# Gene drive technology for suppression of invasive mammals

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# Global impact of invasive species

**IPBES report September 2023*** (86 experts, 49 countries, 1300 references)

- Cost of invasive species is $423 Billion every year
- Cost has quadrupled every decade since 1970

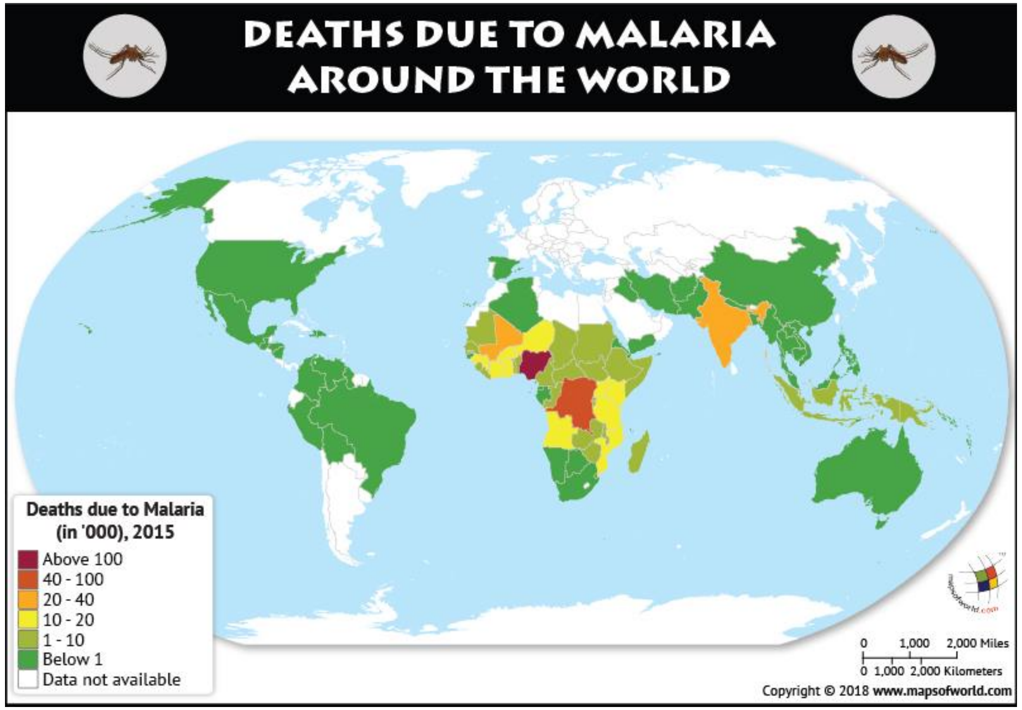
**Invasive mammals**

- Mice, rats, rabbits, feral pigs, feral cats and foxes costing Australia US$20.19 billion (1960-2017)
- A major driver for almost all the 34 mammal extinctions in Australia since 1788

*IPBES (2023). Summary for Policymakers of the Thematic Assessment Report on Invasive Alien Species and their Control of the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. Roy, H. E., Pauchard, A., Stoett, P., Renard Truong, T., Bacher, S., Galil, B. S., Hulme, P. E., Ikeda, T., Sankaran, K. V., McGeoch, M. A., Meyerson, L. A., Nuñez, M. A., Ordonez, A., Rahlao, S. J., Schwindt, E., Seebens, H., Sheppard, A. W., and Vandvik, V. (eds.). IPBES secretariat, Bonn, Germany.

# Why develop gene drives?

- Health, conservation & agriculture
- Humane tool for population suppression



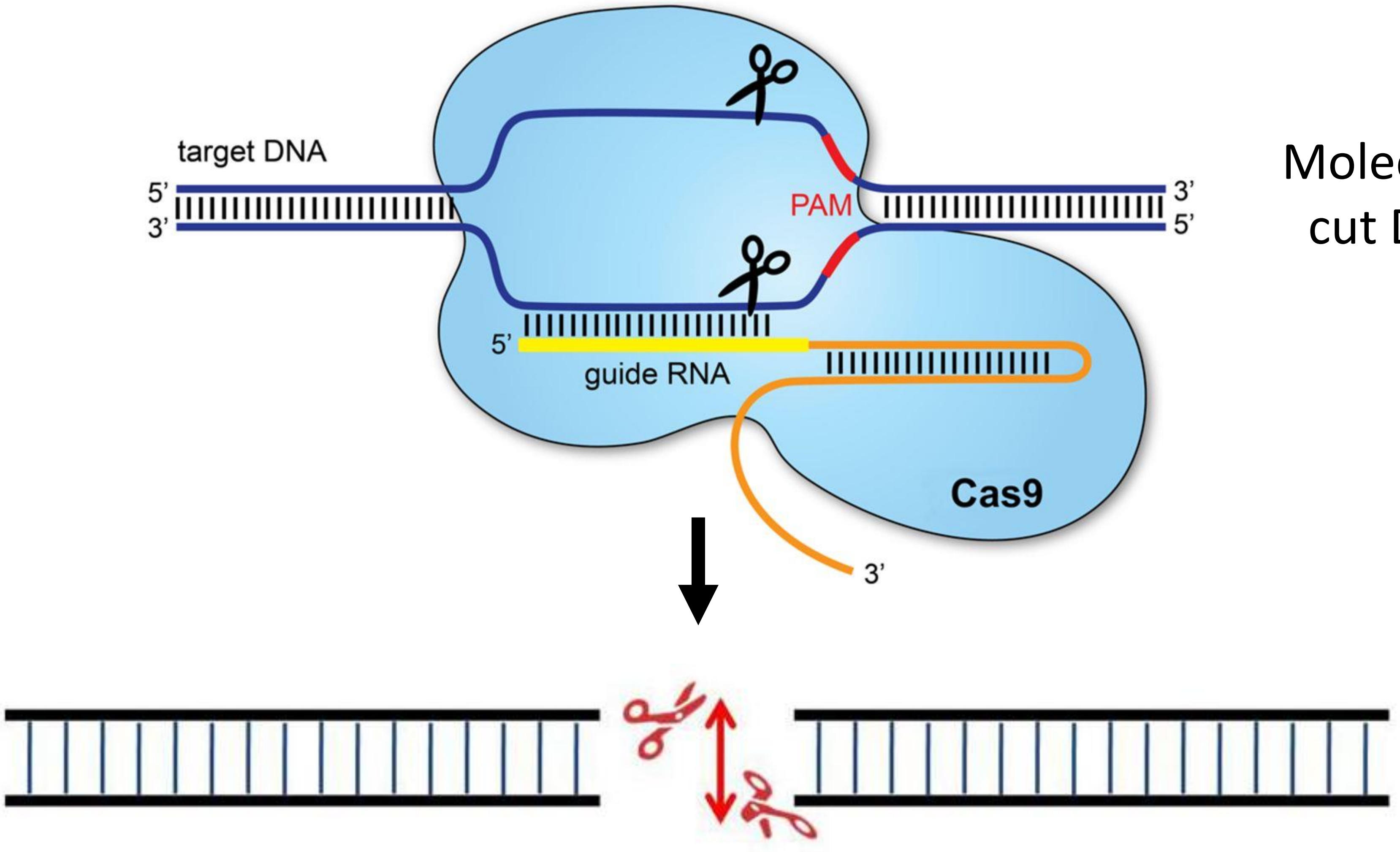

Malaria is responsible for >400,000 deaths per year

Hundreds of mice that have been trapped during the plague on Qld's Darling Downs. *(Supplied: Vicki Green)*

Environmental damage/loss of biodiversity

Agricultural loss of productivity/societal impact

# CRISPR/CAS9 Genome Editing




Molecular scissors that cut DNA at a specific location

CRISPR enables generation of gene drive (transgenic) animals and gene drive activity

# Gene Drive Development

Gene Drive Strategies

1. CRISPR ‘homing’ gene drive (female fertility)

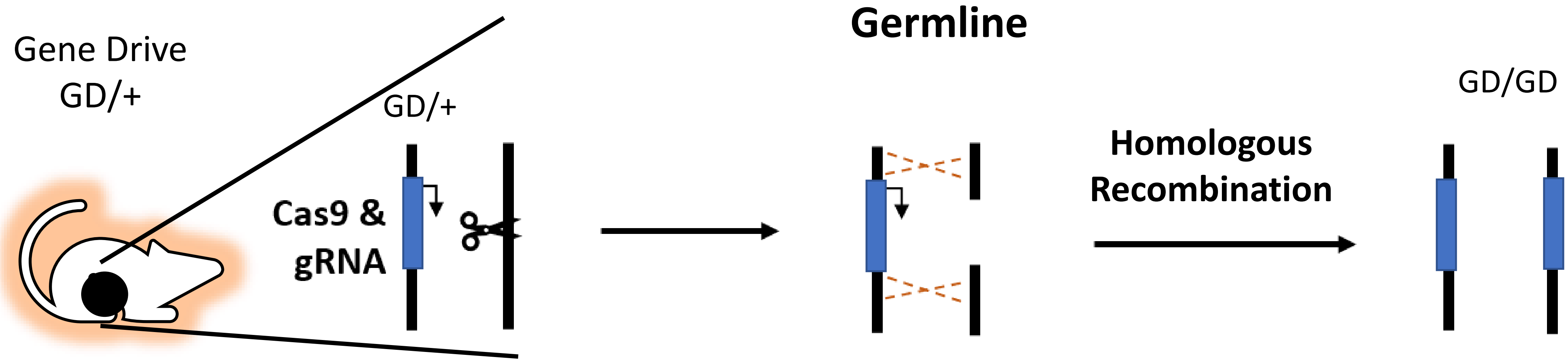
2. X-shredder/driving Y (male bias)

3. *t*-allele + CRISPR = *t*-CRISPR (female fertility)

# Gene Drive Development

<u>Gene Drive Strategies</u>

**1. CRISPR "homing" gene drive  (female fertility)**




- >99% homing mosquitos but inefficient in mice
- Timing and level of Cas9 is likely to be critical

# Gene Drive Development

## Gene Drive Strategies

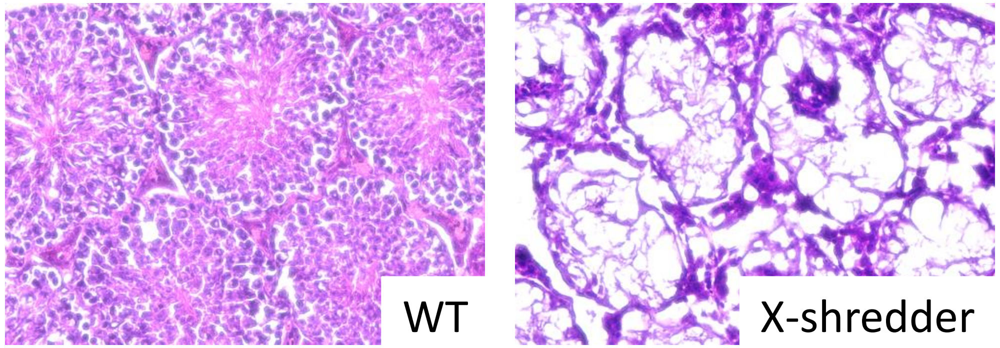
**2. X-shredder/driving Y (male bias)**

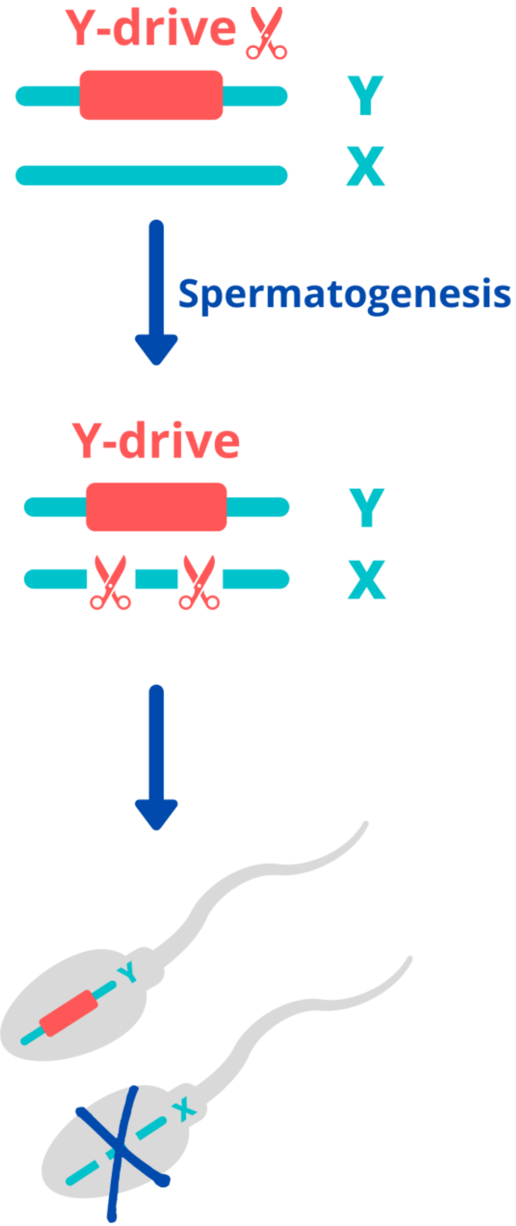
-'Shred' the X-chromosome → male only → population crash

**Investigating the potential of X chromosome shredding for mouse genetic biocontrol**

Mark D. Bunting, Gelshan I. Godahewa, Nicole O. McPherson, Louise J. Robertson, Luke Gierus, Sandra G. Piltz, Owain Edwards, Mark Tizard & Paul Q. Thomas

*Scientific Reports* **14**, Article number: 13466 (2024) | Cite this article



# Rodent Genetic Biocontrol - Laboratory Development

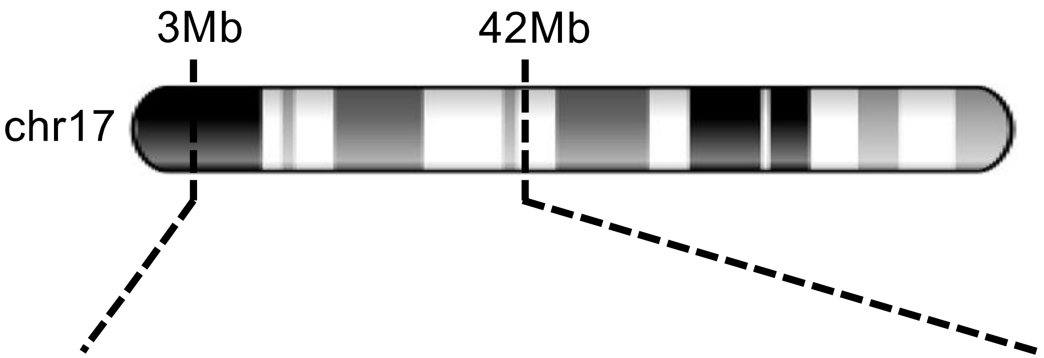
## Gene Drive Strategies

1. CRISPR 'homing' gene drive  (female fertility)

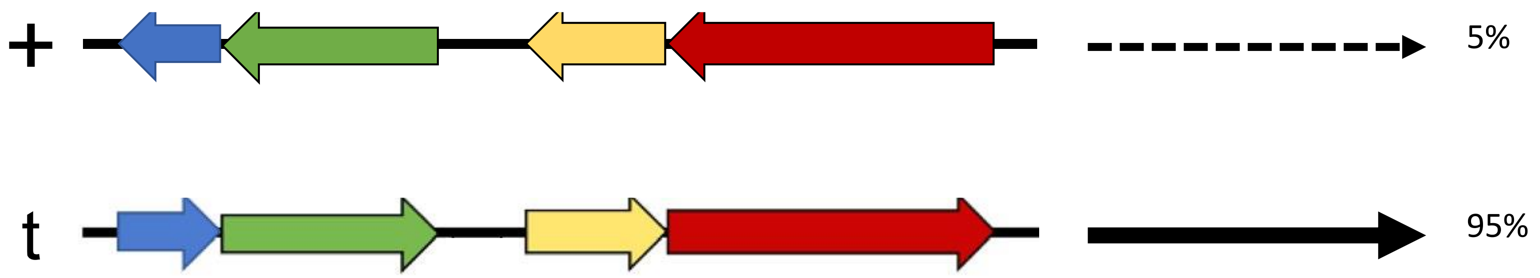
2. X-shredder/driving Y (male bias)

3. ***t*-haplotype strategies (*t*-CRISPR) (female fertility)**
   **- Island-specific version**

# The *t haplotype – a natural* meiotic drive in male mice



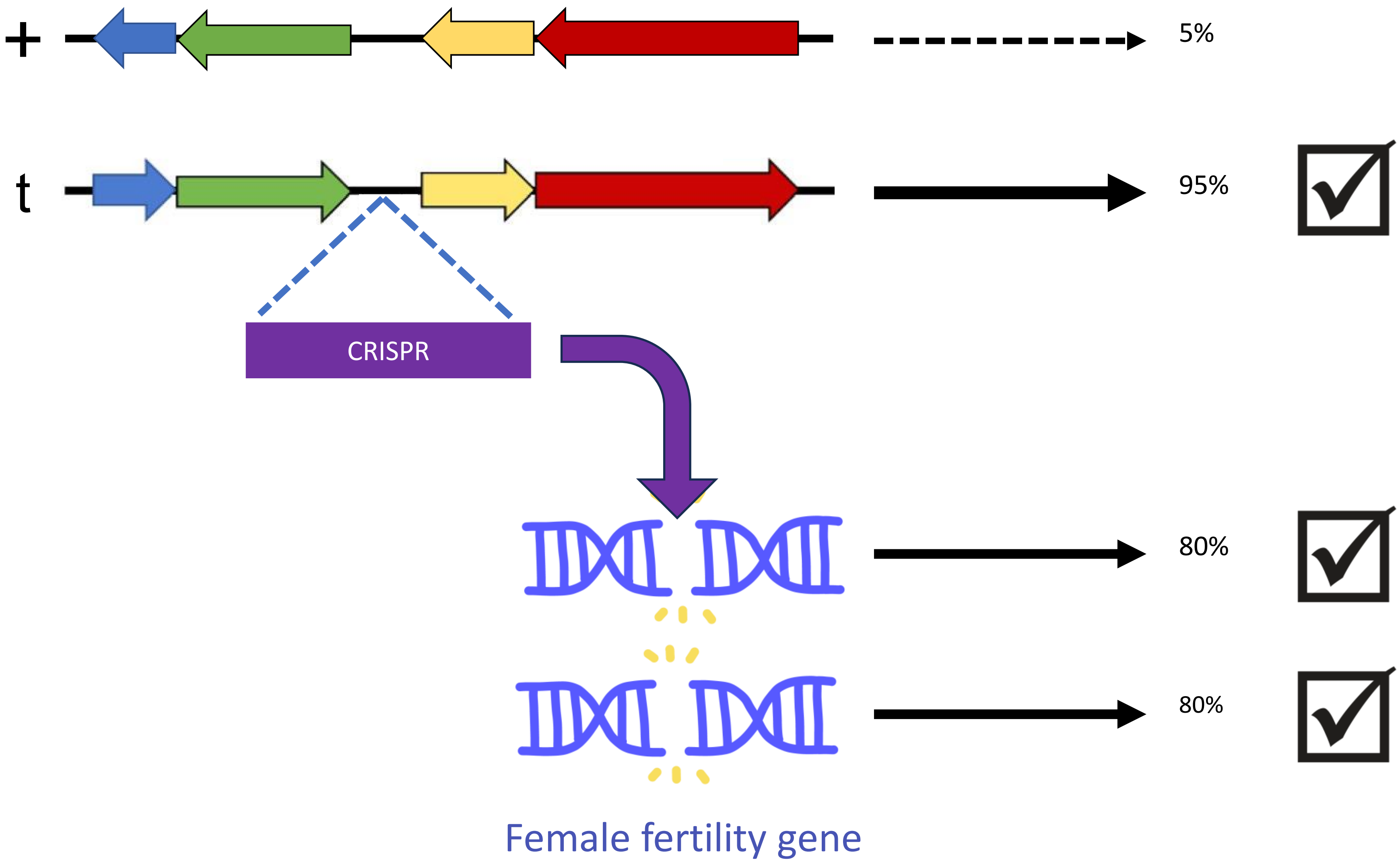

- Two "versions" of chromosome 17 in mice
- t-haplotype is a natural gene drive
- Male mice pass on the "t-haplotype" version to 95% of offspring!




(Arora and Dumont, 2022)

Can we use CRISPR to leverage t-haplotype to suppress invasive mice?

# Generating t-CRISPR mice




Could t-CRISPR suppress mouse population?

# Model framework

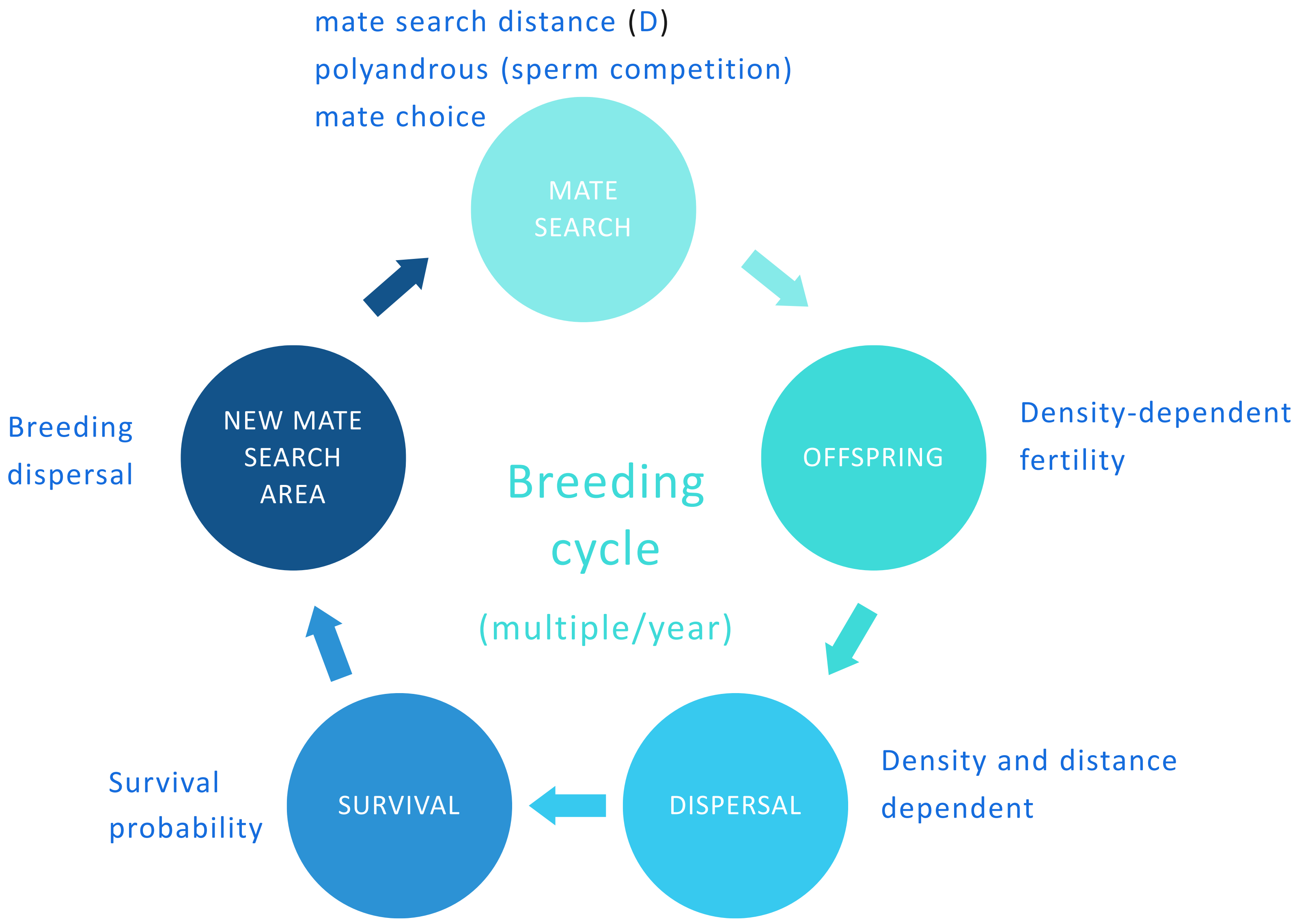
Individual based,
spatially explicit,
stochastic

### Landscape

Array of patches
Individuals use multiple patches
N ~ 200,000

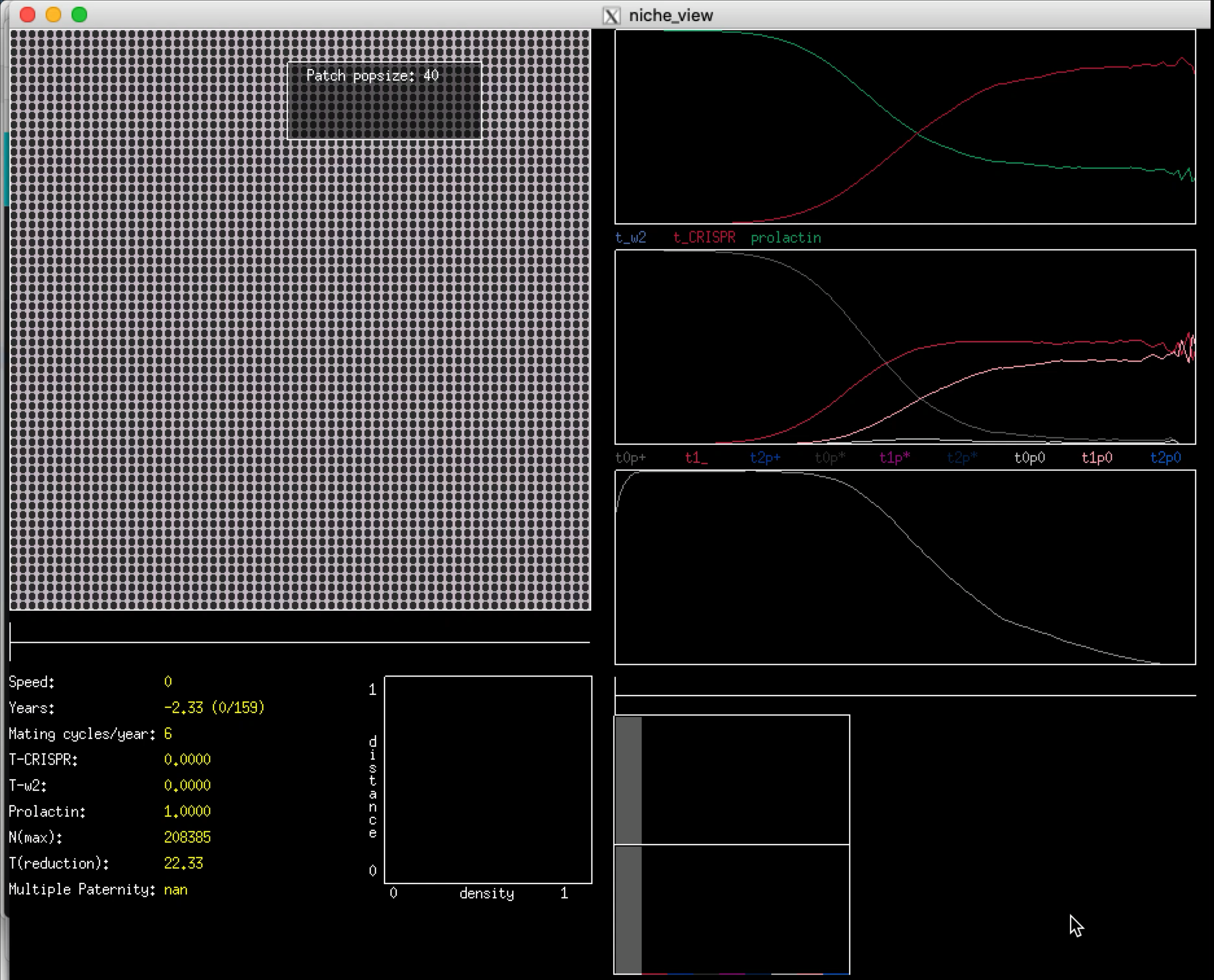
### Individuals

Diploid
Discrete sexes (XX and XY)
Genetically controlled traits




Birand et al. 2022 Molecular Ecology 31:1907–1923.

Aysegul Birand




Stochastic individual-based modelling

Island population of 200,000 mice

Deploy 256 *t*-CRISPR mice (1/patch)

Proof of concept in lab mice

Aysegul Birand

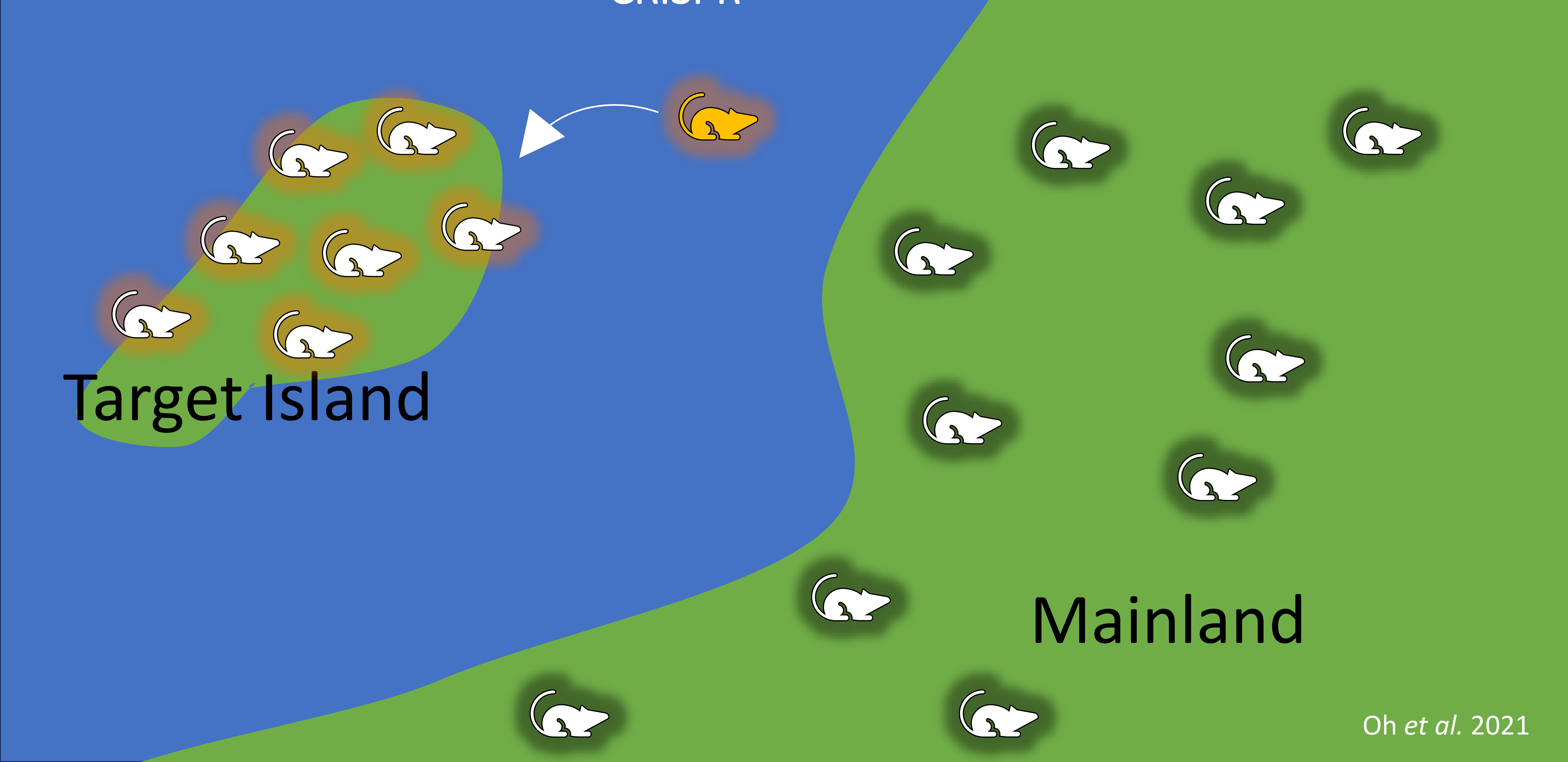
# Leveraging a natural murine meiotic drive to suppress invasive populations

Luke Gierus[a,b,1], Aysegul Birand[c,1], Mark D. Bunting[a,b], Gelshan I. Godahewa[b,d], Sandra G. Piltz[a,b], Kevin P. Oh[e,f], Antoinette J. Piaggio[g], David W. Threadgill[h], John Godwin[i], Owain Edwards[e,j], Phillip Cassey[c], Joshua V. Ross[k], Thomas A. A. Prowse[c] and Paul Q. Thomas[a,b,2]

PNAS 2022 Vol. 119 No. 46 e2213308119

- First proof of concept for a mammalian gene drive
- Generating "island-specific" version (and other strategies)
    - The Office of Gene Technology Regulator (OGTR) granted approval for the all-in-one *t*-CRISPR mouse (Australian first)

# Current Work – Can $t_{CRISPR}$ be spatially confined?




Oh *et al.* 2021

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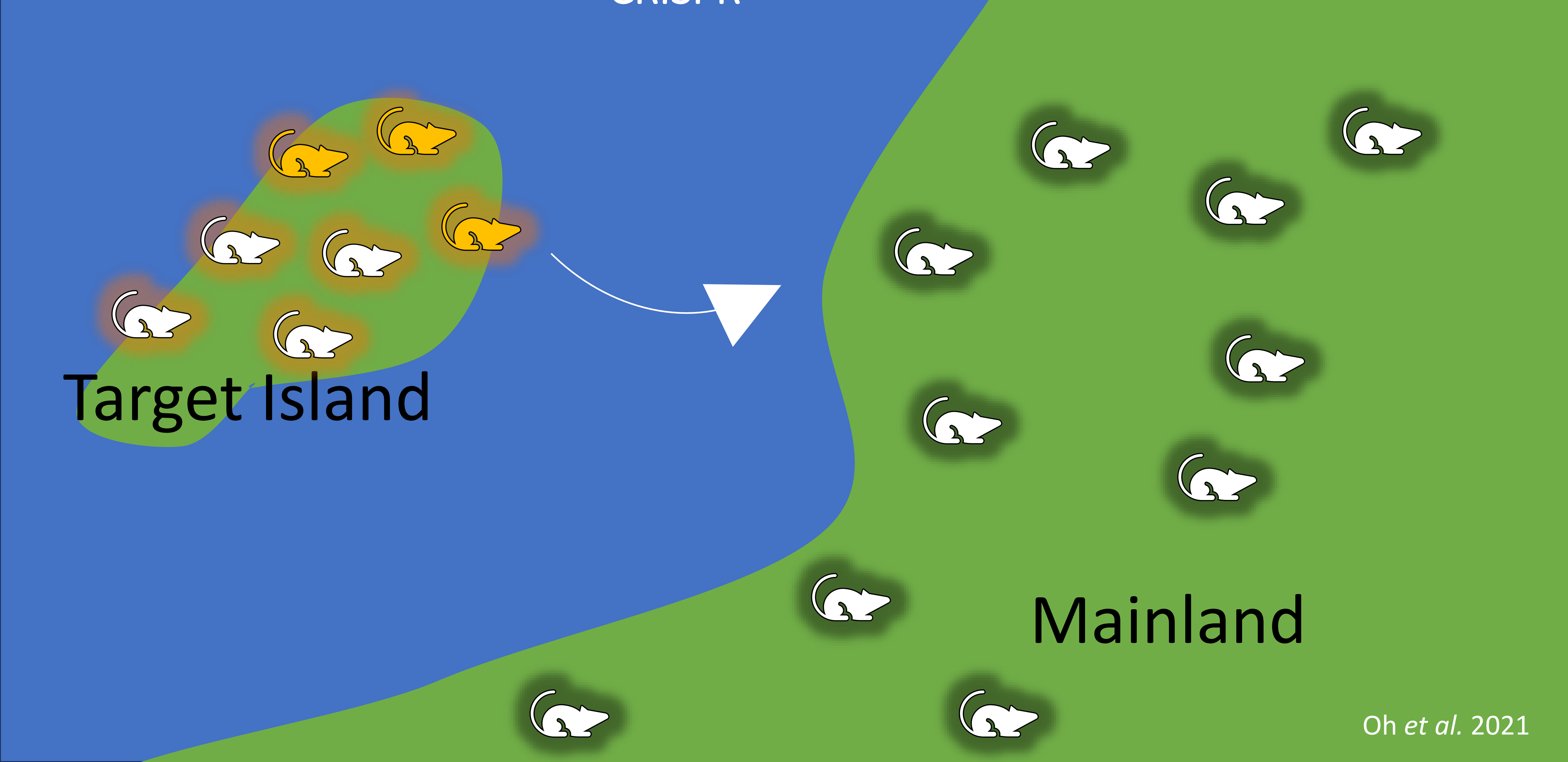


Oh *et al.* 2021

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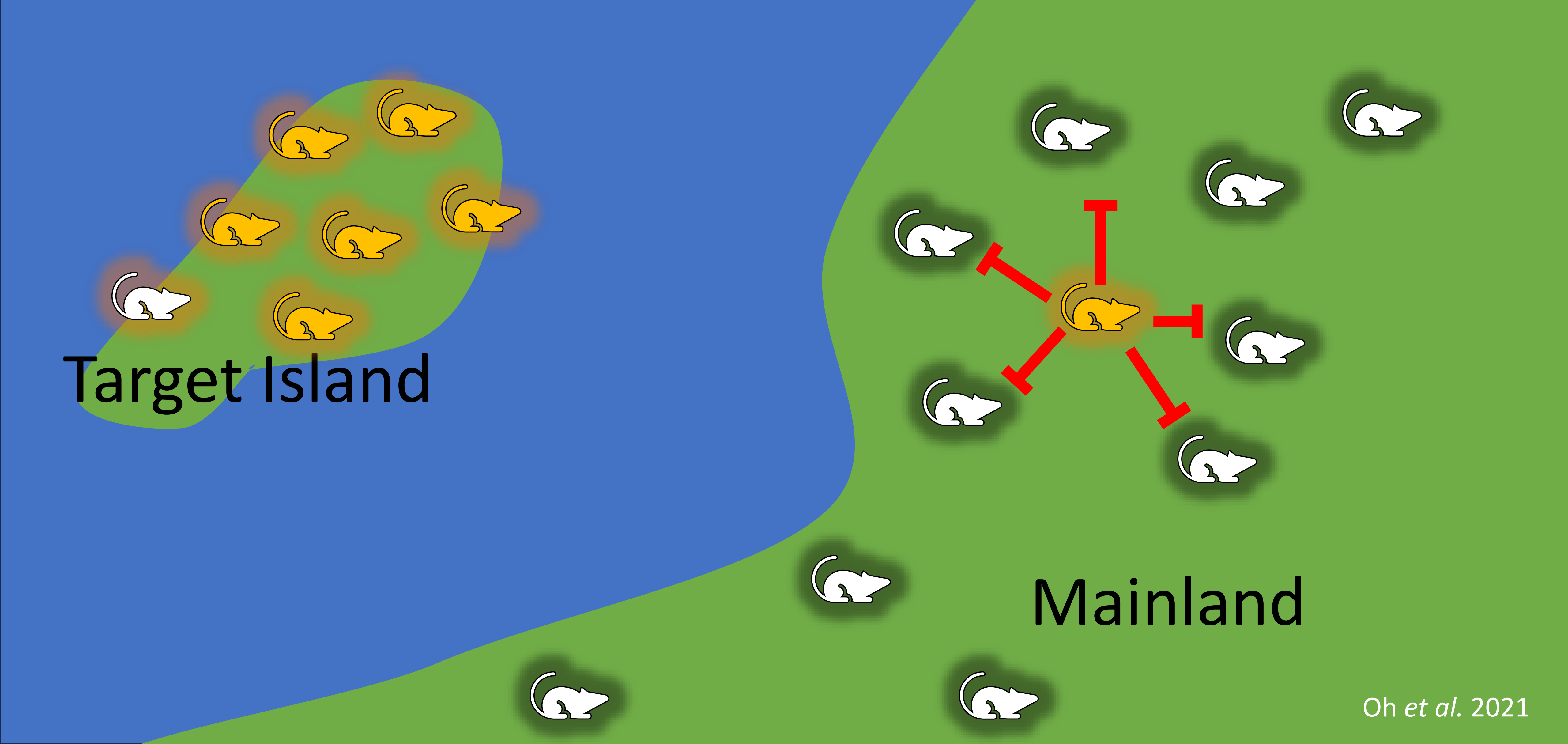


Oh *et al.* 2021

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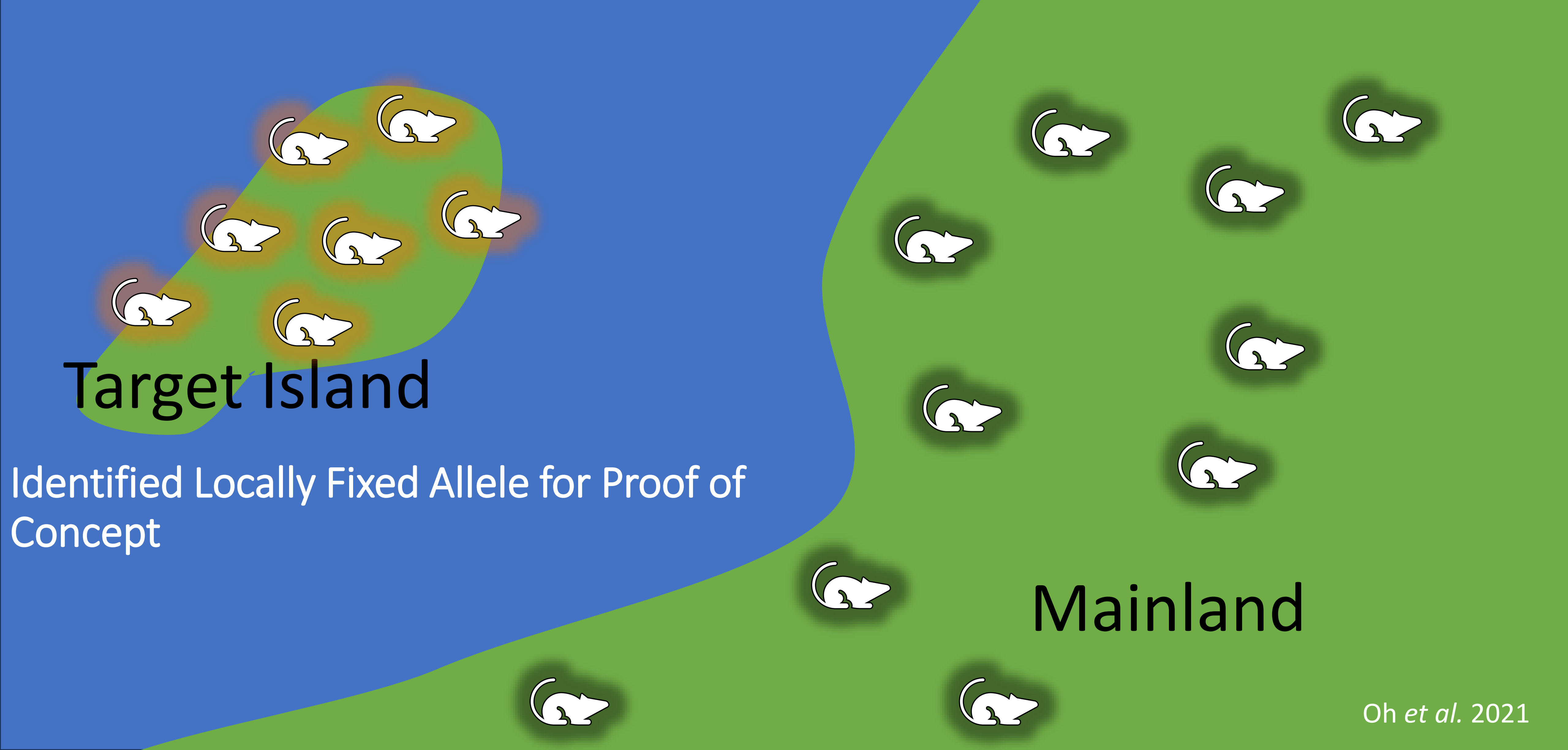



Identified Locally Fixed Allele for Proof of Concept

Oh *et al.* 2021

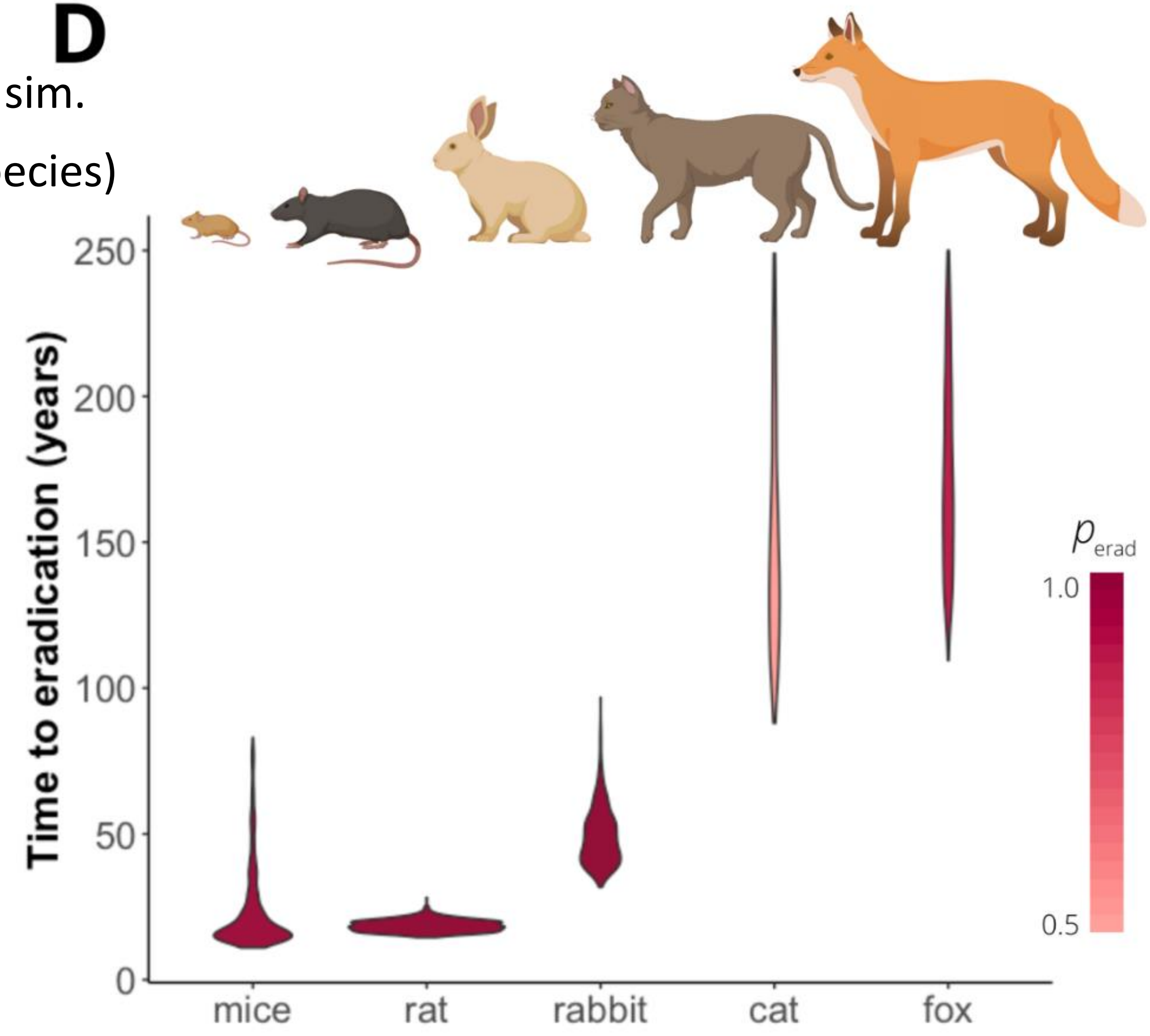
# Conclusions so far…

## Investigated different genetic strategies for rodent suppression…

- *t*-CRISPR → first validated genetic biocontrol strategy for rodent population suppression
- Generating all-in-one drive targeting candidate island “specific” allele (cf. Oh et al 2020…)
- Enclosure trial with CSIRO
- Other strategies ongoing…

# What about other vertebrates?

(1000 sim. per species)




Median time to 50% and 90% reduction, and time to eradication (100%) in years across all species with Y-drive

| Species | 50% | 90% | 100% |
|---|---|---|---|
| Mouse | 6.7 | 9.2 | 17.7 |
| Black rat | 9.0 | 11.7 | 18.5 |
| Rabbit | 16.8 | 24.1 | 48.0 |
| Cat | 71.0 | 92.0 | 143.2 |
| Fox | 74.0 | 103.5 | 169.0 |

**Larger mammal genetic biocontrol**

- Generally longer timeframes than rodents (rabbits similar to rodents)
- Technical challenges (transgenesis, facilities, genetics, reproductive technology)
- Domesticated non-model animal (cats)

Birand et al. 2022 NeoBiota 74: 93-103

Aysegul Birand

# Gene drives now in plants!

nature plants

Article https://doi.org/10.1038/s41477-024-01701-3

**_Cleave and Rescue_ gamete killers create conditions for gene drive in plants**

Received: 13 October 2023

Accepted: 16 April 2024

Published online: 17 June 2024

Georg Oberhofer, Michelle L. Johnson, Tobin Ivy, Igor Antoshechkin & Bruce A. Hay

nature plants

Article https://doi.org/10.1038/s41477-024-01692-1

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

Received: 10 October 2023

Accepted: 9 April 2024

Published online: 17 June 2024

Yang Liu[1], Bingke Jiao[1,2], Jackson Champer[3] & Wenfeng Qian[1,2]

- Meiotic “Cleave and Rescue” drives
- >90% transmission bias
- Other plants (weeds)?

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