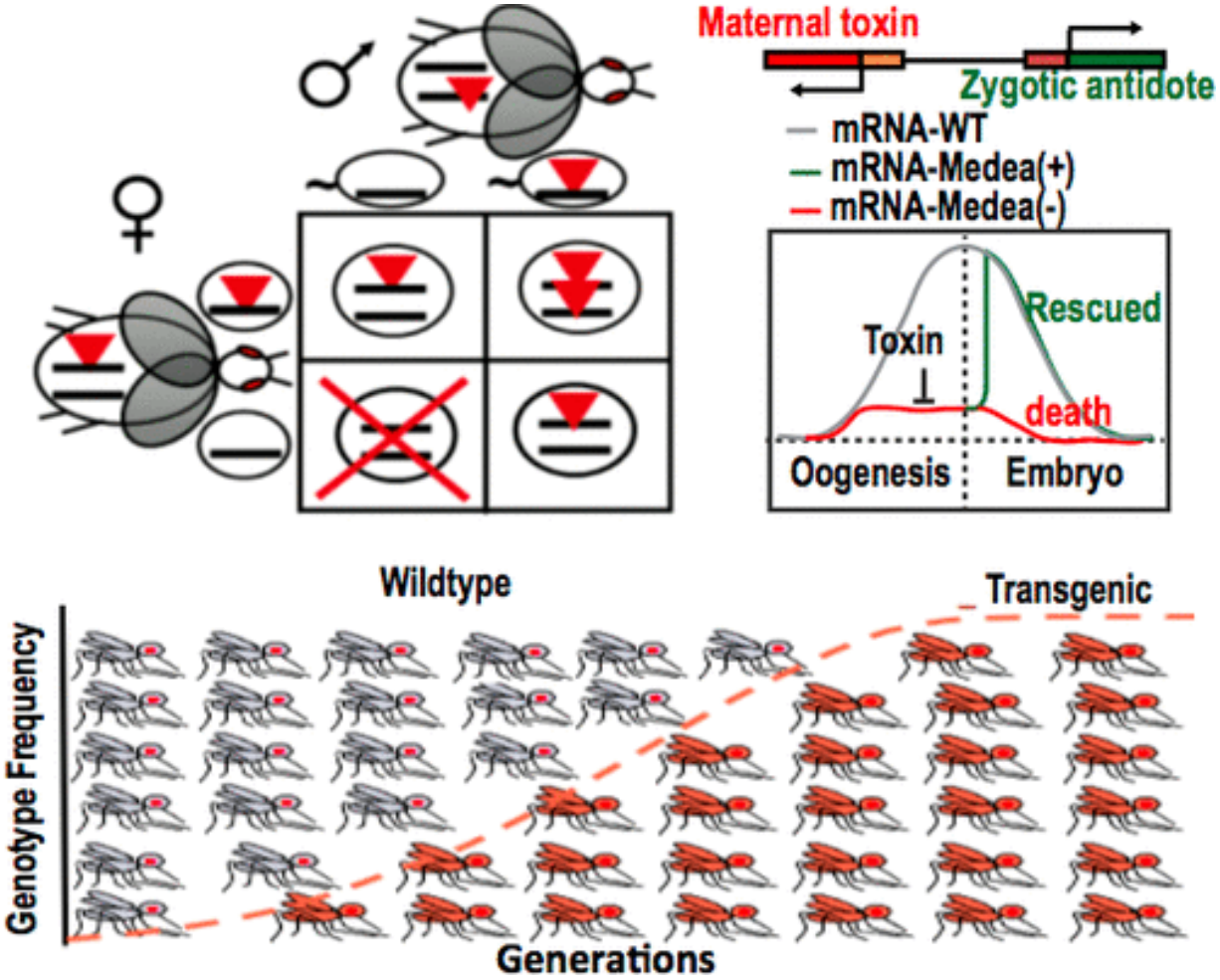
Maternal toxin (MEDEA)

- They spread by causing death of individuals not carrying MEDEA
- More challenging to engineer (different components, less transferable to other species)
- (Usually) threshold-dependent
- Proposed for population replacement approaches (in flies, eg D. suzukii)



Akbari et al, *CS Synth. Biol.* 2014

Gene drive is not a single ‘thing’

Many ‘drives’ exists in nature and many are engineered, classified by:

Molecular components	HEGs, CRISPR/Cas, antidote-toxins, etc
Aim of intervention	population suppression, parasite refractoriness, etc
Intended effect	sterility, mating, feeding, behavioural traits, etc
Time of action	germline, postgametic, adult
Spatial scale	non-localized, localized, private alleles

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General considerations and challenges to gene drives

Considerations and challenges	
Efficacy	Fitness cost, efficacy of cargo, frequency of release (threshold), release logistics
Persistence	Dependent of type: until population is suppressed or potentially indefinite. Persistence not equal to spread
Localization	Dependent on type and scope of intervention.
Resistance	The main limitation of gene drives in wild population (strategies to mitigate resistance: conserved target site, multiplexing, control of expression, etc)
Regulatory	Novelty. Risk benefit analysis on case by case basis. Supra-national (or regional) regulations may be required (depending on scope of intervention)
Stakeholder	Public acceptance, responsible science, misinformation, novelty

Thank you for your attention!

a.simoni@pologgb.com