Fighting biodiversity loss with gene drive tools

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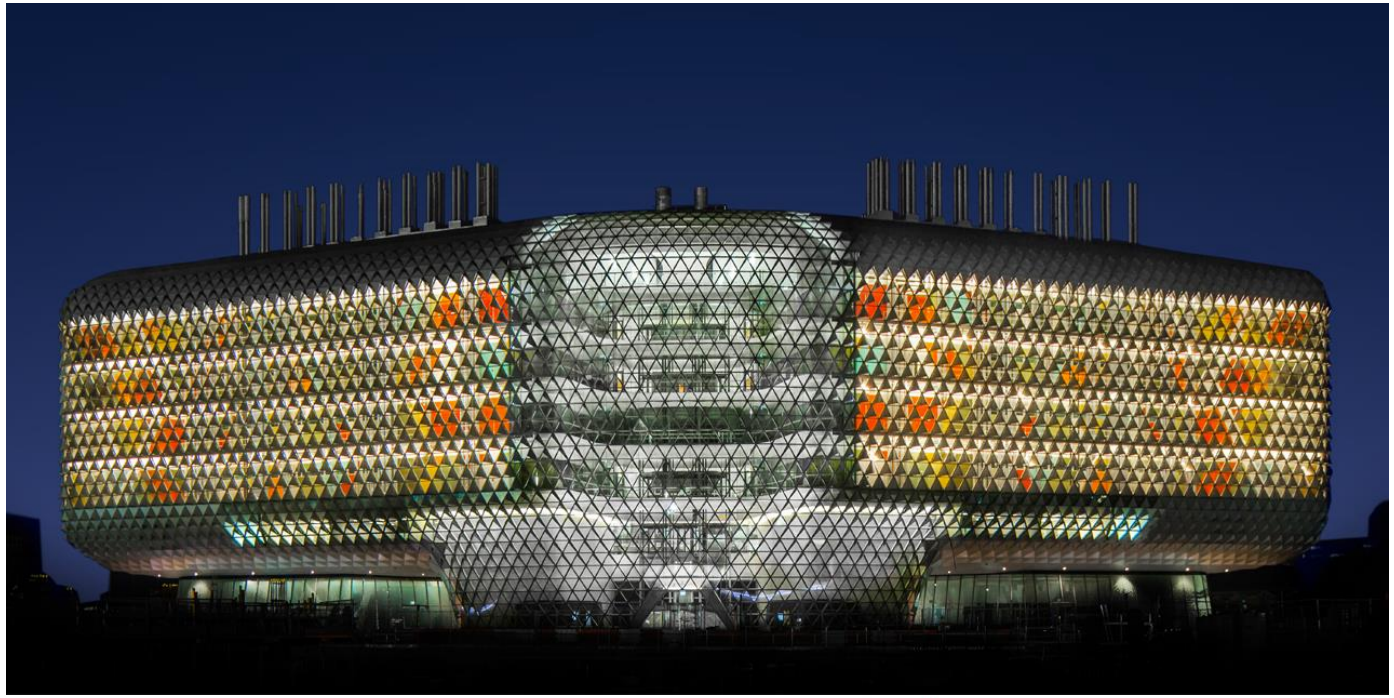


THE UNIVERSITY of ADELAIDE

SUB CRUCE LUMEN

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.

Why develop gene drives in rodents?

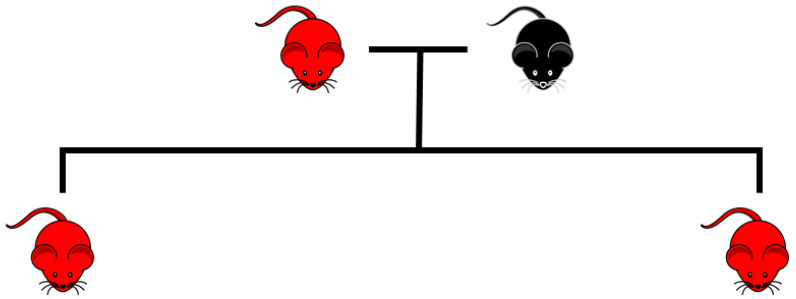
(Peter Brown, CSIRO)

Environmental damage/loss of biodiversity
Devastation of bird nesting sites
Baits are toxic (secondary poisoning), expensive and population limited

What is a Gene Drive?

- Genes come in pairs – one copy from each parent
- Transmission to next generation is determined by a coin toss
- Gene drives are natural or synthetic genetic modifications
- Gene drives have **enhanced** inheritance (like a coin with 2 heads)

Gene drive mouse



Mice are the ideal species to start building vertebrate gene drives

- Non-lethal
- Landscape scale
- Species-specific

Gene drive development in mammals

Gene Drive Strategies

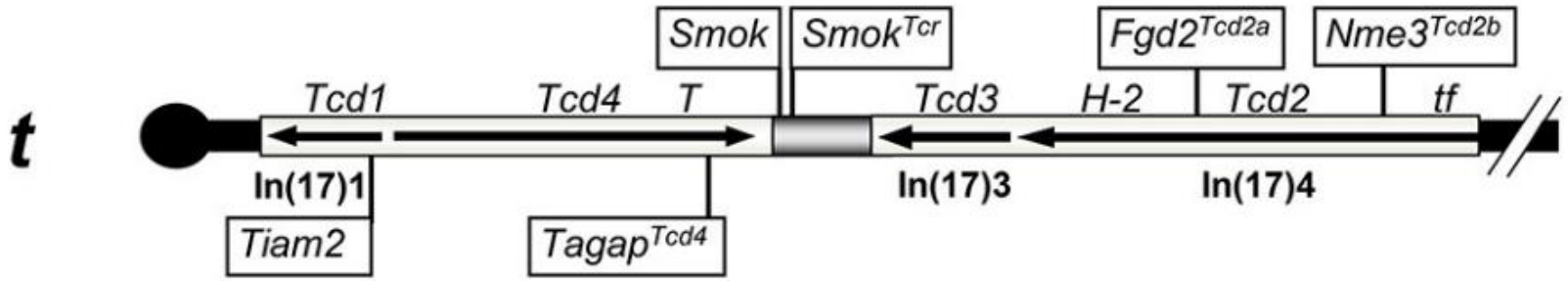
1. CRISPR “homing” gene drive (female fertility)
   - ”homing” is inefficient in mice

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

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

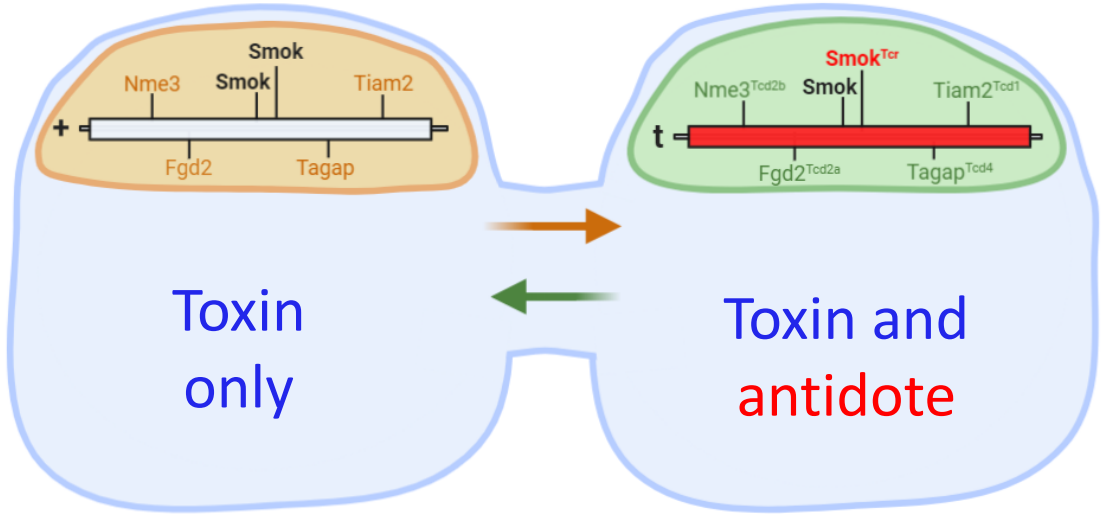
The *t* haplotype – a natural meiotic drive in male mice

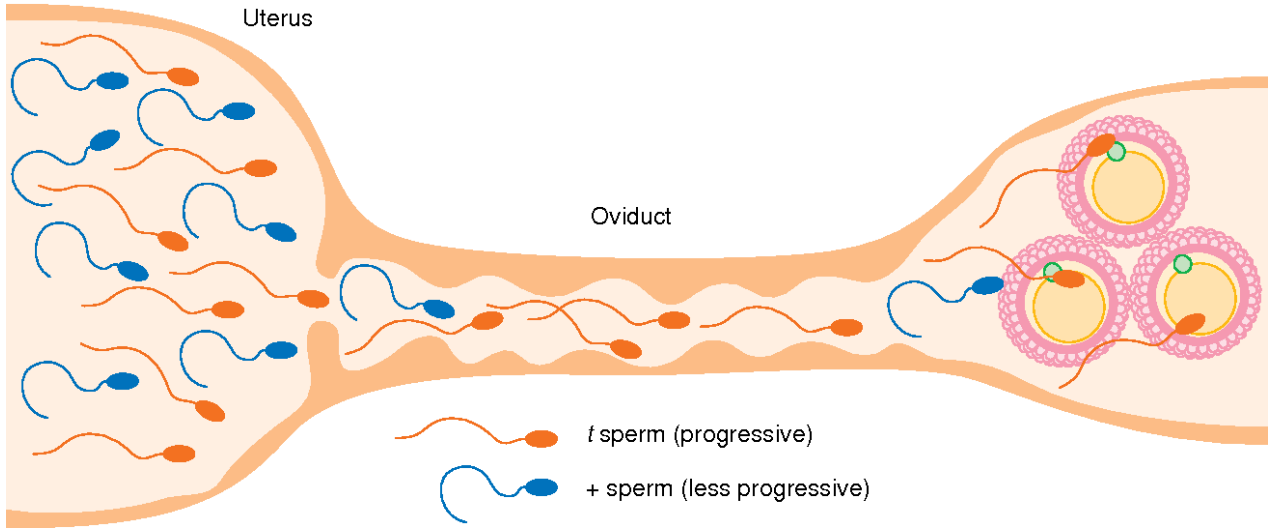
- Locus discovered in 1927 (still somewhat mysterious!)
- *t* haplotype is a naturally occurring meiotic drive on chromosome 17 (40Mb) (only in mice)
- Manipulates spermatogenesis by a toxin-antitoxin system
- Male heterozygotes pass on up to 95% (females 50%) (t^{w2})
- Male homozygotes infertile (t^{w2})



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

Developing sperm





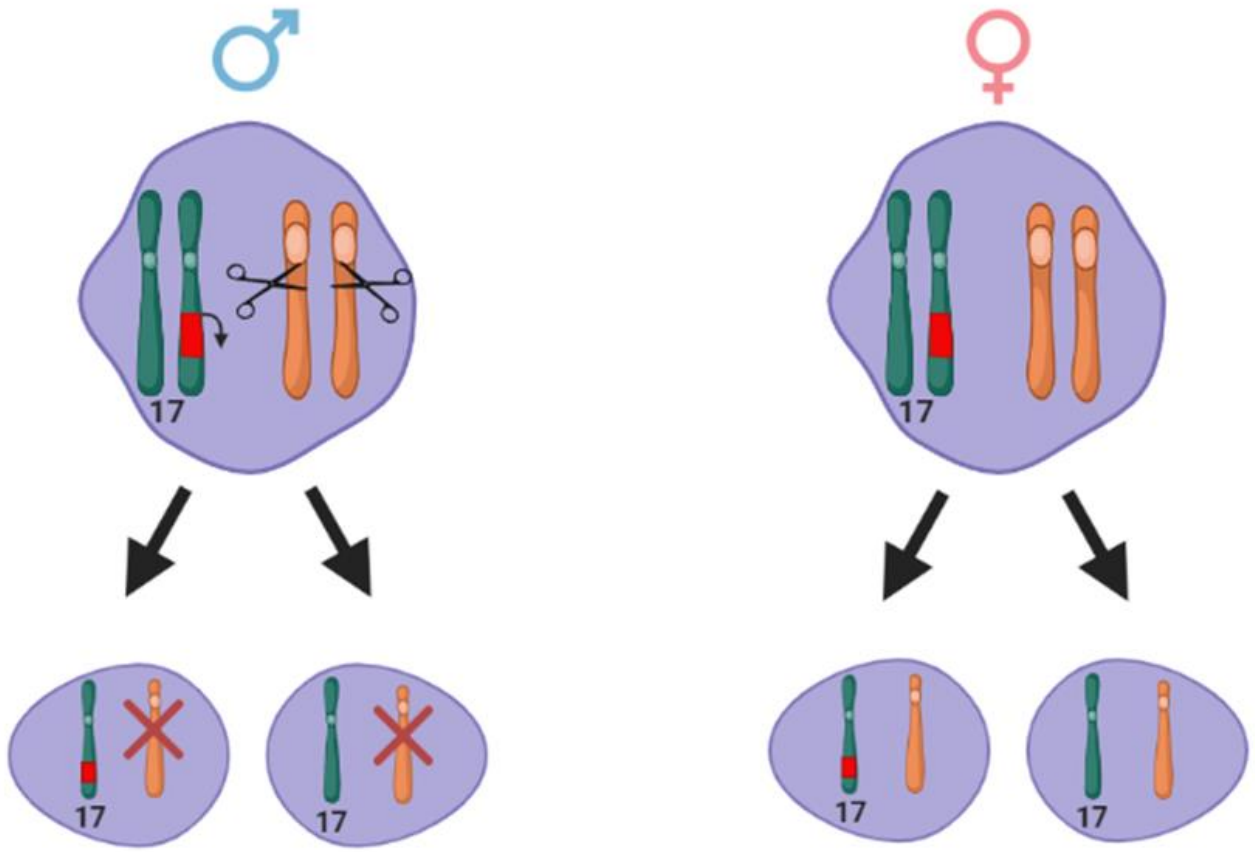
Olds-Clarke et al 1997

Motility ☹ Motility ☺

t-haplotype carrying sperm outcompete (WT) Chr 17 carrying sperm from the same male

t-haplotype carrying sperm are not as fit as WT sperm from WT (non-carrier) mice

t-CRISPR strategy – using males to spread a female infertility mutation



Transmission

T	95%	5%	50%	50%
Fertility mutation	100% (80%)	100% (80%)	0%	0%

_t_-CRISPR features

Males transmit *t*-CRISPR to 95% of offspring

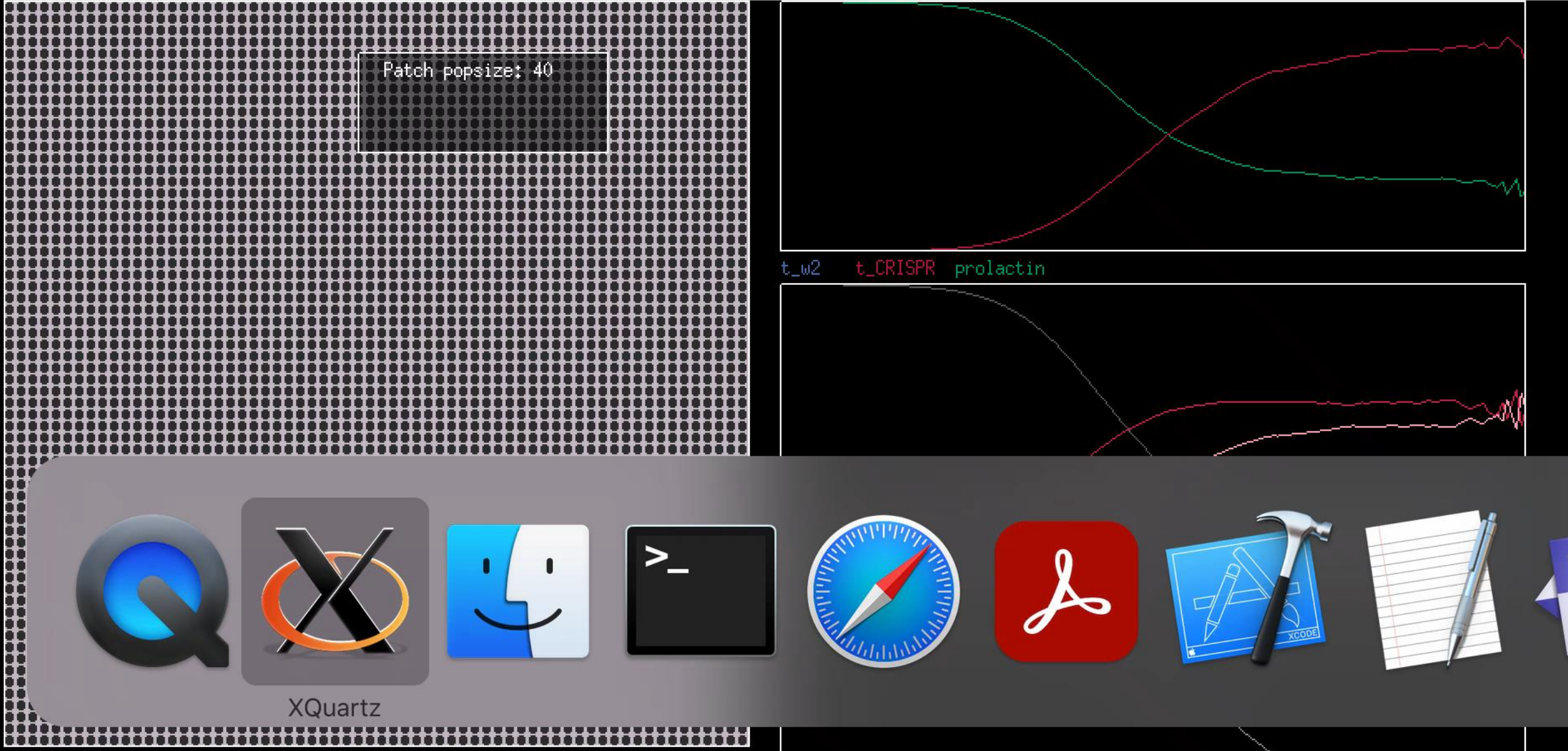
CRISPR generates KO mutations in female fertility gene (*Prl*)

Prl homozygous females are sterile

t-CRISPR homozygous males are sterile

t-CRISPR homozygous females are fertile

Gierus, Birand et al (2022) PNAS



256 t-CRISPR mice into 200,000

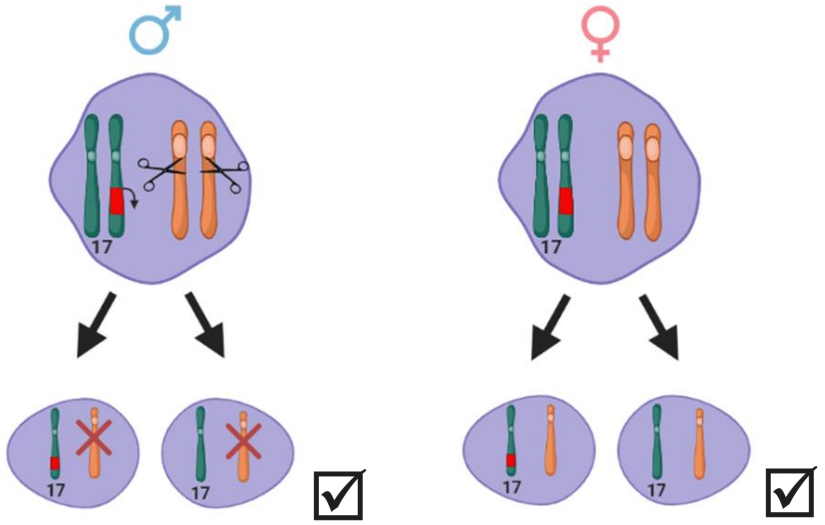
t-CRISPR Summary

Males

- *t* transmission of ~95% (not reduced by transgene insertion)
- *Prl* indel of ~80% (sperm)

Females

- t transmission of ~50%
- No Prl indels



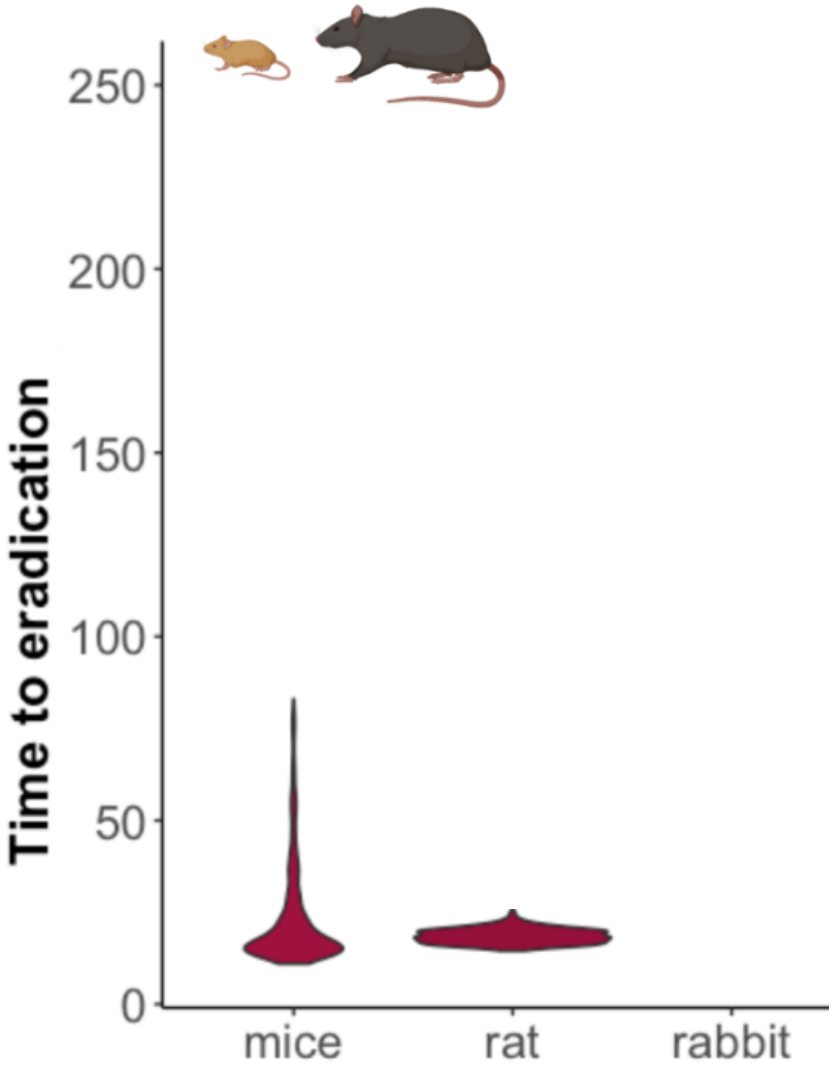
☑ **t-CRISPR strategy proof of concept (first for vertebrates)**

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

Beyond mice: potential for genetic biocontrol in mammals



t-CRISPR is mouse-specific → new transferable approaches

Time to eradication for mice and rats is very similar

Birand et al. 2022 NeoBiota 74: 93-103

Aysegul Birand

Conclusions and future work

Investigated 3 different genetic strategies for rodent suppression

- *t*-CRISPR → first validated genetic biocontrol strategy for mouse population suppression
- Generating and validating safe (targeted) version gene drives is essential
- Gene drive have potential beyond mice → develop transferable strategies for other pest mammals (e.g. rats)
- Stakeholder and Regulator engagement is key

Acknowledgements

Genetic Biocontrol
Luke Gierus
Gelshan Godahewa
Louise Robertson
Mark Bunting

Modeling (Adelaide Uni)
Aysegul Birand
Thomas Prowse
Josh Ross
Phill Cassey

Robinson Research Institute
Nicole McPherson

CSIRO
Kevin Oh
Owain Edwards
Mark Tizard

SAGE
Sandie Piltz
Melissa White

GBIRd consortium
(AUS/USA/NZ)

***t* mice**
David Threadgill
John Godwin

Gene Drive Funding
PFNZ2050 & CAGT Ltd
Australian Research Council Linkage Grant with CAGT Ltd. (NZ)
Australian Research Council Discovery Grant
CSIRO Post-doctoral Fellowship
NSW and **SA** State Governments

Thomas lab 2023