Gene drive technology for suppression of invasive mammals

Prof Paul Thomas

Director

Genome Editing Program

SA Genome Editing Facility

THE UNIVERSITY of ADELAIDE

SAHMRI
South Australian Health & Medical Research Institute

Global impact of invasive species

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

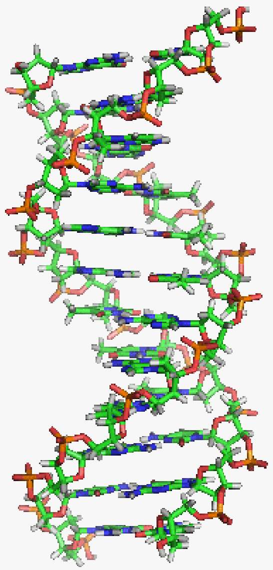
- Cost of invasive species is $423 Billion every year
- Cost has quadrupled every decade since 1970

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

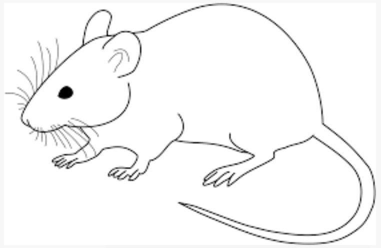
*IPBES (2023). Summary for Policymakers of the Thematic Assessment Report on Invasive Alien Species and their Control of the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. Roy, H. E., Pauchard, A., Stoett, P., Renard Truong, T., Bacher, S., Galil, B. S., Hulme, P. E., 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.

Overview



1. Genetic biocontrol (gene drives)
   - -what are they?
   - -how do they work (CRISPR)

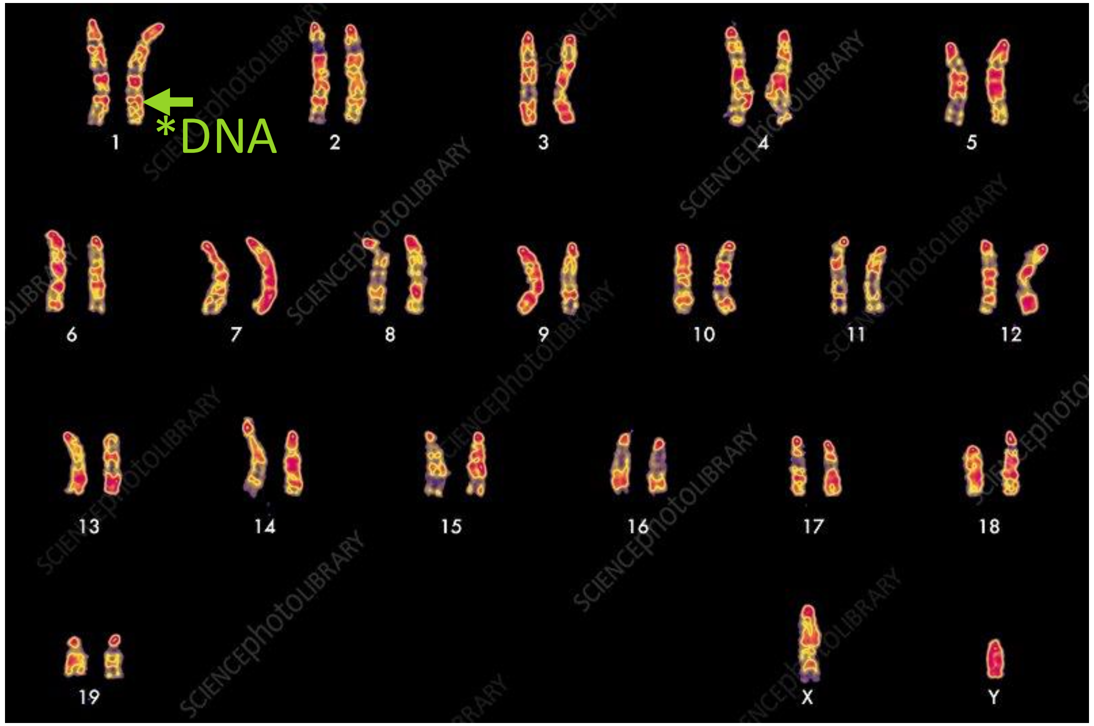
2. In what species have gene drives been developed?
   - -invertebrates
   - -rodents



3. Could gene drives be developed in other mammals?
   - -potential for suppression (modelling)
   - -challenge/barriers

Genetics and transgenic animals 101

Mouse genome on 20 pairs of chromosomes



*DNA "Transgenic" mouse

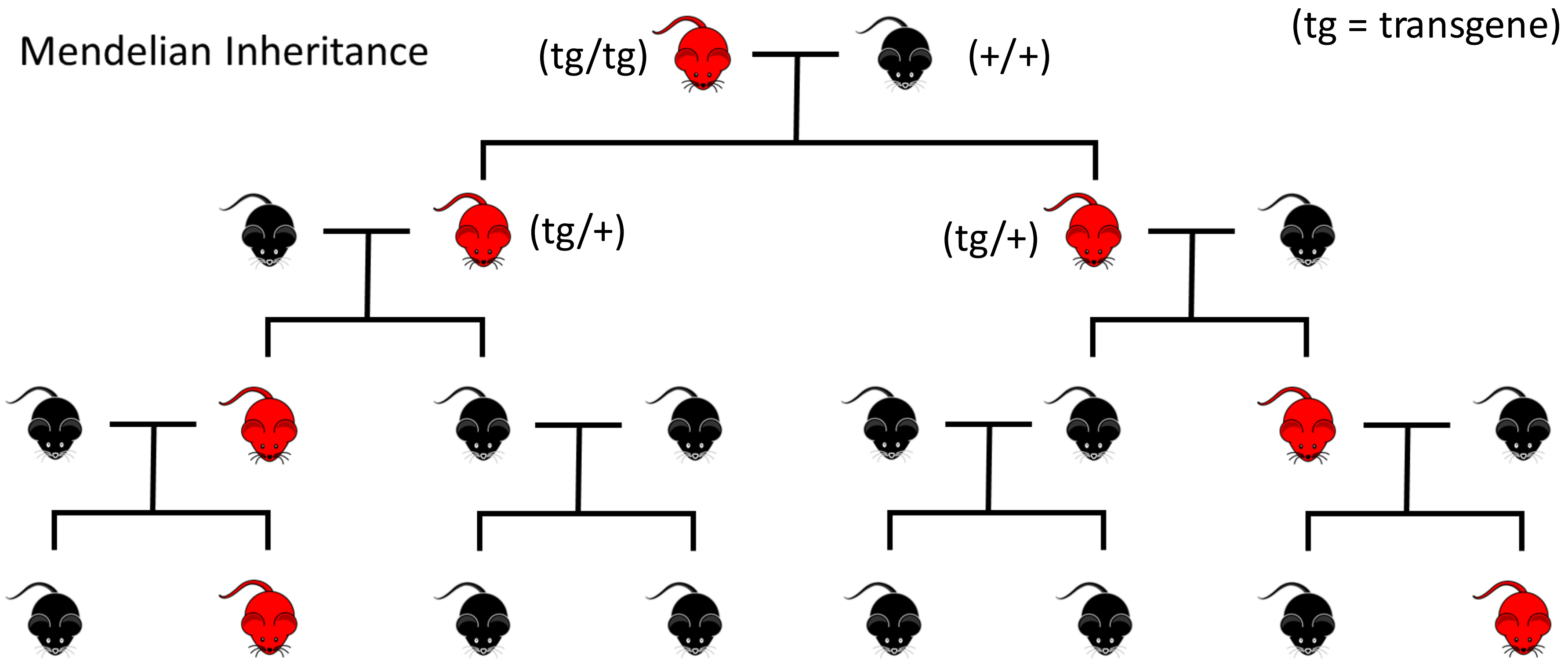
Every cell contains the blueprint for life…. (2.4) billions of DNA building blocks → 20,000 genes

Transgenesis is adding a "foreign" gene into the genome (*DNA) → new "phenotype"

(synthetic) gene drives are a type of transgenic animal which have **biased** inheritance

What is a Gene Drive?

- Genetic construct (transgene) that promotes its own inheritance at a rate greater than Mendelian inheritance
- Potentially spreads through entire population and allows population-level genetic engineering (modification or suppression (fertility or sex bias))



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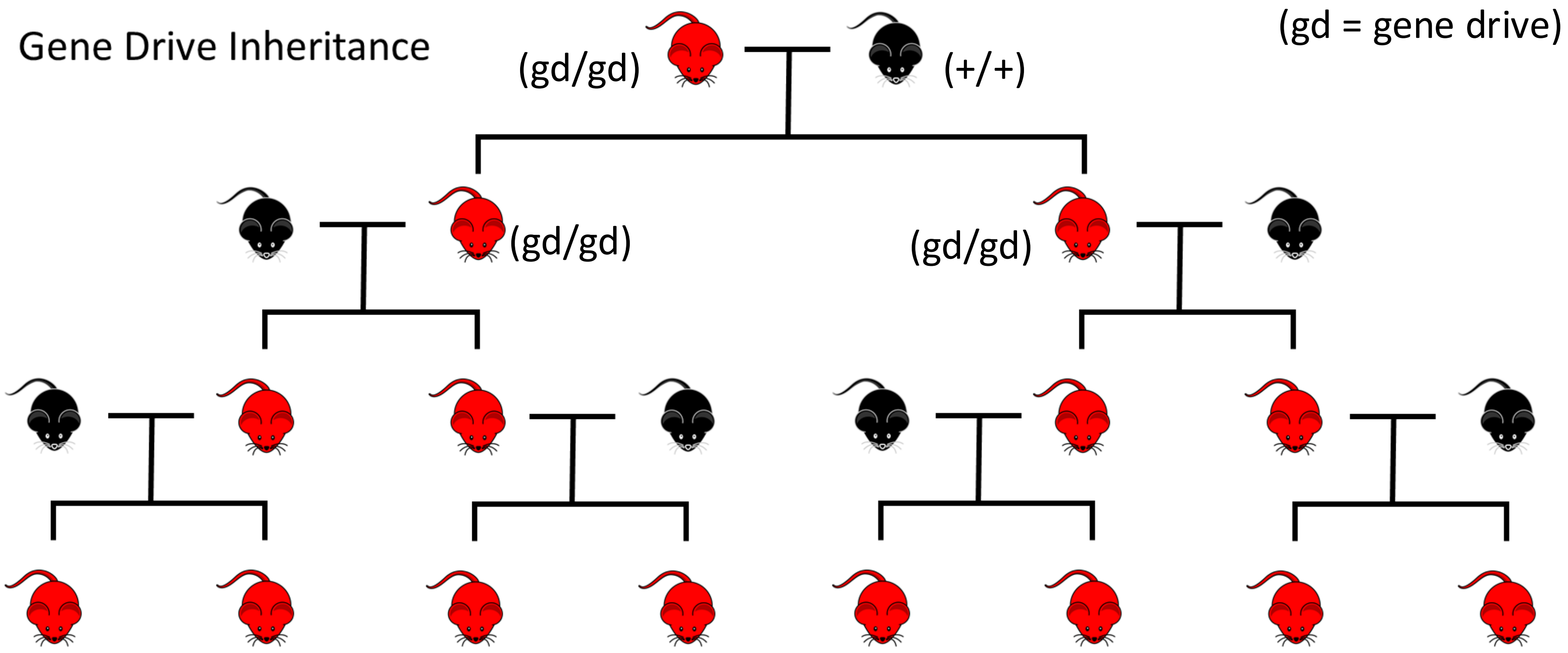

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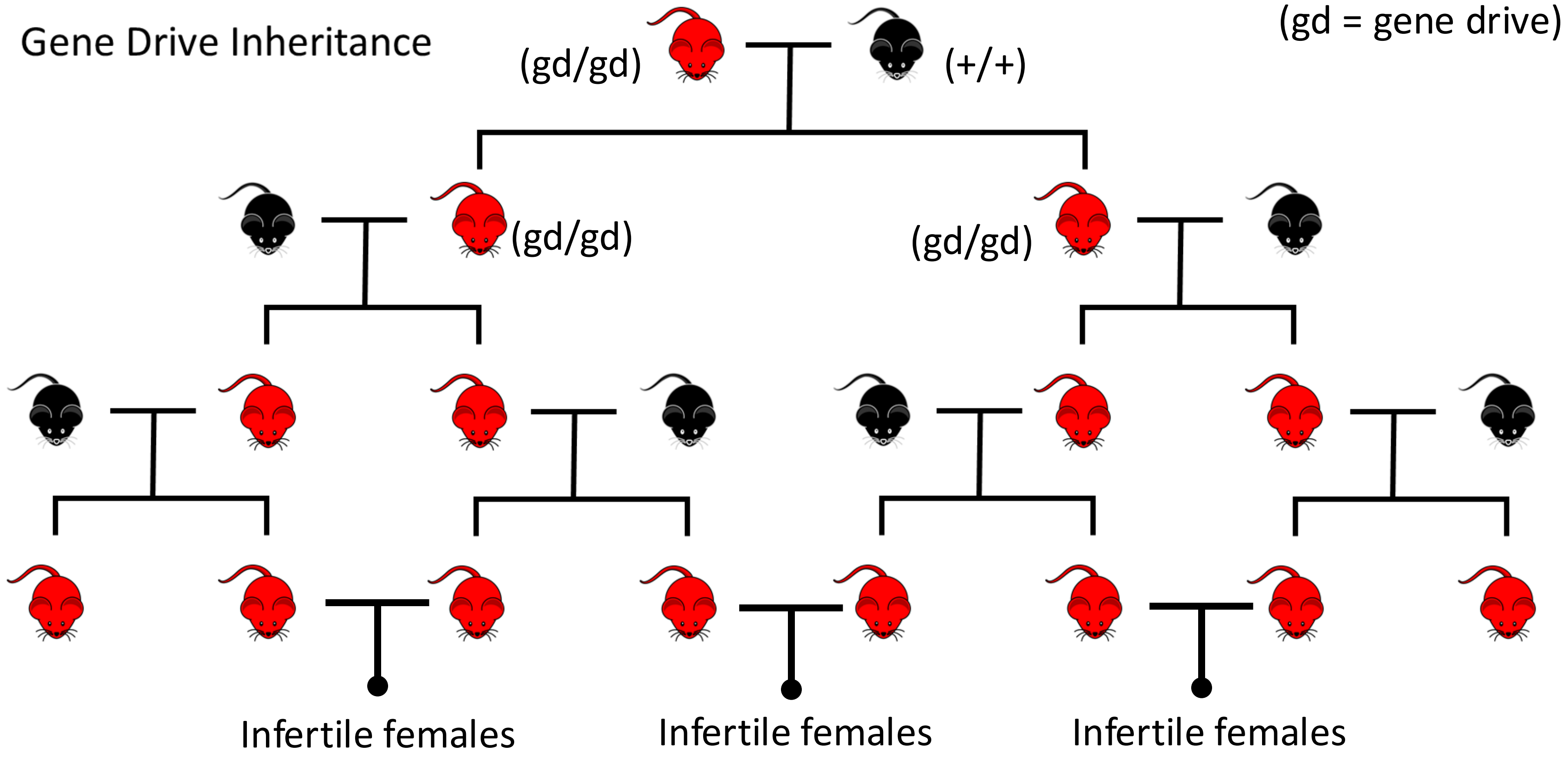

“Homing” female infertility drive

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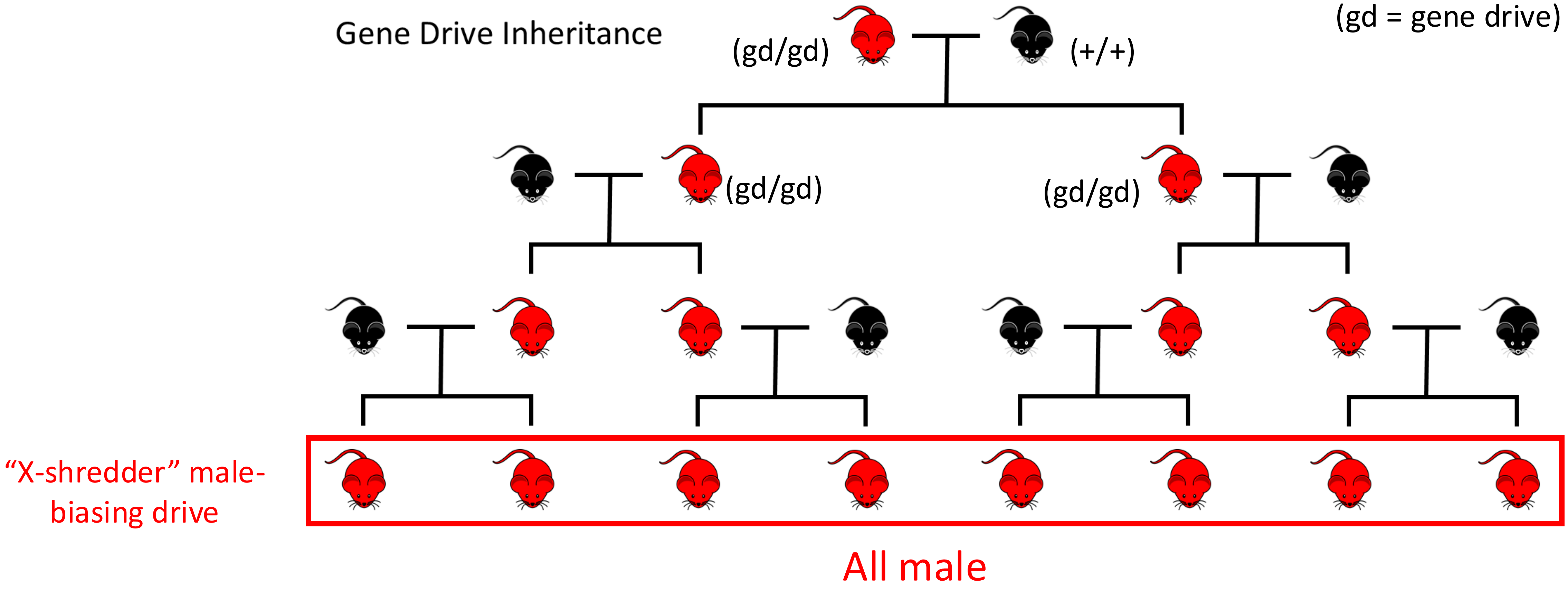

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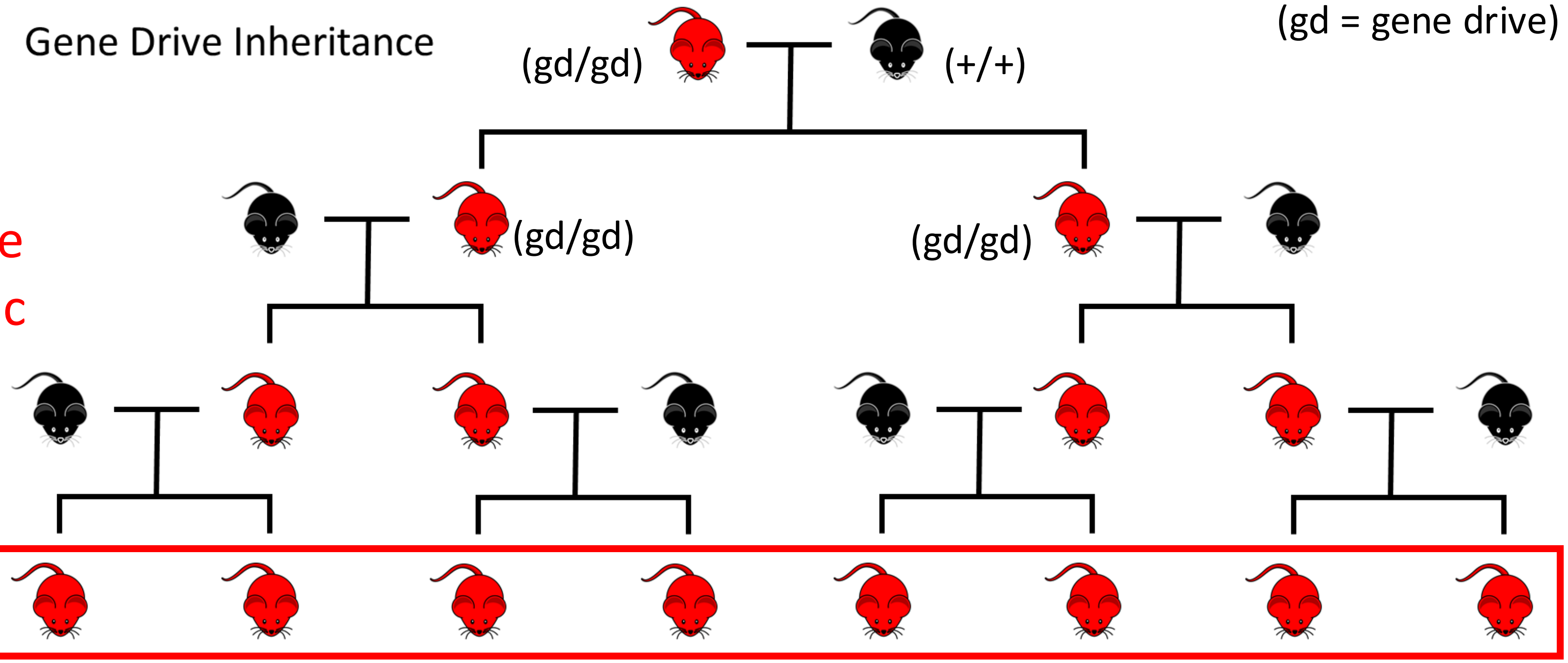
Gene Drive Inheritance

(gd = gene drive)



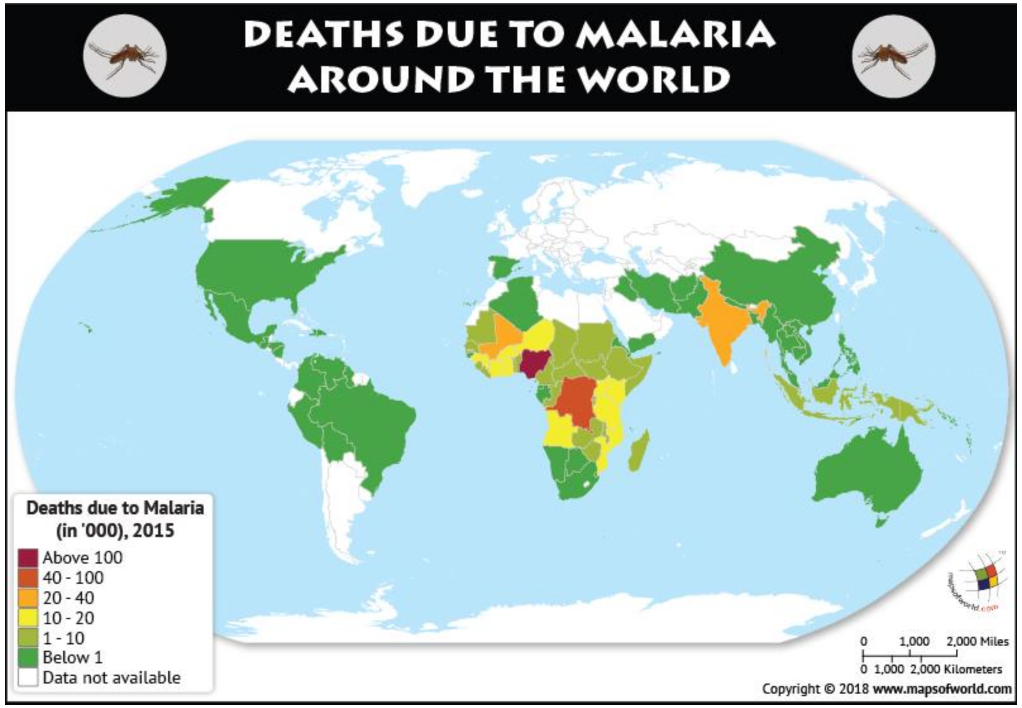
- Non-lethal
- landscape scale
- Species-specific

“X-shredder” male-biasing drive

All male

Why develop gene drives?

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



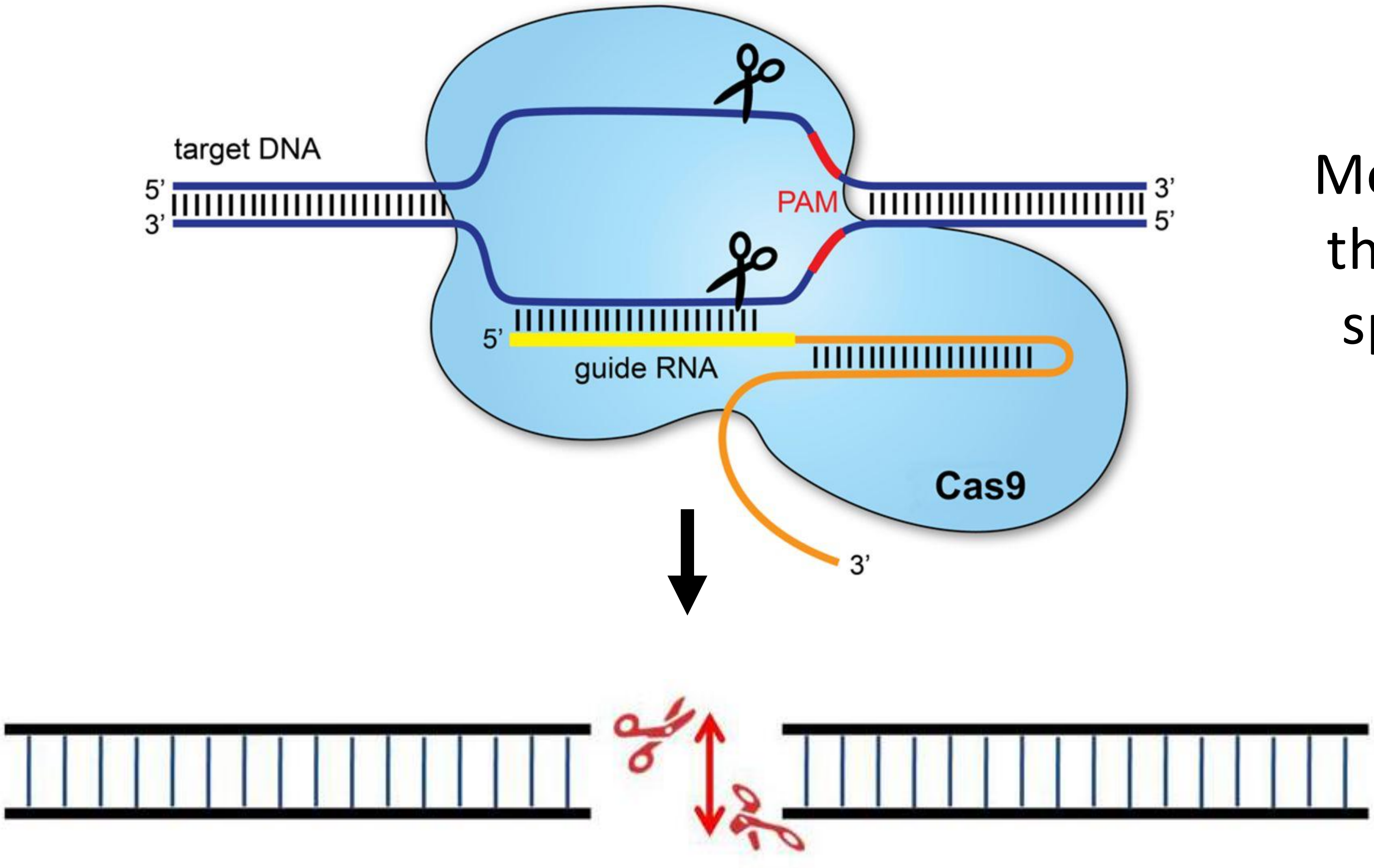
Malaria is responsible for >400,000 deaths per year

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)

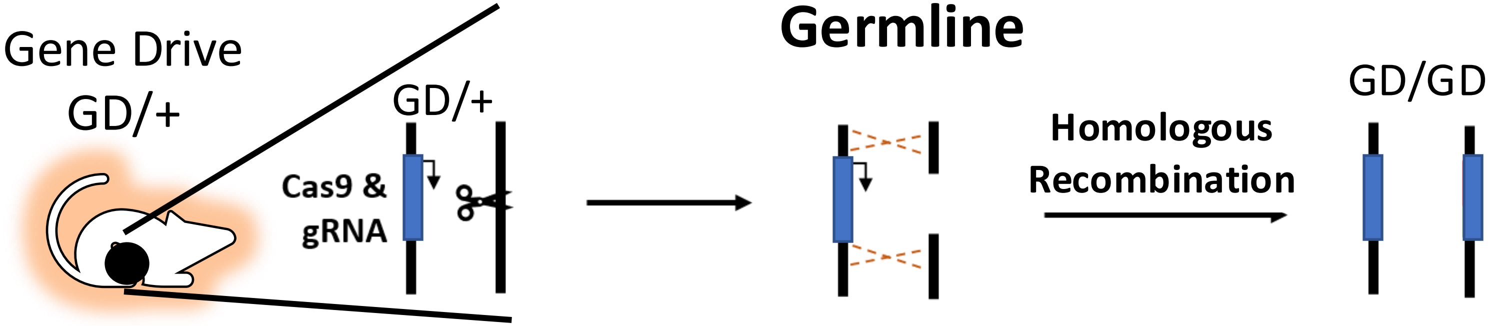
2. X-shredder/driving Y (male bias)

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

Gene Drive Development

Gene Drive Strategies

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



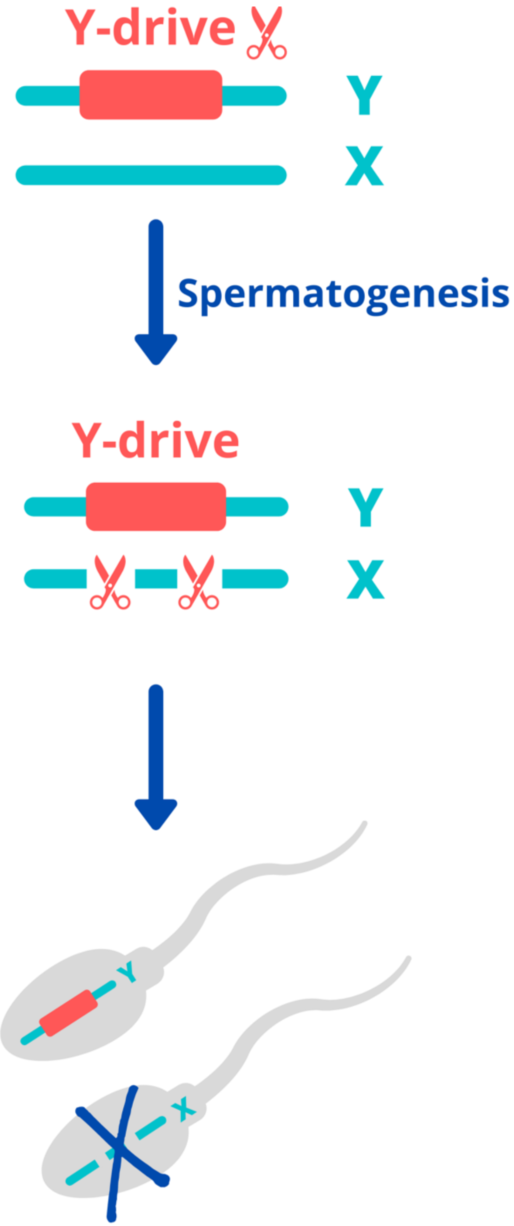
- >99% homing mosquitos but inefficient in mice
- Timing and level of Cas9 is likely to be critical

Gene Drive Development

<u>Gene Drive Strategies</u>

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

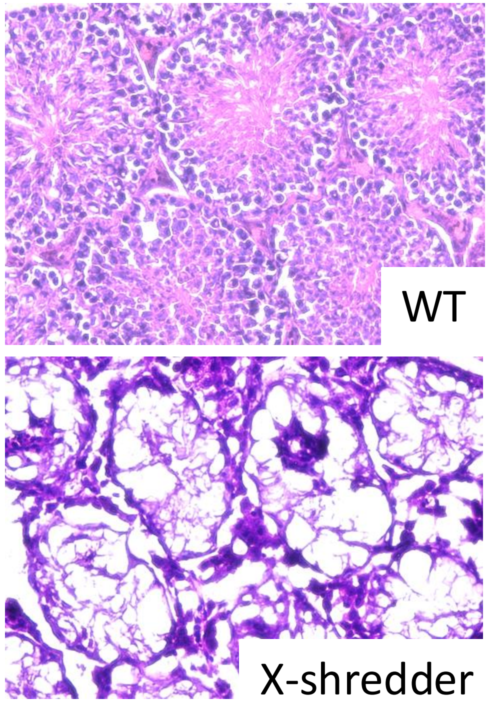
-'shred' the X-chromosome → male only → population crash



Investigating the potential of X chromosome shredding for mouse genetic biocontrol

Mark D. Bunting[1,2], Gelshan I. Godahewa[1,2,3], Nicole O. McPherson[1,2], Louise J. Robertson[1,2], Luke Gierus[1,2], Sandra G. Piltz[1,2], Owain Edwards[3], Mark Tizard[4] & Paul Q. Thomas[1,2]✉

Scientific Reports | (2024) 14:13466



Rodent genetic biocontrol - laboratory development

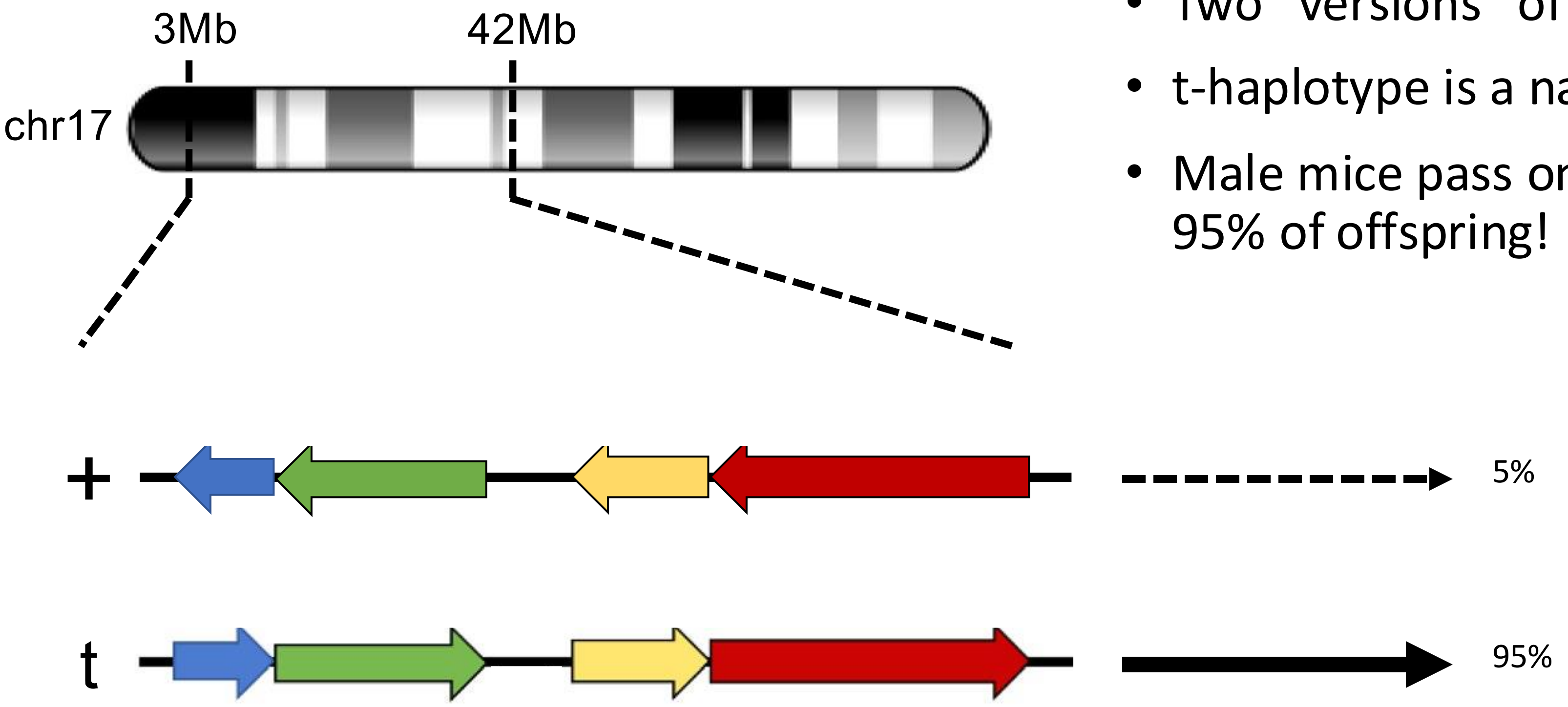
Gene Drive Strategies

1. CRISPR “homing” gene drive (female fertility)

2. X-shredder (male bias)

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

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

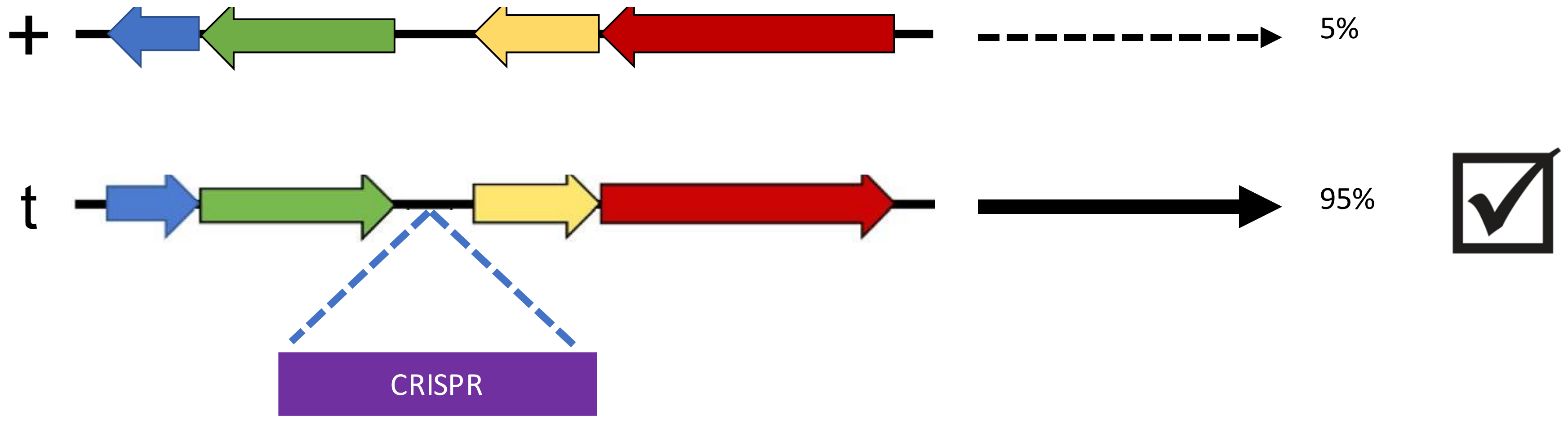


- Two “versions” of chromosome 17 in mice
- t-haplotype is a natural gene drive
- Male mice pass on the “t-haplotype” version to 95% of offspring!

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

(Arora and Dumont, 2022)

Generating t-CRISPR mice



Model framework

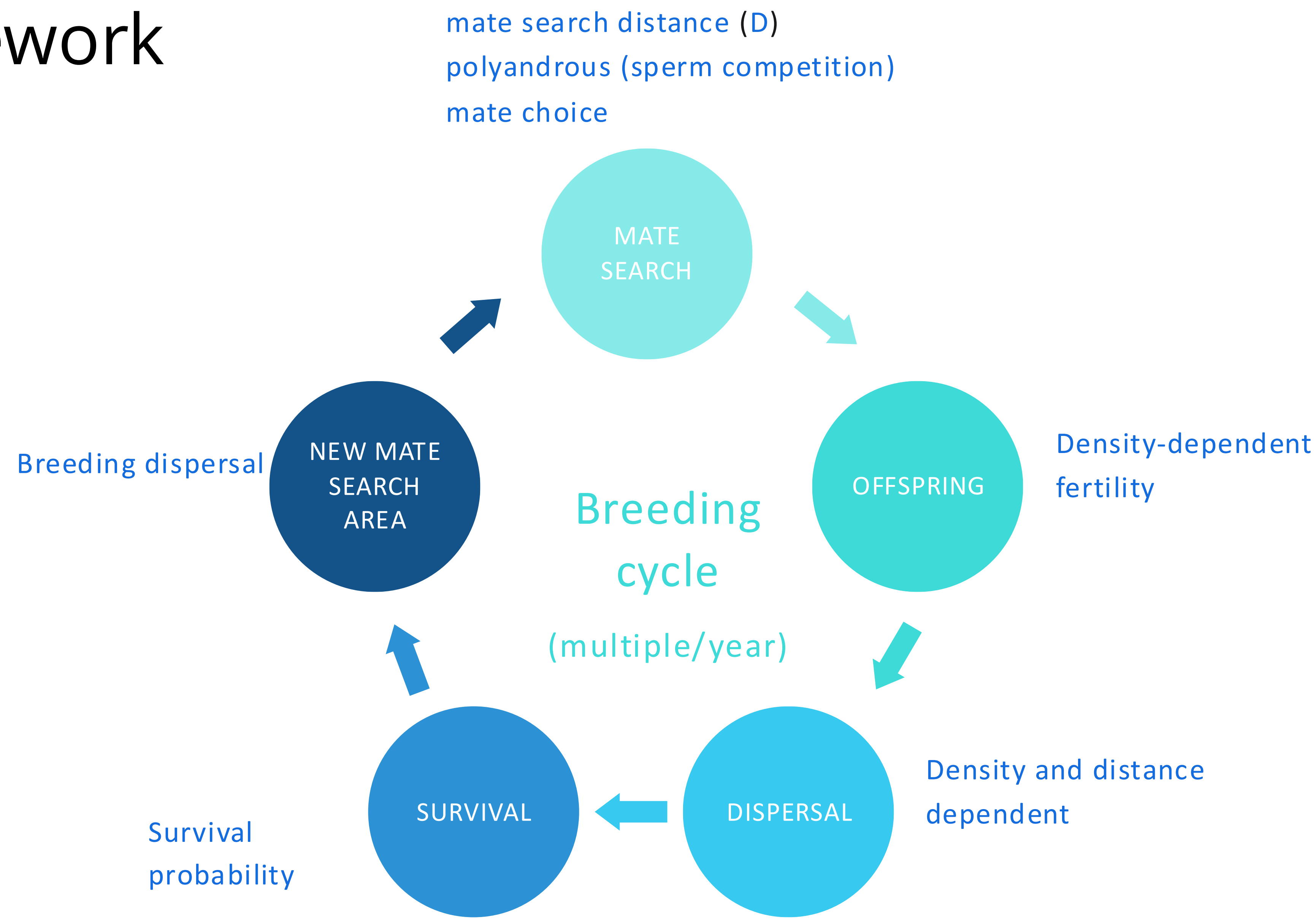
Individual based,
spatially explicit,
stochastic

Landscape

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

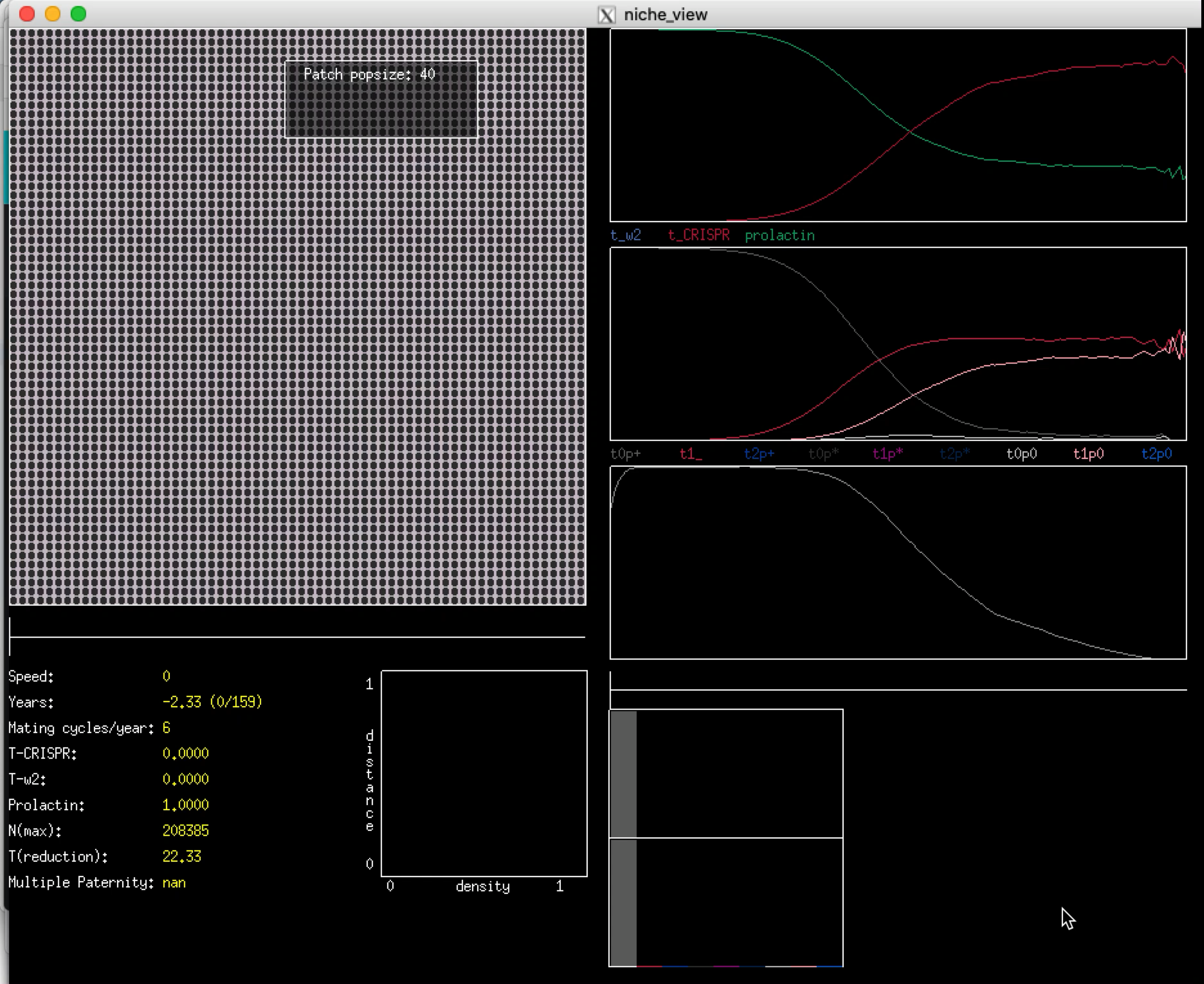
Individuals

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]

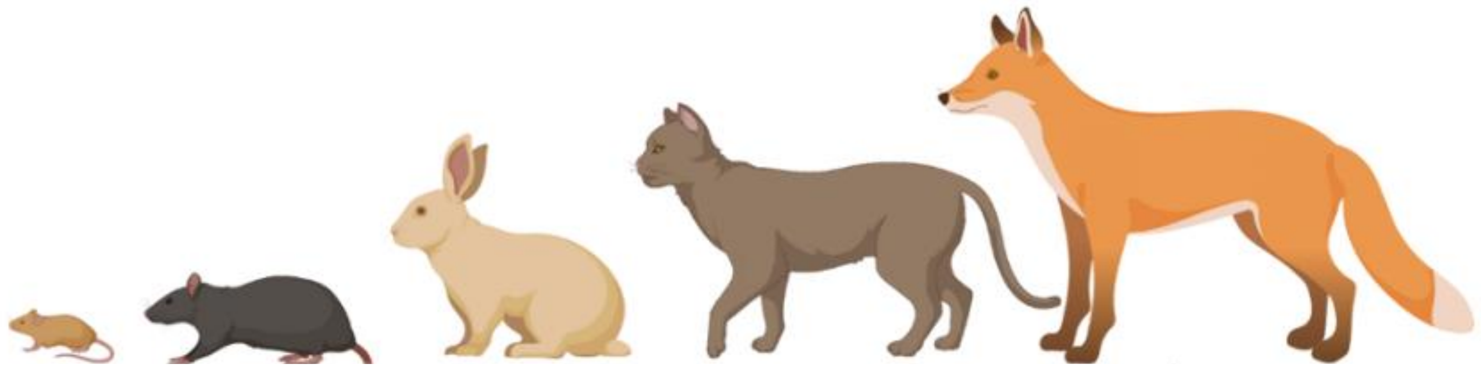
PNAS 2022 Vol. 119 No. 46 e2213308119

- First proof of concept for a mammalian gene drive
- Generating "island-specific" version (and other strategies)
- Stakeholder and regulator engagement
- International engagement (GBIRd)

What about other invasive pest mammals?

What about other vertebrates?

N ~ 200,000

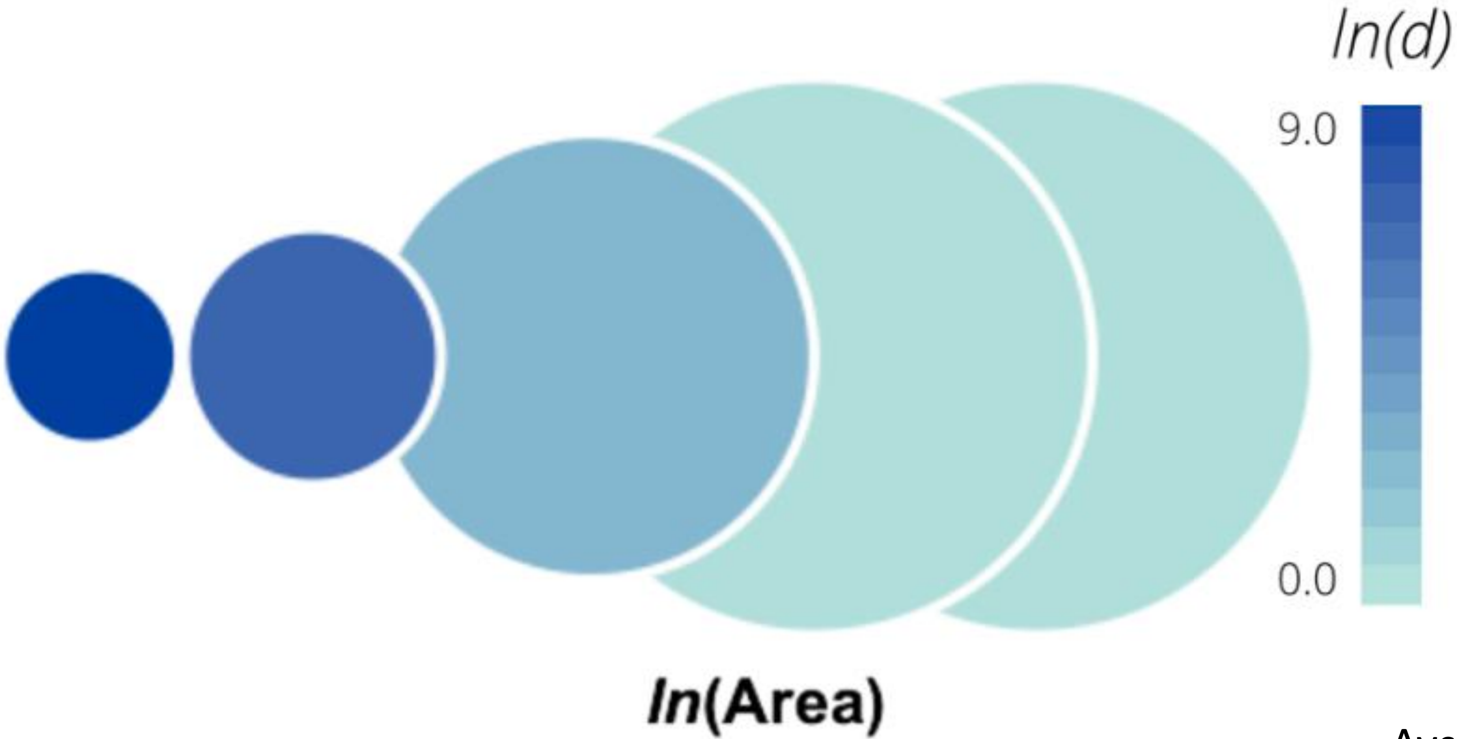


X-SHREDDER

Male biassing drive

HOMING

female infertility drive



Aysegul Birand

Life-history parameters

Survival probability

Probability of polyandry

Dispersal

Parameters:

Species	b	n_c	age_m	ω	p_m	d	A	Δ_i	D
mouse	6	6	2	0.53	0.46	5000	40	0.4	3
black rat	4	6	2	0.62	0.68	1000	200	2	8
rabbit	4	4	3	0.82	0.20	25	8000	12.5	8
cat	4	2	5	0.85	0.25	2	100000	25	4
fox	4	2	5	0.88	0.76	2	100000	45	8

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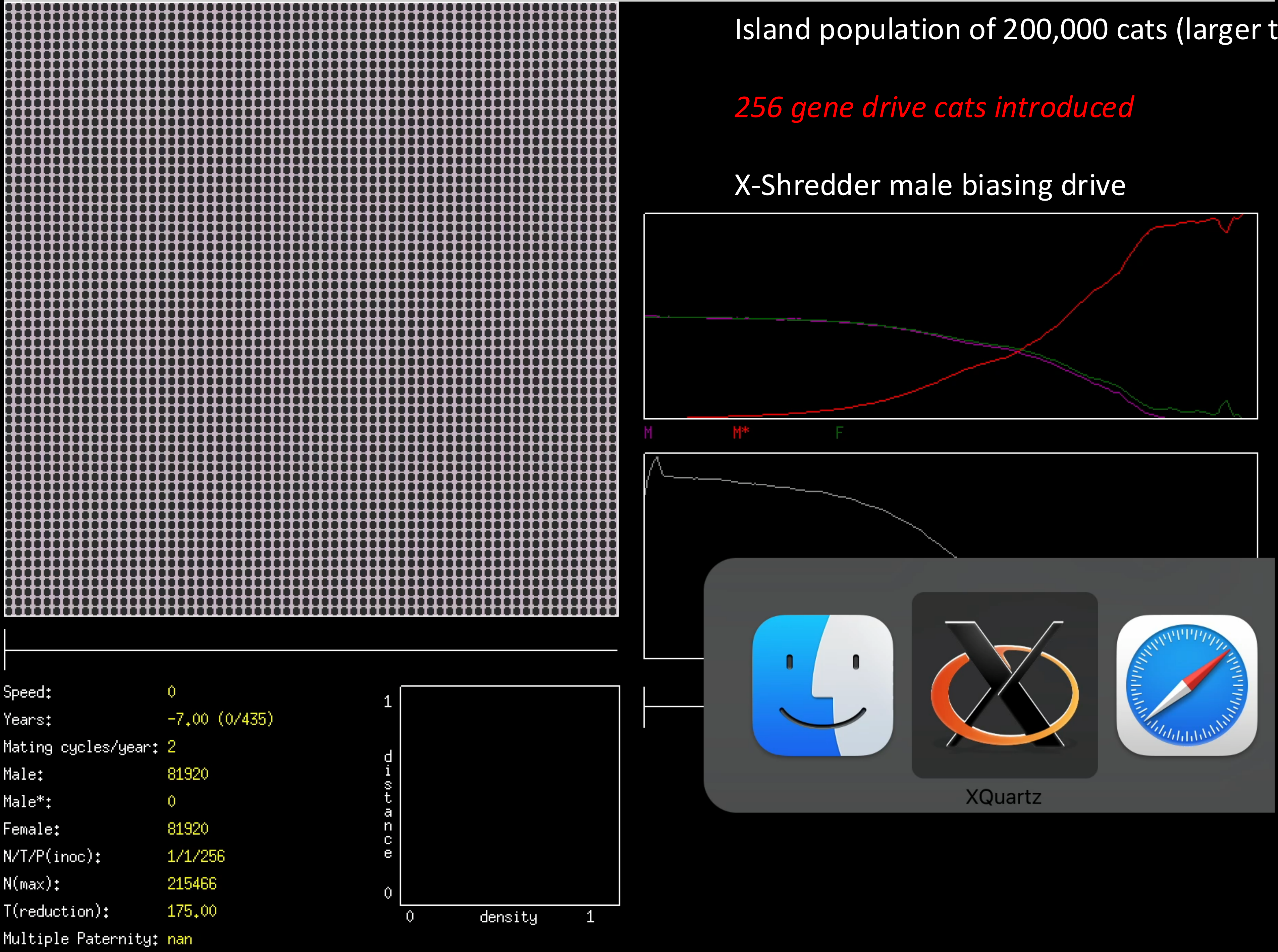
Island population of 200,000 cats (larger than Tasmania)

256 gene drive cats introduced

X-Shredder male biasing drive



Eradication is much slower than mice…

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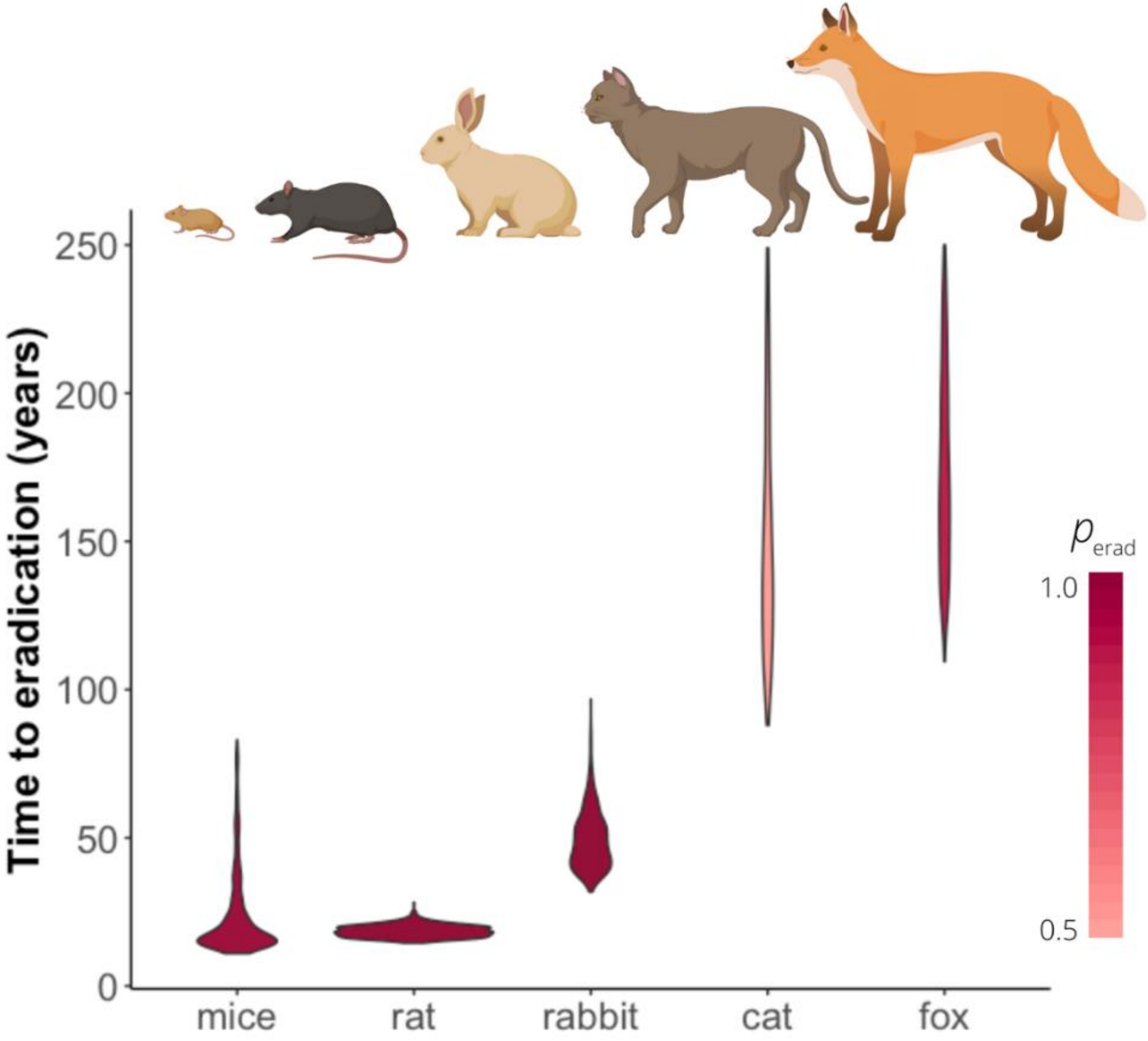
Results

(1000 sim.
per species)



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

Birand et al. 2022 NeoBiota 74: 93-103

Aysegul Birand

Conclusions and Challenges

Genetic biocontrol (gene drive) technology is progressing in insects and mice – potential for disease control, conservation and agriculture

-stakeholder engagement, regulation, technical hurdles (inc. target population specificity)

- “safety switch” to prevent suppression of non-target populations (e.g. native range)

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)

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

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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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THE UNIVERSITY of ADELAIDE

SUB CRUCE LUMEN

SAHMRI
South Australian Health & Medical Research Institute

Thomas lab

paul.thomas@adelaide.edu.au