## **Gene drives**

## **Proof of concept**

### Kyrou et al., 2918

- The doublesex locus in Anopheles gambiae
  - Female & male versions
  - Disruption of the female version
    - Male is not affected
    - Homozygous females become sterile







Altered gene does not spread

Gene drive inheritance



Altered gene is always inherited

Wikipedia commons

## Uses

- Eliminate/reduce vectors of disease
- Eliminate/reduce invasive species
- Target insect pests to eliminate/reduce them
- Target weeds to eliminate/reduce them
- Reverse herbicide resistance
  - Edit resistance alleles
- Drive a beneficial allele through a breeding program

Their proposed uses have elicited a lot of anxiety, including proposed moratoria and global bans on the use of gene drives.

# **Big questions around gene drives**

- How does a gene drive system work?
- How widespread are drive systems in nature?

## Synthetic toxin-antidote drives

#### Oberhofer et al, 2024



The "toxin" is the CRISPR Cas9 gene that KO's the plant's gene. The antidote is the a cleavage resistant version of the KO'd gene. It will drag the cargo along.

## How widespread are gene drives?

- Animals
  - o Mouse
  - o Drosophila
- Fungi
  - o Neurospora
- Plants
  - Maize
  - o Mimulus
  - o Rice
  - o Rye
  - o Tomato
  - o Tobacco
  - o Wheat
- B chromosomes
  - >2000 spp of plants and animals

- Gene drive systems seem to be found where we've looked at cytogenetic phenomena extremely well
- Therefore, gene drive is probably very common in nature

# Maize abnormal chromosome 10

Longley, 1938



FIGURE 11.—Chromosome X: A, Normal type; B, one of the abnormal types.  $\times$  1,500.

## **Discovery of meiotic drive in plants**

#### Rhoades, 1942

• Tried to map distance from R:



• The knob is <u>neocentric</u>, i.e., exhibits some of the same properties of the centromere, and moves pole-ward ahead of the centromere itself



up in the end (basal and micropylar) megaspores of the linear tetrad.

Two Ana II chromosomes, with the one on the right showing neocentric activity.

• In maize, the female gametophyte forms from the basal megaspore of the linear tetrad, which therefore tends to contain the knobbed chromosome.

## The Rhoades model

#### Dawe et al., 2018

- In a heteromorphic pair, a CO occurs between the centromere and the knob
- In female meiosis, only the most basal megaspore is retained

Dawe Lab, unpublished

 Neocentromere activity favors the knobbed chromosome in this cell





Dawe et al., 2018



## **KINDR localizes to 180-bp knobs**

#### Dawe et al., 2018

- Kindr is responsible for drive
- Note hybridization to the 180-kp knobs but not the TR1 repeats
  - (green + red overlay = yellow)



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• Knocking out Kindr removes drive

# Kindr RNAi DH194 (43% R) + DH195 (48% R) Ab10 (80% R)

**TRKIN localizes to TR1 knobs** 

Dawe lab, unpublished





## Increased transmission of alleles linked to knobs Rhoades & Dempsey, 1957

10 Haplotype	3 Haplotype	% GI	% Lg	% A
Ab10 / N10	K3L / k3L	51.7	72.5	63.6
Ab10 / N10	k3L / k3L	50.6	50.8	52.3
N10 / N10	K3L / k3L	50.0	50.9	51.7
N10 / N10	k3L / k3L	53.1	50.4	51.5

# Knobs in maize & teosinte are in gene-rich areas

Buckler et al., 1999

• Most maize genes are located near knobs and thus have been affected by meiotic drive during evolution



## How common is gene drive?

Kanizay et al, 2013

- Looked at Ab10 frequencies in maize/teosinte populations
- Ab10 is widespread but is in a population



## Why haven't gene drive systems achieved fixation?

#### Rhoades, 1942; Higgins et al., 2017

• Ab10 in maize transmits only 42% pollen viability



• Ab10 also shows decrease in kernel mass



## Intragenomic conflict

#### Kanizay et al., 2013



- Reduces Ab10 meiotic drive in Ab10/K10L2 heterozygotes
- Deleterious mutations accumulate linked to knobs
- K10L2 haplotype may have evolved to suppress Ab10 meiotic drive
- The maize genome also contains Kindr and Trkin pseudogene arrays that produce small RNAs
  - May have evolved to silence genes and suppress drive

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- If gene drives are common and they boost their inheritance above Mendelian ratios, why haven't they become fixed?
- Drosophila sex-ratio drive system
  - $\circ$  XX<sup>SR</sup> × XY
  - $\circ$  X<sup>SR</sup>Y is eliminated  $\rightarrow$  only X<sup>SR</sup>X females survive
  - Unsustainable over long periods

#### Courret et al., 2018

- Mapped 5 QTLs for suppressors of SR drive in *Drosophila*
- SR drive can be deleterious for the population



The genome evolves to suppress SR drive

#### Champer et al., 2017

- Rapid rate of resistance develops in CRISPR-based systems
- Strong selection pressure for mutations in guide RNA recognition sequence



#### IV-G - Gene drives PBGG 8900

#### Price et al., 2019



## organisms

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Until this obstacle is overcome, the technology is unlikely to succeed in the wild.