Gene Drives: Science and Application on Food and Agriculture

Maria Genaleen Q. Diaz
Institute of Biological Sciences
College of Arts and Sciences

Leading Breakthroughs: Gene Drives for a Sustainable Agriculture and Biodiversity Conservation

09 December 2024

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Outline

- Definition
- Gene drive and genome editing
- Mechanism of inheritance
- Some types and uses of gene drives
- Gene drives for pest control

Gene Drive

- gene drive, drive, meiotic drive, driving Y chromosome, selfish gene, selfish genetic elements
- Scientists have long known the occurrence of *selfish genetic elements*
- Gene drives naturally occur.

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Gene Drive Definition

- process/phenomenon:

  a gene drive is a process that promotes or favors the biased inheritance of certain genes from generation to generation

  (Alphey LS et al., 2020, PNAS)

  → prevalence of a genetic element or allele is increased

  → leads to preferential increase of a genotype from one generation to the next and potentially spread throughout the population

Gene Drive Definition

- material object:

  a gene drive is any genetic element able to bias its inheritance within a population

  (Alphey LS et al., 2020, PNAS)

  → composed of one or more genetic elements that can cause the process of biased inheritance in its favor

  → presence of gene drive elements will not necessarily cause gene drive; some confer preferential inheritance only when present in the population above a threshold frequency

Gene Drive Definition

- intention:

  gene drive is a tool to effect certain changes in a population

  (Alphey LS et al., 2020, PNAS)

  → intended to introduce new trait(s) into an interbreeding population so as to effect a change in the characteristics of the population

  → may cause effects directly, for example by inserting into and disrupting a target gene

Synthetic Gene Drive

- A gene drive system that is created through recombinant DNA techniques

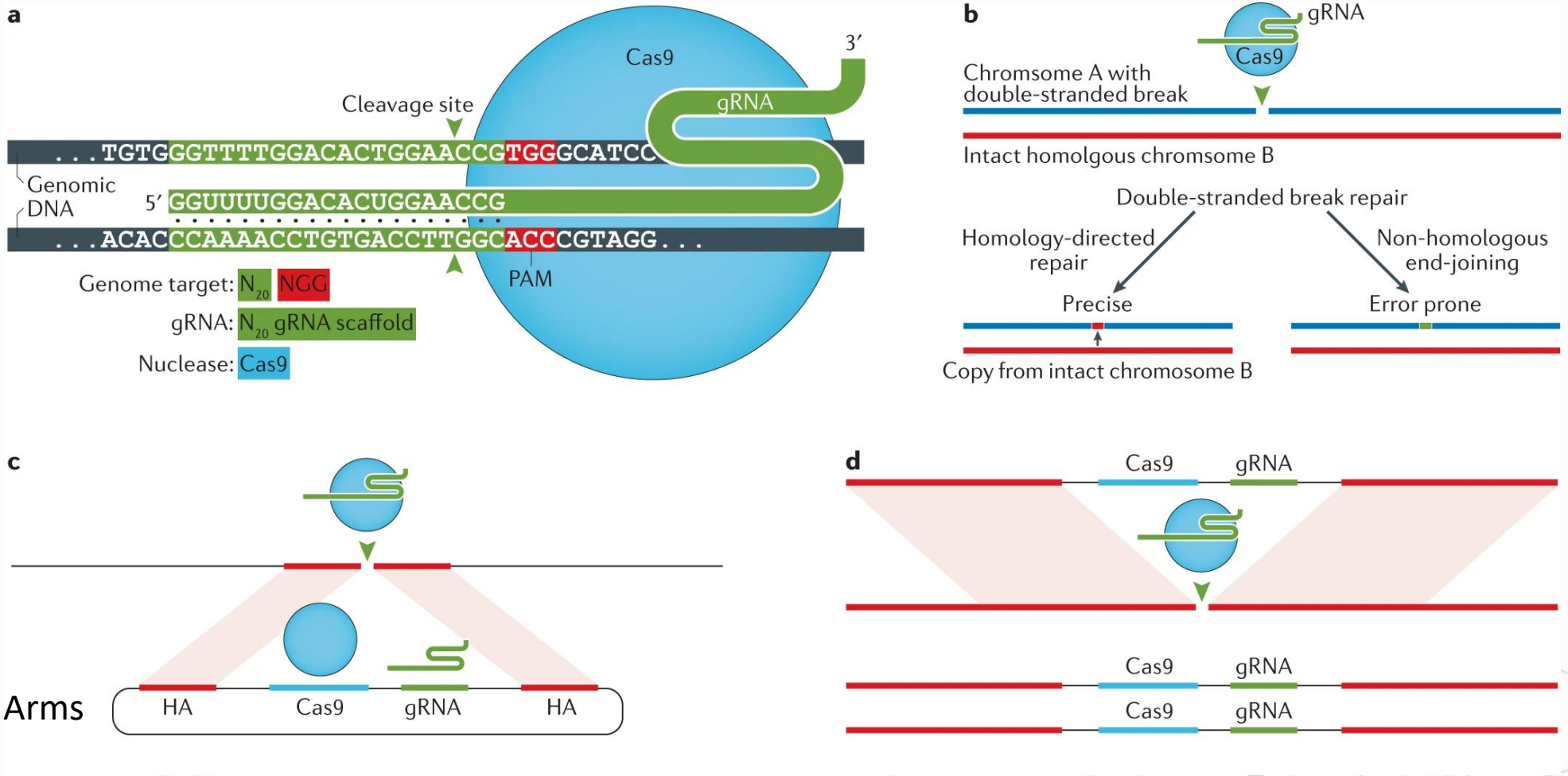
- Basic criteria which foster efficient gene drive

  → organisms must have an inheritance pattern that can be biased (typically, sexually reproducing)

  → for practicality, the organism must have a short generation time

Gene Drive and Gene Editing

- CRISPR/Cas system is a perfect tool to create a gene drive



HA – Homology Arms

Bier, E. Gene drives gaining speed. Nat Rev Genet 23, 5–22 (2022). https://doi.org/10.1038/s41576-021-00386-0

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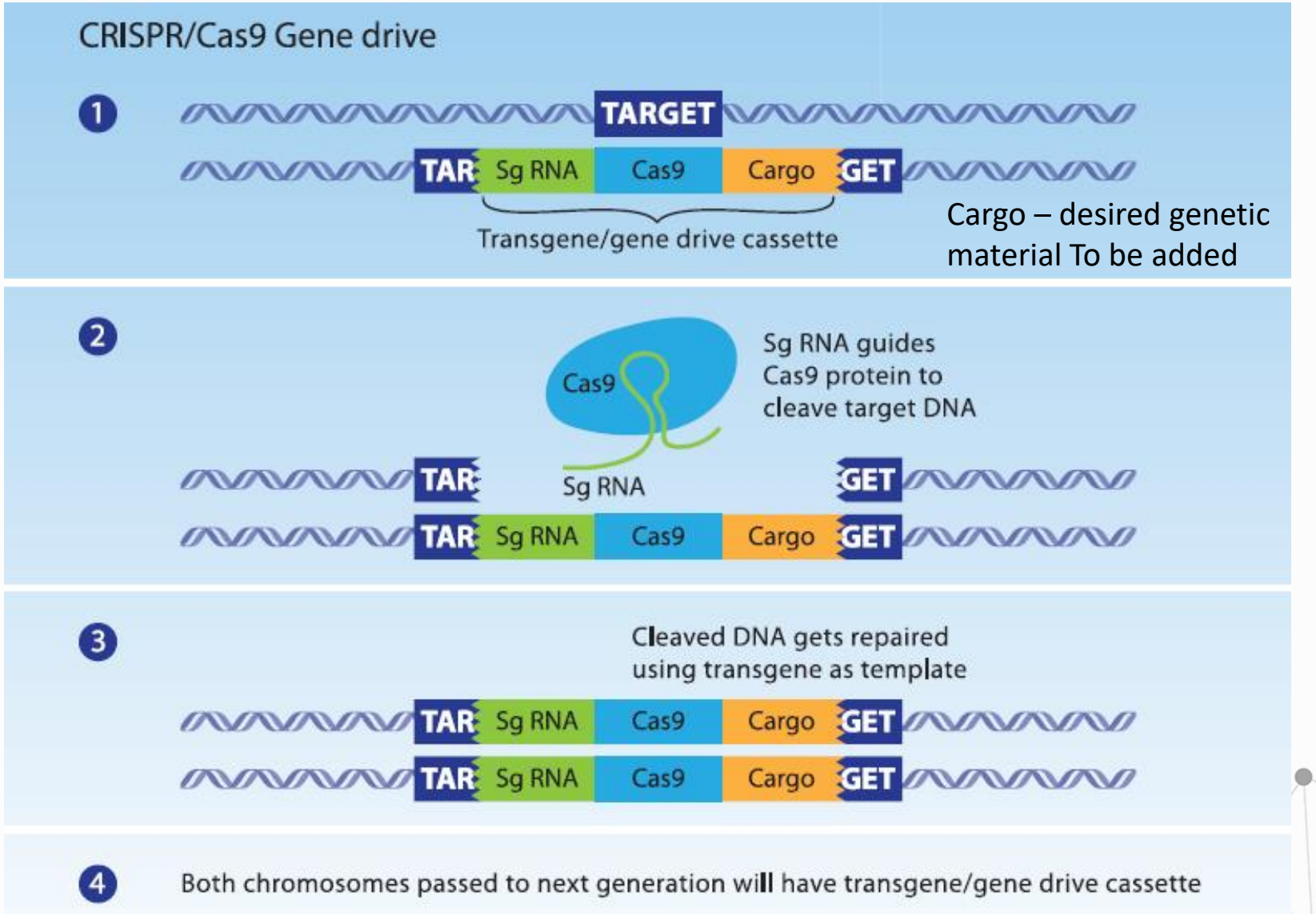
- Creation of gene drives are now mostly based on gene editing



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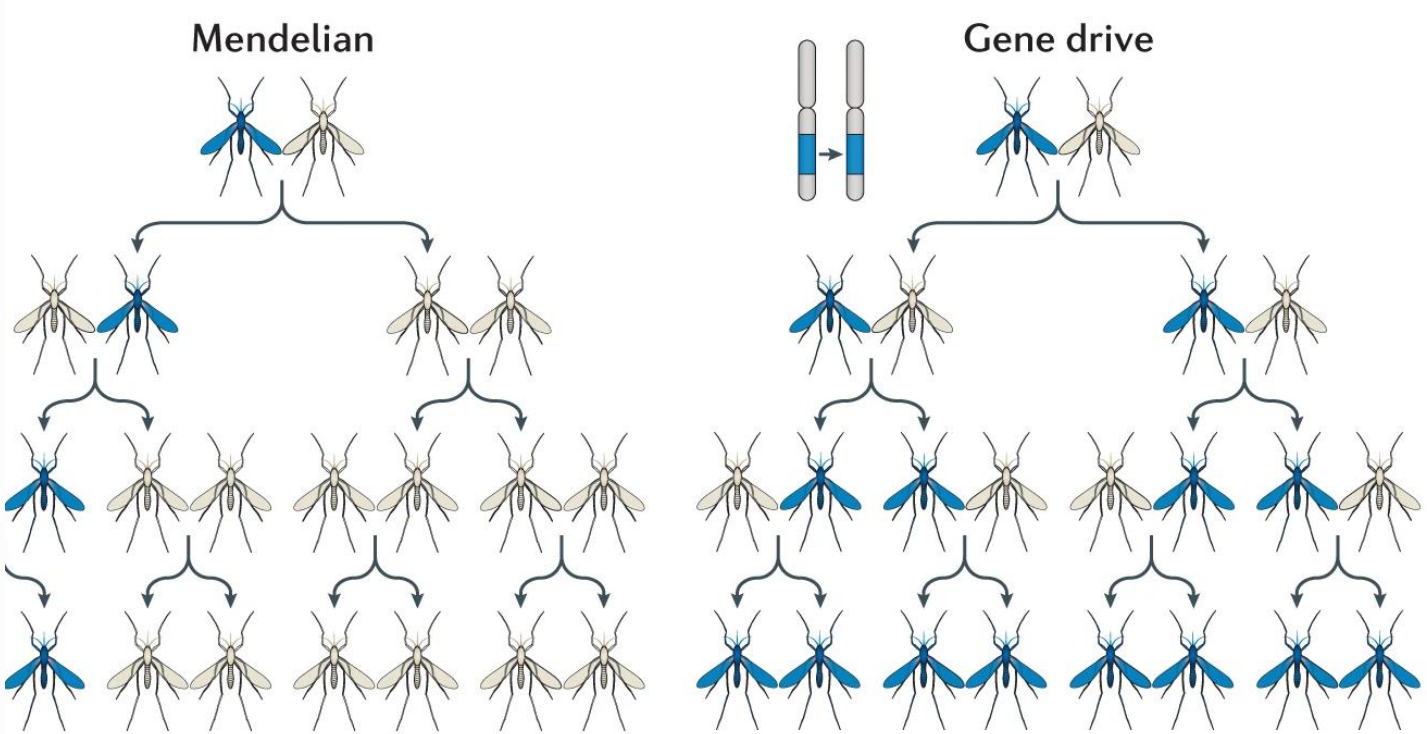
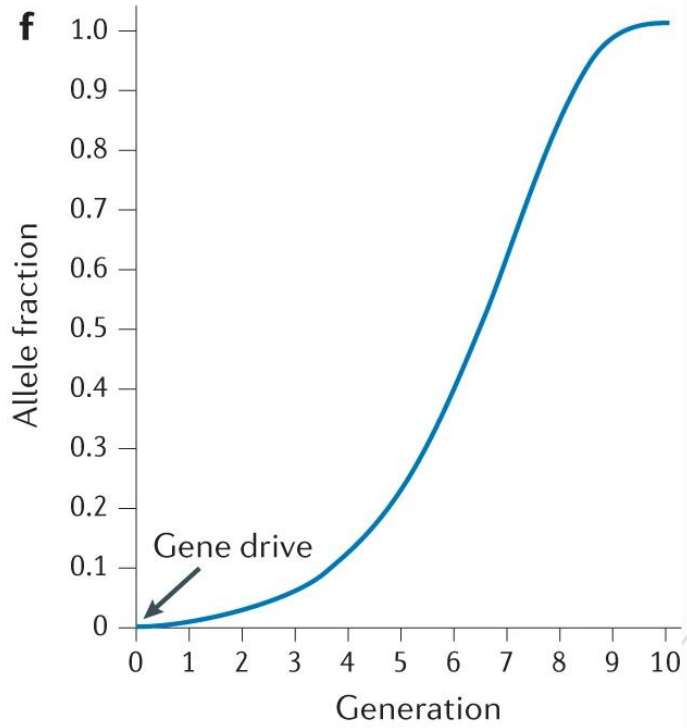
Mechanism of Inheritance

Transmission to progeny at super-Mendelian (>50%) frequency





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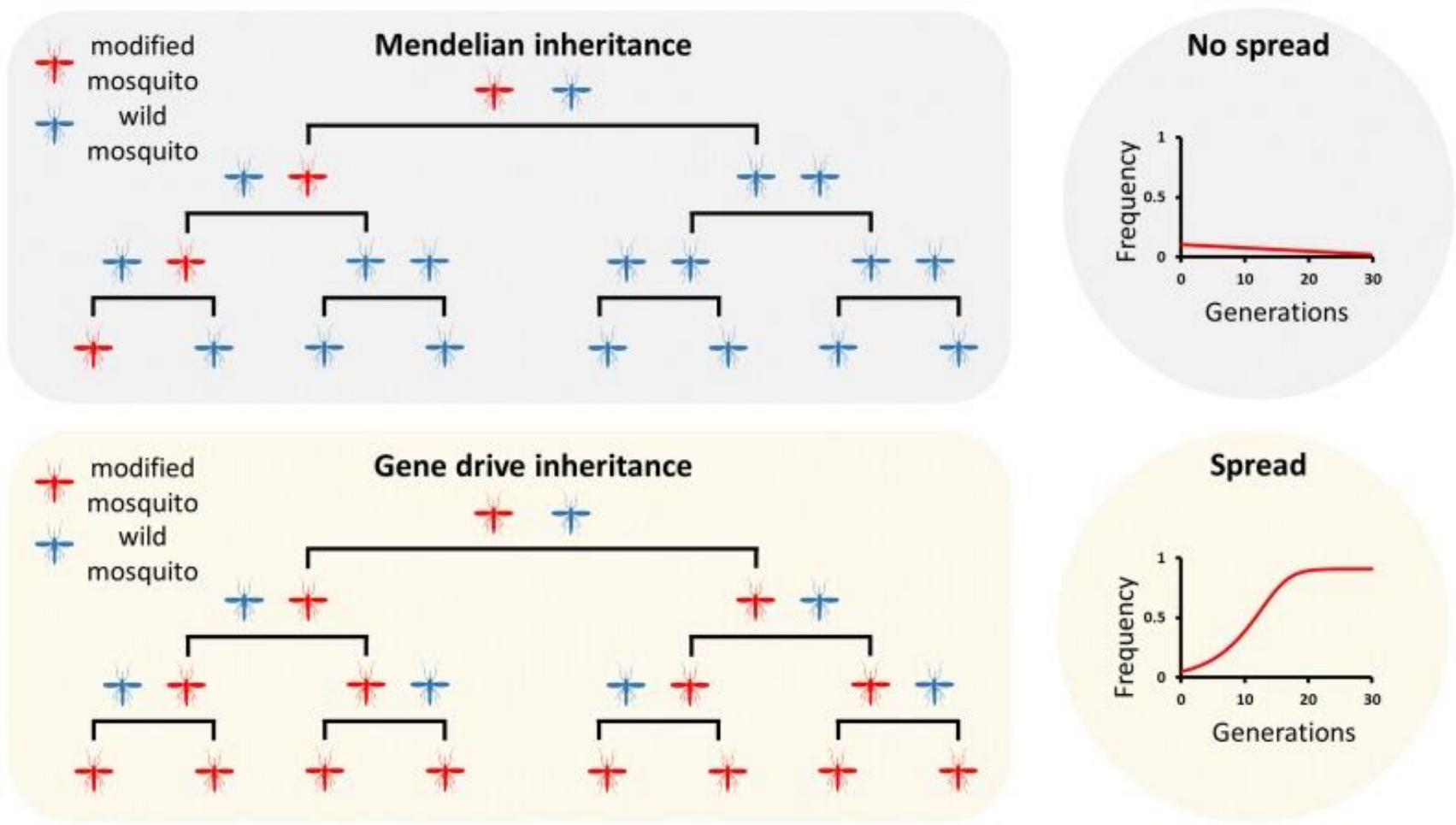
Mechanism of Inheritance



Andrew Hammond and Roberto Galizi, 2017; doi: 10.1080/20477724.2018.1438880

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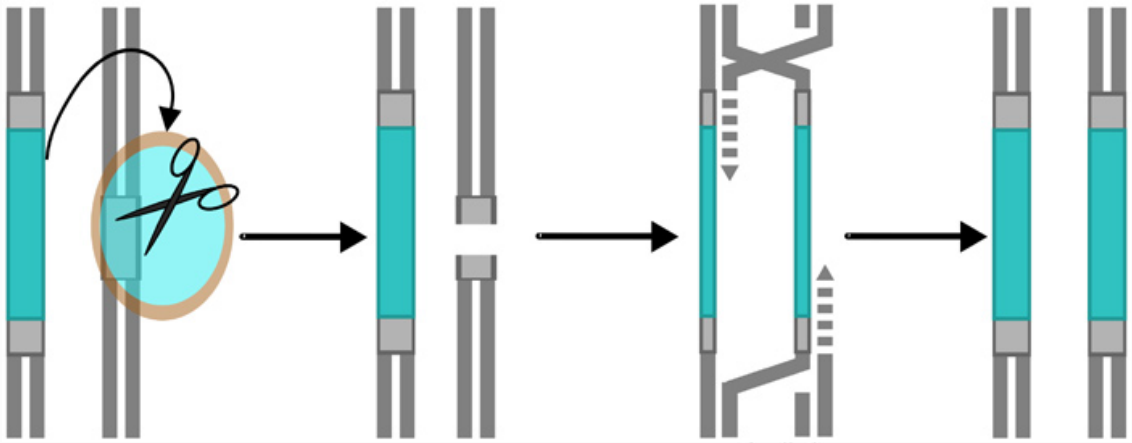
Some Types and Uses of Gene Drives

1. Homing-based

- insertion of a gene drive nuclease with its own recognition site that cleaves DNA and then makes copies of chromosomes with the gene drive



Di Carlo et al., 2015; doi:10.1038/nbt.3412

- uses: targets essential genes, population suppression, population replacement

2. Sex distorter or Y-drive

- insertion of gene drive to change balance between sexes
- targeting the X chromosome during male gametogenesis generates male bias; reduces the number of females
- use: population suppression by changing balance of sexes

3. Split gene drive

- components of gene drive are split between chromosomes; one spreads through drive but other through Mendelian inheritance

- uses: limited target populations controlled in short periods, spatially limited or threshold dependent

4. Maternal Effect Dominant Embryonic Arrest (MEDEA)

- gene drive involves a toxin expressed from a maternal promoter and zygotic antidote
- when the gene drive spreads, it causes the death of the organism that does not have the construct since the toxin will kill any individual that does not contain the antidote
- use: population replacement

Gene Drives for Pest Control

- Pests such as weeds, rodents, and invertebrate species cause significant economic losses worldwide

  → threats to agricultural productivity and food safety

- Two key population control methods:

  - **Population suppression** – the spread of a genetic element that causes the number of individuals in a population to decrease

  - **Population replacement** – the spread of a genetic element through a population that causes a population's genotype to change

- The use of gene drives for pest control has long been considered.

- With the use of CRISPR/Cas9 technology, the creation of gene drives to control pests is more possible.

- Example: spotted wing drosophila (SWD), *Drosophila suzukii*, the first agricultural pest in which gene drive was implemented

PNAS RESEARCH ARTICLE | AGRICULTURAL SCIENCES

CRISPR/Cas9-based split homing gene drive targeting *doublesex* for population suppression of the global fruit pest *Drosophila suzukii*

Amarish K. Yadav[a], Cole Butler[b], Akihiko Yamamoto[a], Anandrao A. Patil[a,1], Alun L. Lloyd[b], and Maxwell J. Scott[a,2]

Edited by Anthony James, University of California, Irvine, CA; received January 27, 2023; accepted May 4, 2023

Genetic-based methods offer environmentally friendly species-specific approaches for control of insect pests. One method, CRISPR homing gene drive that target genes essential for development, could provide very efficient and cost-effective control. While significant progress has been made in developing homing gene drives for mosquito disease vectors, little progress has been made with agricultural insect pests. Here, we report the development and evaluation of split homing drives that target the *doublesex* (*dsx*) gene in *Drosophila suzukii*, an invasive pest of soft-skinned fruits. The drive component, consisting of *dsx* single guide RNA and DsRed genes, was introduced into the female-specific exon of *dsx*, which is essential for function in females but not males. However, in most strains, hemizygous females were sterile and produced the male *dsx* transcript. With a modified homing drive that included an optimal splice acceptor site, hemizygous females from each of the four independent lines were fertile. High transmission rates of the DsRed gene (94 to 99%) were observed with a line that expressed Cas9 with two nuclear localization sequences from the *D. suzukii nanos* promoter. Mutant alleles of *dsx* with small in-frame deletions near the Cas9 cut site were not functional and thus would not provide resistance to drive. Finally, mathematical modeling showed that the strains could be used for suppression of lab cage populations of *D. suzukii* with repeated releases at relatively low release ratios (1:4). Our results indicate that the split CRISPR homing gene drive strains could potentially provide an effective means for control of *D. suzukii* populations.

Significance

Spotted wing drosophila (*Drosophila suzukii*) is a vinegar fly with a worldwide distribution that does significant economic damage to soft-skinned fruits. We made and evaluated split CRISPR homing gene drives that target the conserved female-specific exon of the *doublesex* gene, which is essential for sexual development in *Drosophila*. Our results suggest that homing gene drives could provide a cost-effective approach for suppression of *D. suzukii* populations.

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Article | Published: 17 June 2024

Overriding Mendelian inheritance in *Arabidopsis* with a CRISPR toxin–antidote gene drive that impairs pollen germination

Yang Liu, Bingke Jiao, Jackson Champer & Wenfeng Qian

Nature Plants **10**, 910–922 (2024) | Cite this article

2480 Accesses | **3** Citations | **67** Altmetric | Metrics

Abstract

Synthetic gene drives, inspired by natural selfish genetic elements and transmitted to progeny at super-Mendelian (>50%) frequencies, present transformative potential for disseminating traits that benefit humans throughout wild populations, even facing potential fitness costs. Here we constructed a gene drive system in plants called CRISPR-Assisted Inheritance utilizing *NPG1* (*CAIN*), which uses a toxin–antidote mechanism in the male germline to override Mendelian inheritance. Specifically, a guide RNA–Cas9 cassette targets

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Opportunities

- Gene drives have the potential to provide significant benefits in terms of control of undesirable species (e.g., insects/vectors, weeds)

- Reduction of the reliance on pesticides, herbicides

  → minimizes environmental harm

- Gene drives (endonuclease-based) may be a valuable tool for working with polyploid species if can be designed to drive edits across all homeologous alleles and gene copies within a genome.

Challenges

- Not all pest species are suitable for control using gene drives.
- Mode of reproduction/mating system, fecundity, ploidy, genome size may affect the utility of gene drives
- Identification of the gene targets; availability of genome sequence and transformation system for the organism

- Biosafety and ethical issues surrounding gene drive research and releases

- Methods for controlling the spatial and temporal spread of gene drives and techniques to reverse their propagation in populations, when necessary.

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Thank you for listening

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