Genetic Biocontrol of Invasive Rodents Program

Innovative Development for Preventing and Responding to Extinction Threats, Pandemics and Food Insecurity

Pandemic Prediction and Forecasting Science and Technology Working Group

February 22, 2017

CSIRO

ISLAND CONSERVATION
Preventing Extinctions

LANDCARE RESEARCH
MANAAKI WHENUA

NC STATE UNIVERSITY

A&M

USDA

SUB CRUCE LUMEN
THE UNIVERSITY of ADELAIDE

Key Points

Invasive species - rodents

- Impact health, environment, food, economy

Gene drives - naturally occurring and manufactured

Robust program development

- US, AU, NZ partnership
- Shared values

Invasive Species

Defined as…

An organism… that occurs outside of its natural range…whose introduction causes or is likely to cause economic or environmental harm, or harm to human, animal, or plant health.

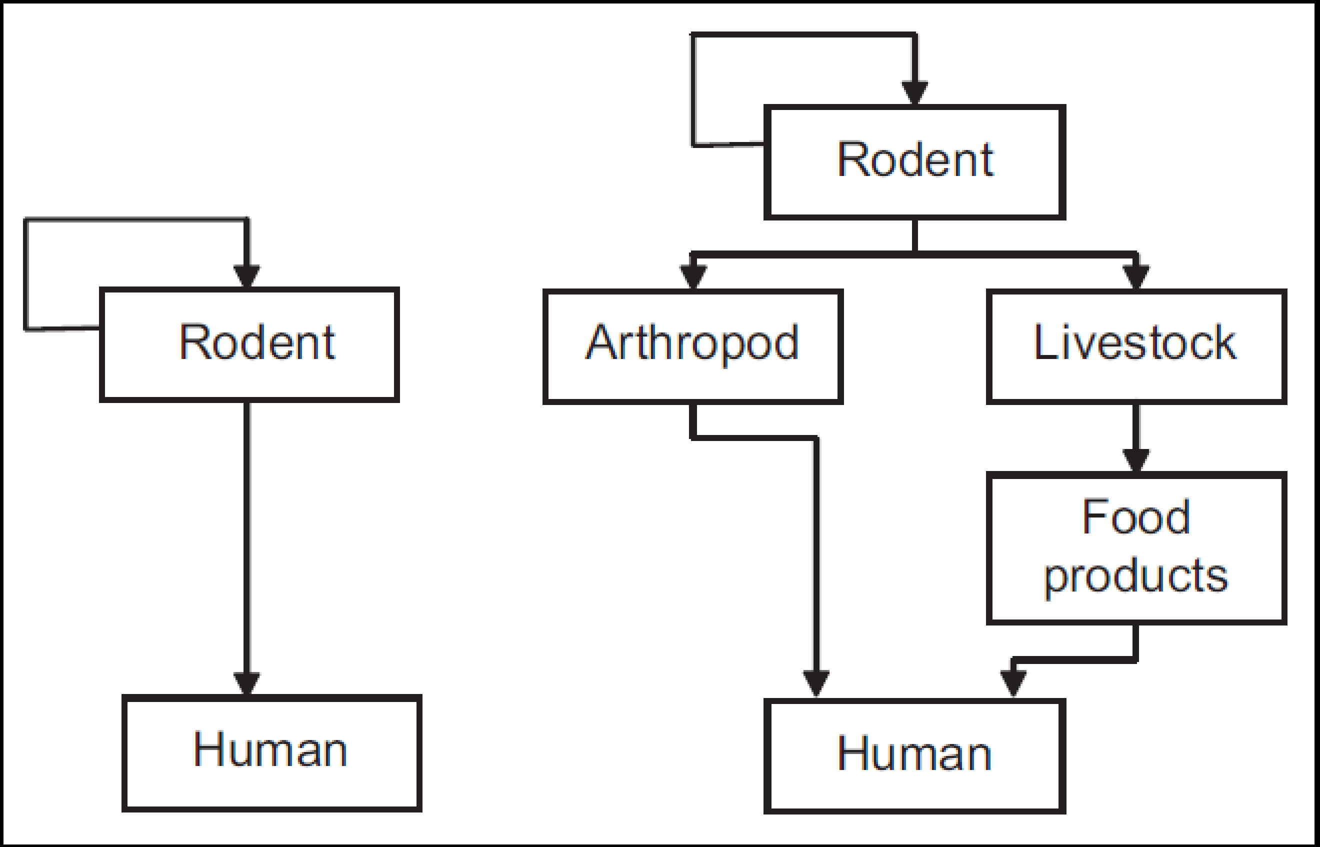
Executive Order 13751

Health Impacts

N.Y. / REGION

Rare Disease Strikes a Bronx Area All Too Familiar With Rats

By MARC SANTORA and NOAH REMNICK FEB. 15, 2017



This is an official

CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
January 24, 2017, 14:00 ET (2:00 PM ET)
CDCHAN-00400

Investigation of Seoul Virus Outbreak Associated with Home-based, Rat-breeding Facilities in Wisconsin and Illinois

ARTICLE

EXPOSURE TO URBAN RATS AS A COMMUNITY STRESSOR AMONG LOW-INCOME URBAN RESIDENTS

Danielle German and Carl A. Latkin
Johns Hopkins Bloomberg School of Public Health

Gene Drives

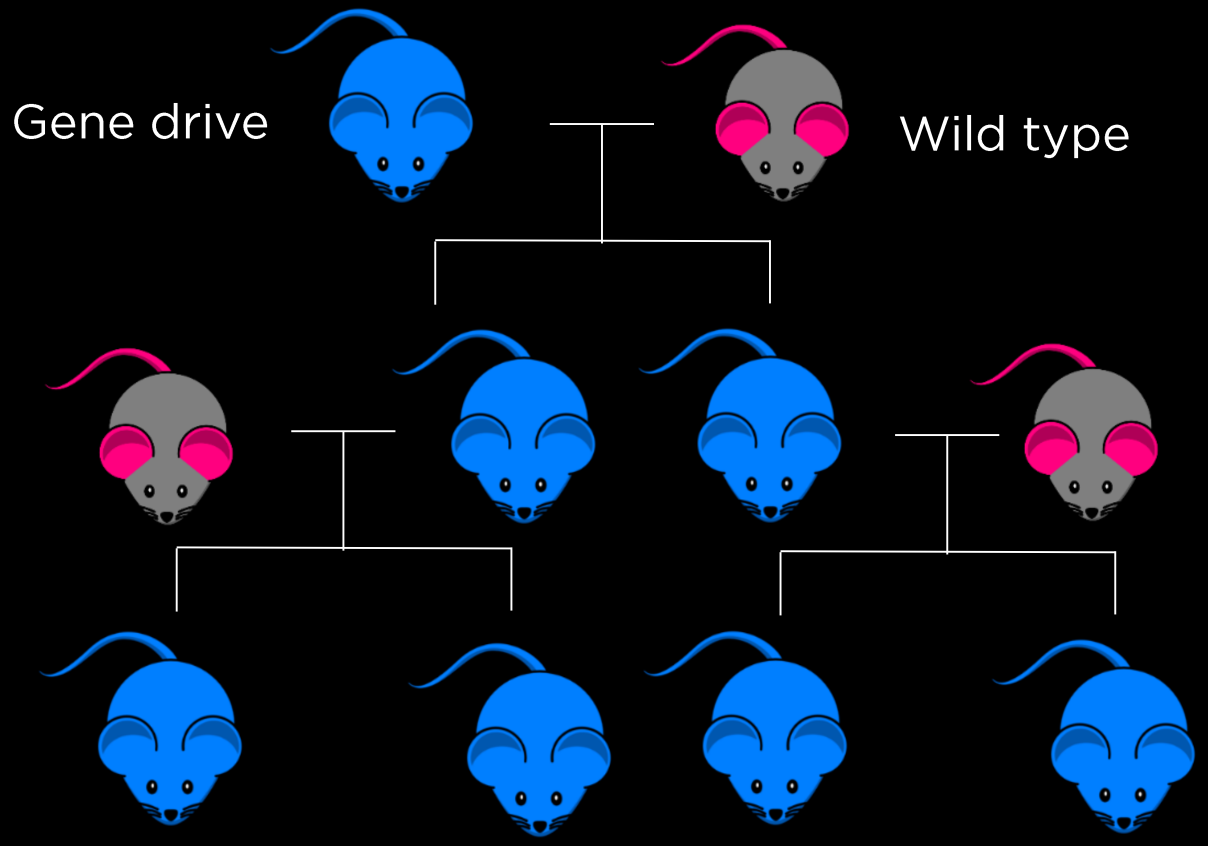
Gregor Mendel described ‘selfish genes’ in 1860

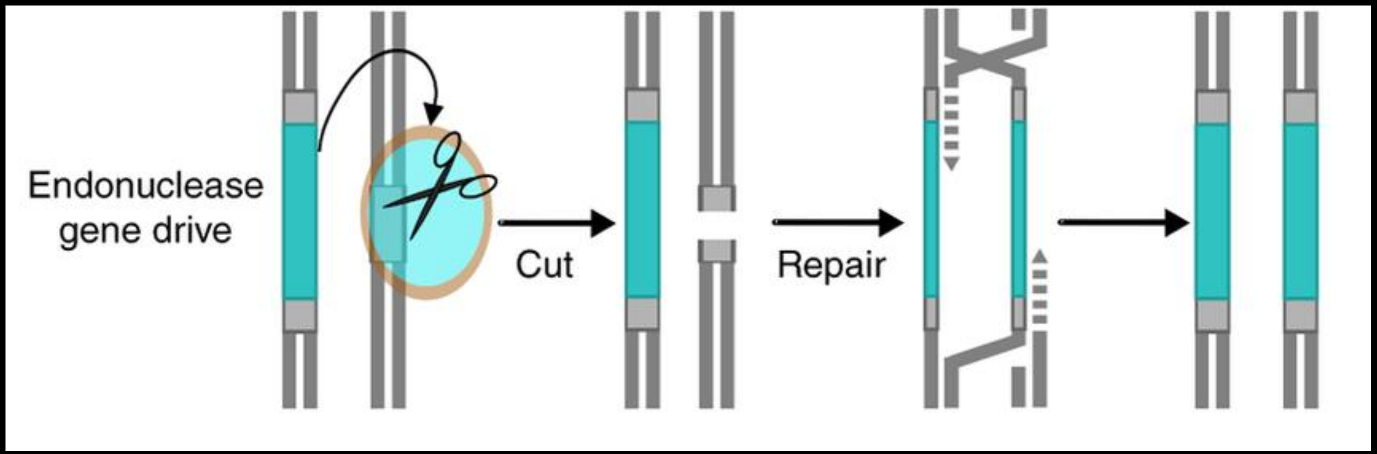
‘Selfish’ P element

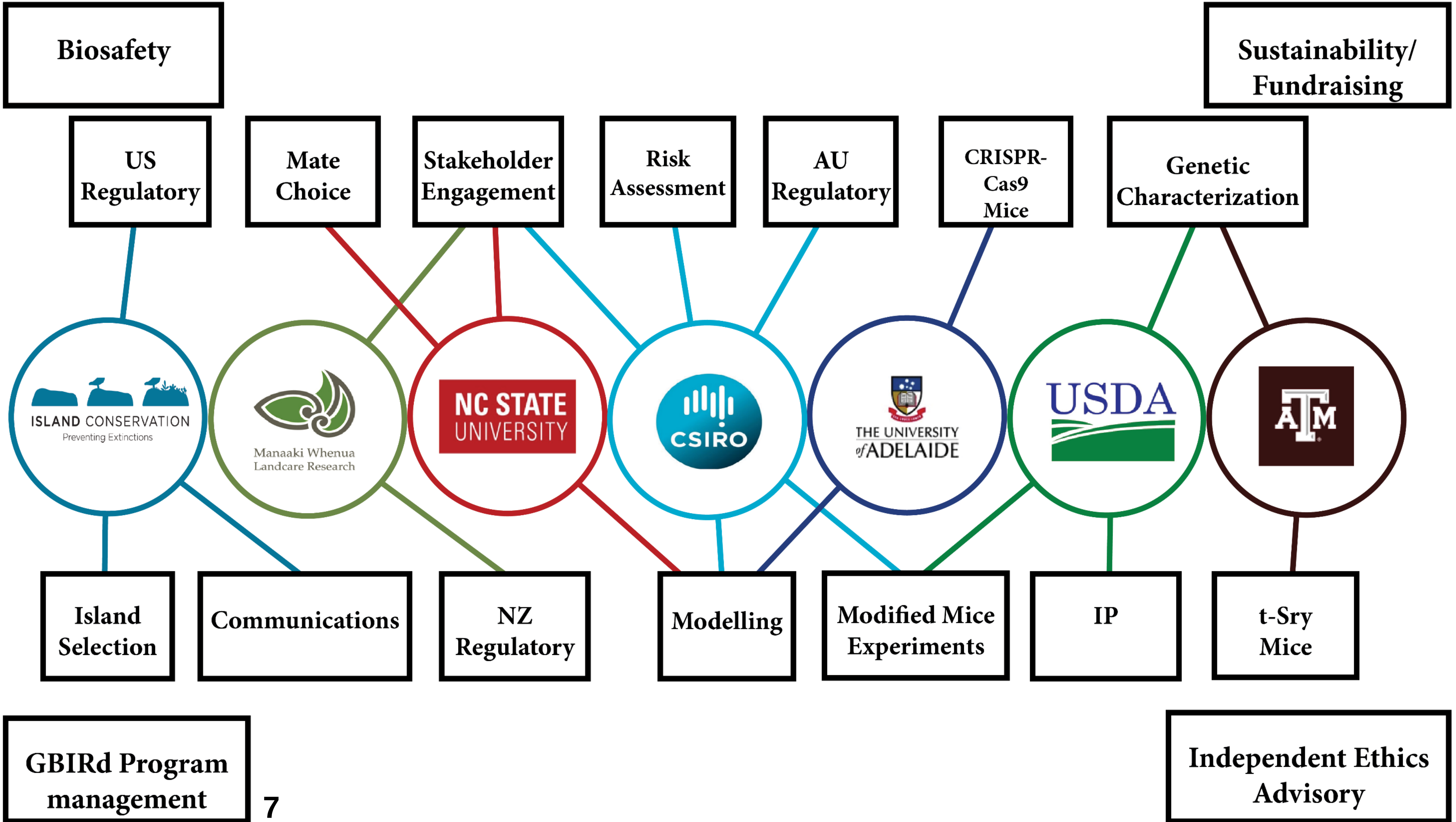
Proposal to link selfish elements to ‘Gene drives’

Gene Drives

- Cause genes to be inherited more frequently than normal – up to 100%
- Sexual reproduction
- Ability to modify wild populations *by design*
  - Insert new, modify or delete genes
- CRISPR-Cas9





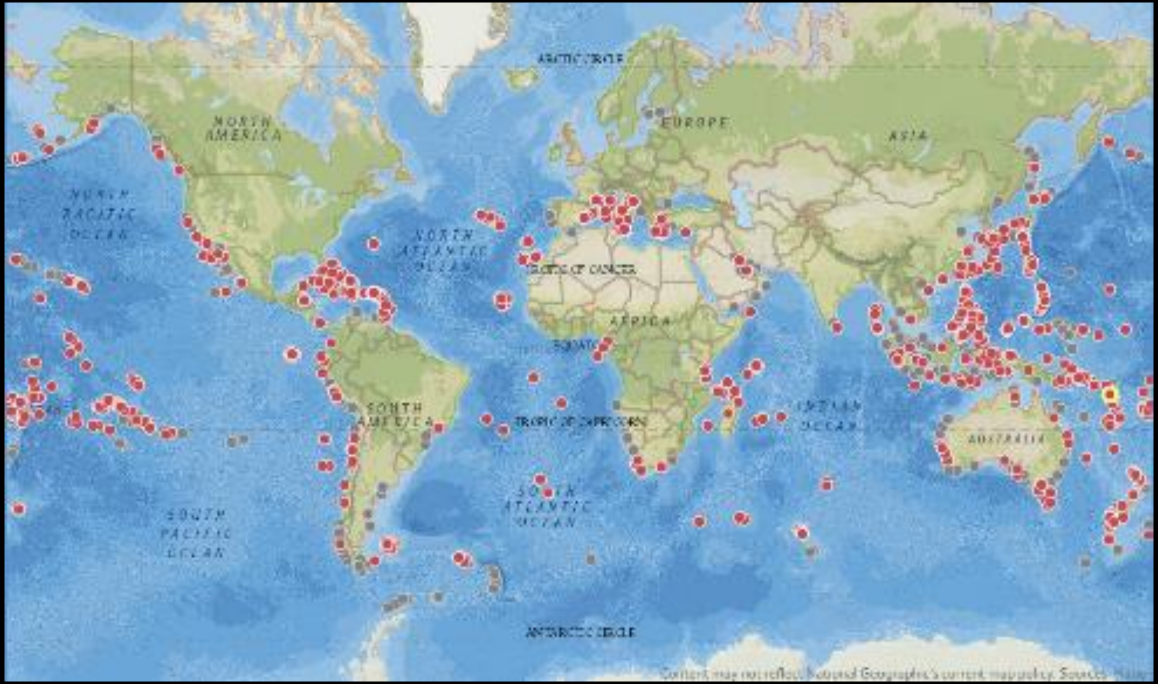


Biosafety
Sustainability/ Fundraising
US Regulatory
Mate Choice
Stakeholder Engagement
Risk Assessment
AU Regulatory
CRISPR-Cas9 Mice
Genetic Characterization
ISLAND CONSERVATION
Preventing Extinctions
Manaaki Whenua Landcare Research
NC STATE UNIVERSITY
CSIRO
THE UNIVERSITY of ADELAIDE
USDA
ATM
Island Selection
Communications
NZ Regulatory
Modelling
Modified Mice Experiments
IP
t-Sry Mice
GBIRd Program management
Independent Ethics Advisory

Environmental Impacts

Invasive rodents

- 4 species impact 88% of critically endangered & endangered vertebrate species on islands
- Linked to 30% of all extinctions in last 500 years
- Cascading effects
- Ecosystem services



DIISE 2015, Doherty et al. 2016

Food Security Impacts

- US suffers >$19bn in agricultural losses from invasive rodents

- Globally, 280 million undernourished people could benefit if pre- and post-harvest losses by rodents were reduced

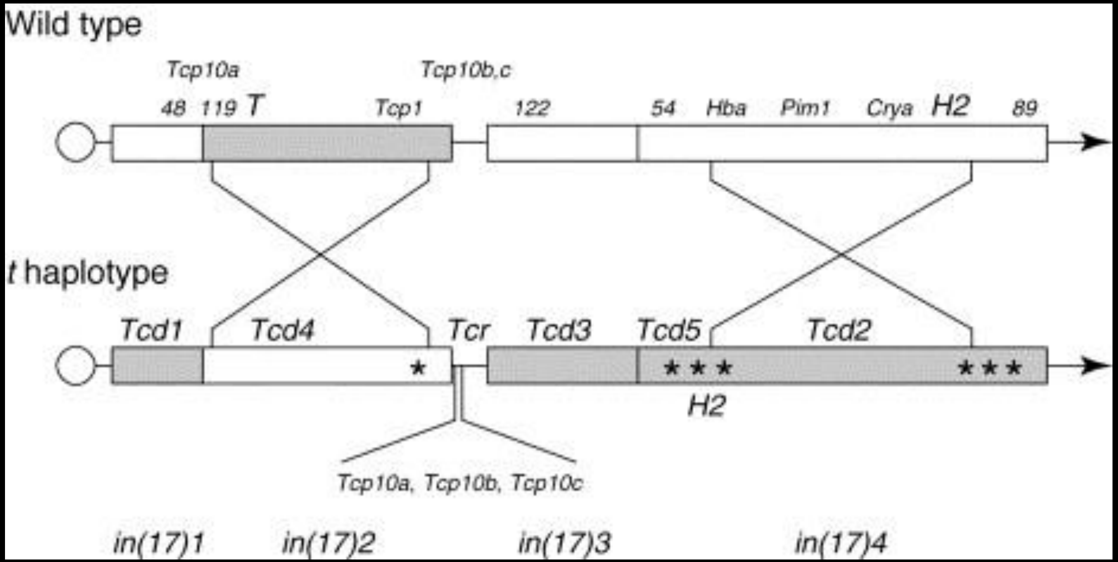
Meerburg et al. 2009, Pimentel et al. 2005

Conventional rodent control

- Usually involves lethal control techniques (poisoning, trapping)
- Issues:
  - Cost of repeat application
  - Limited effectiveness at low density
  - Environmental contamination
  - Animal welfare
  - Non-target effects on other species
  - Inaccessible to low income families

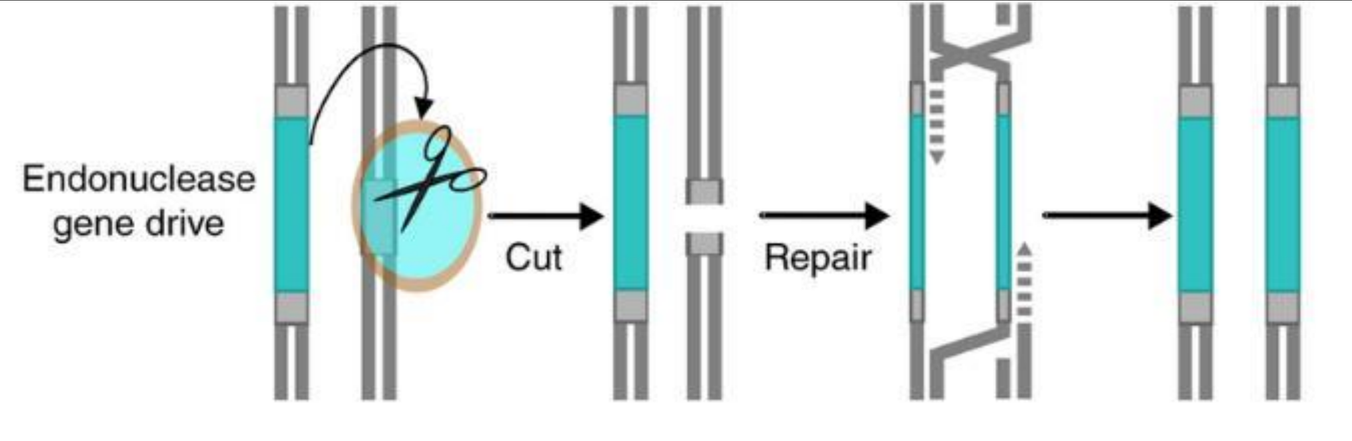
Gene Drive

T-Complex – natural



93.6% n = 1178

CRISPR/Cas9 - manufactured



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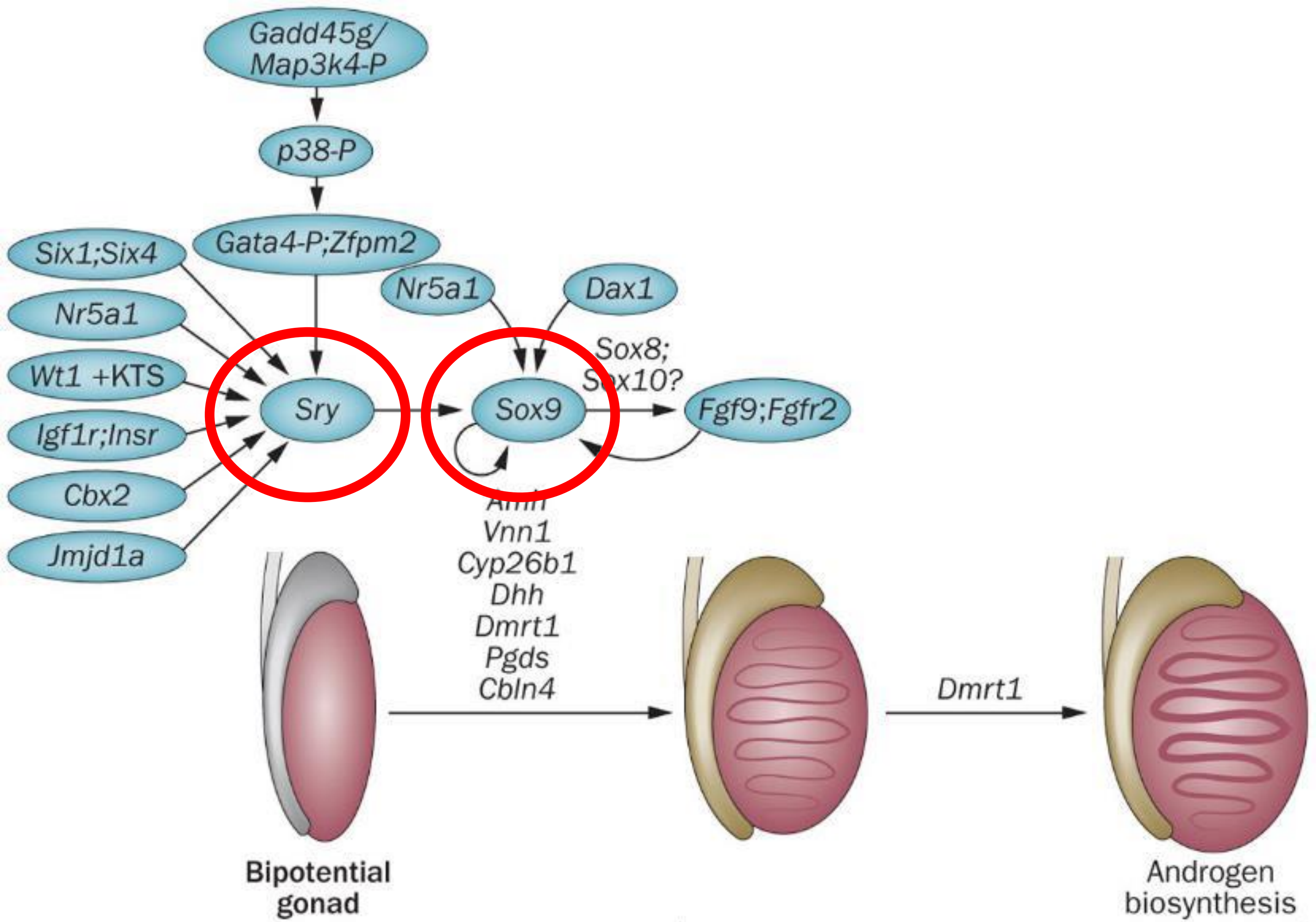
Mammalian Sex Determination

Bias sex ratio

- *Sry*
- *Sox9*

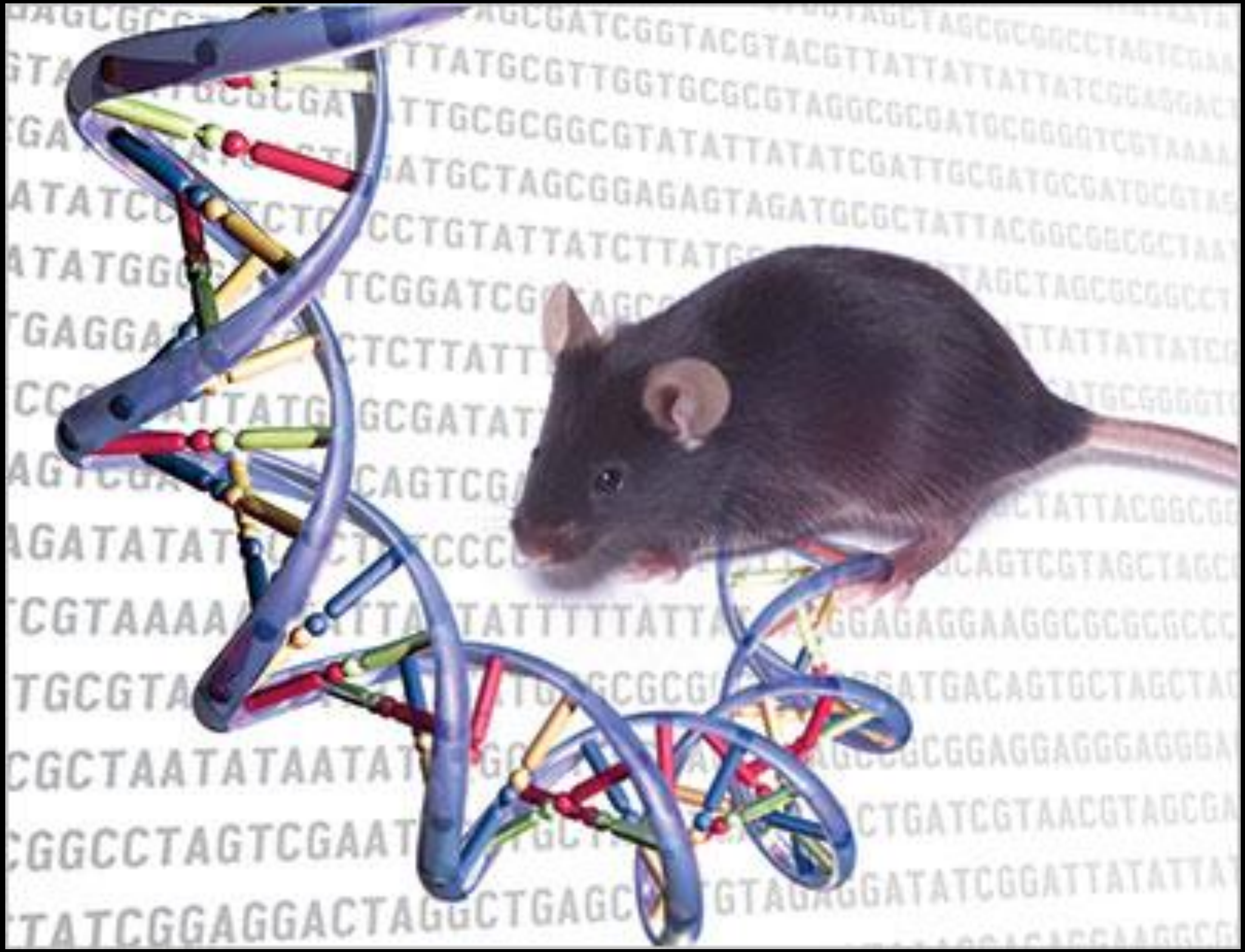


Eggers *et al.* 2014

Technical approach - Start with mice

- Model vertebrate for genetics
- Short generation-time
- Are small and husbandry is straight-forward
- Invasive in many countries

Technology platform



Risks – actively looking for deal-breakers

Doesn’t drive; unstable, not target specific

- Multiple approaches underway
- Biosecure trials and modelling

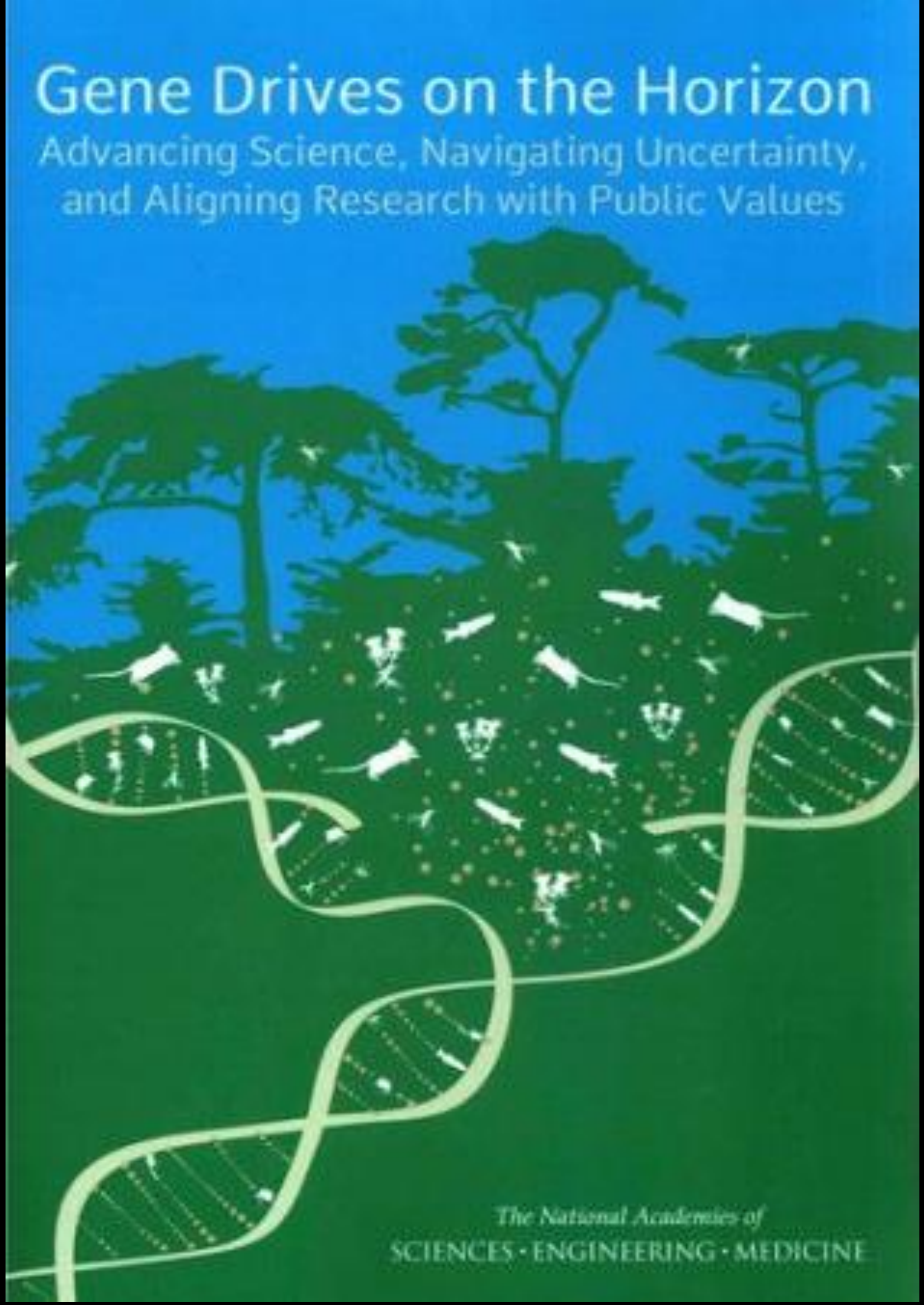
Unwanted geographic spread

- Target private alleles not present in native populations

Socio-political unacceptance

- Proactive inclusive approach underway

No deal breakers identified yet

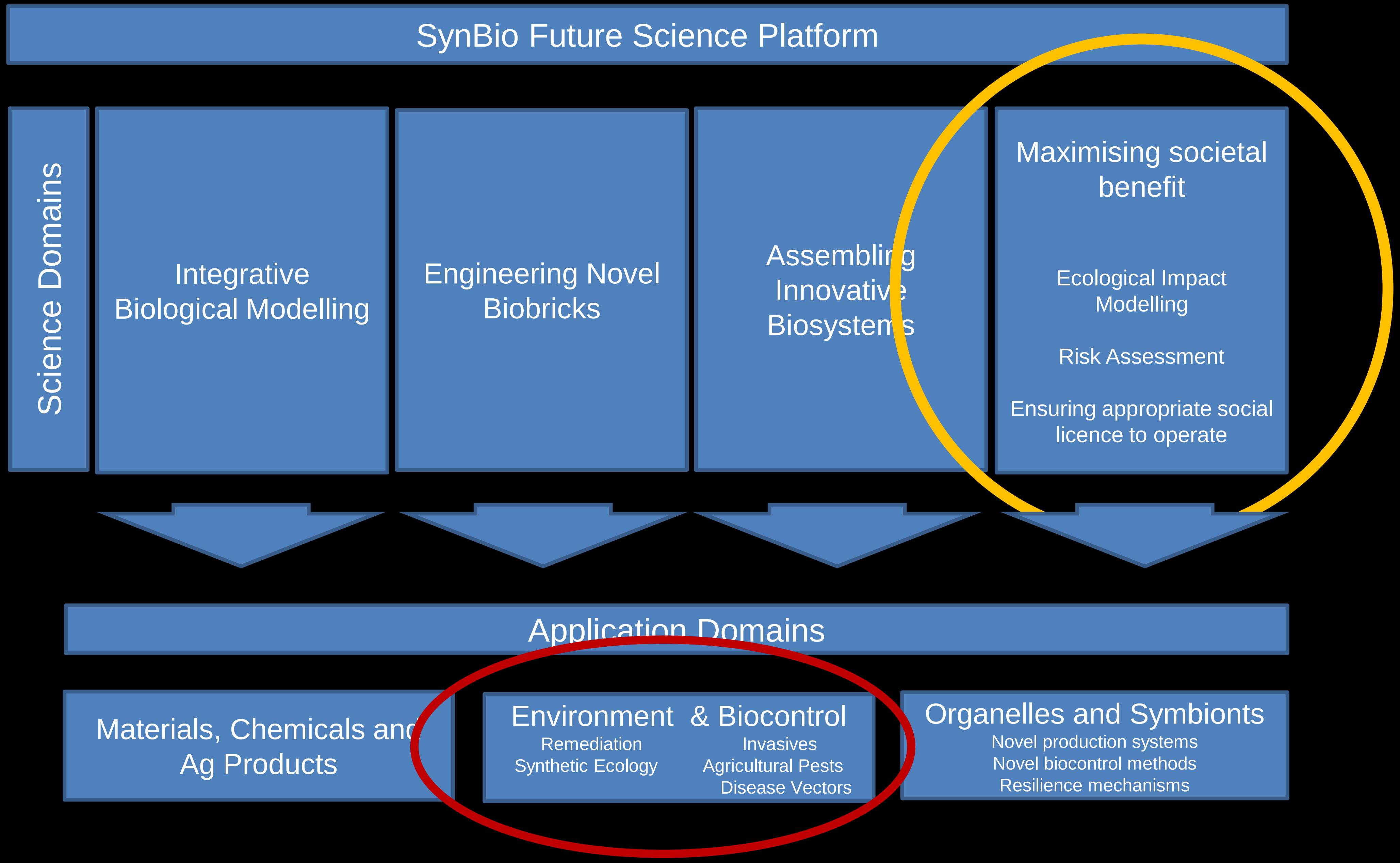


NASEM 2016; Kaebnick et al. 2016

Leverage biology

- Population ~1000 house mice
- Released 42 male & 35 female mice from Eday Island
- After 18 months, all mice trapped were hybrids (n=70)
- Males were disproportionately responsible for 'invasion'
- Leverage biology and promiscuity

Berry et al. 1991; Jones et al. 1995; Scriven 1992


SynBio Future Science Platform
Science Domains
Integrative Biological Modelling
Engineering Novel Biobricks
Assembling Innovative Biosystems
Maximising societal benefit
Ecological Impact Modelling
Risk Assessment
Ensuring appropriate social licence to operate
Application Domains
Materials, Chemicals and Ag Products
Environment & Biocontrol
Remediation
Synthetic Ecology
Invasives
Agricultural Pests
Disease Vectors
Organelles and Symbionts
Novel production systems
Novel biocontrol methods
Resilience mechanisms

Consultation with Australian Regulators

Australian Government
Department of Health
Office of the Gene Technology Regulator

CSIRO

Australian Government
Australian Pesticides and Veterinary Medicines Authority

CSIRO-RSN Symposium on the Use of Gene Drive Technology in Controlling Pests and Diseases

June 29th 2016, Discovery Centre, Black Mountain, Canberra

Australian Government
Department of Health
Office of the Gene Technology Regulator

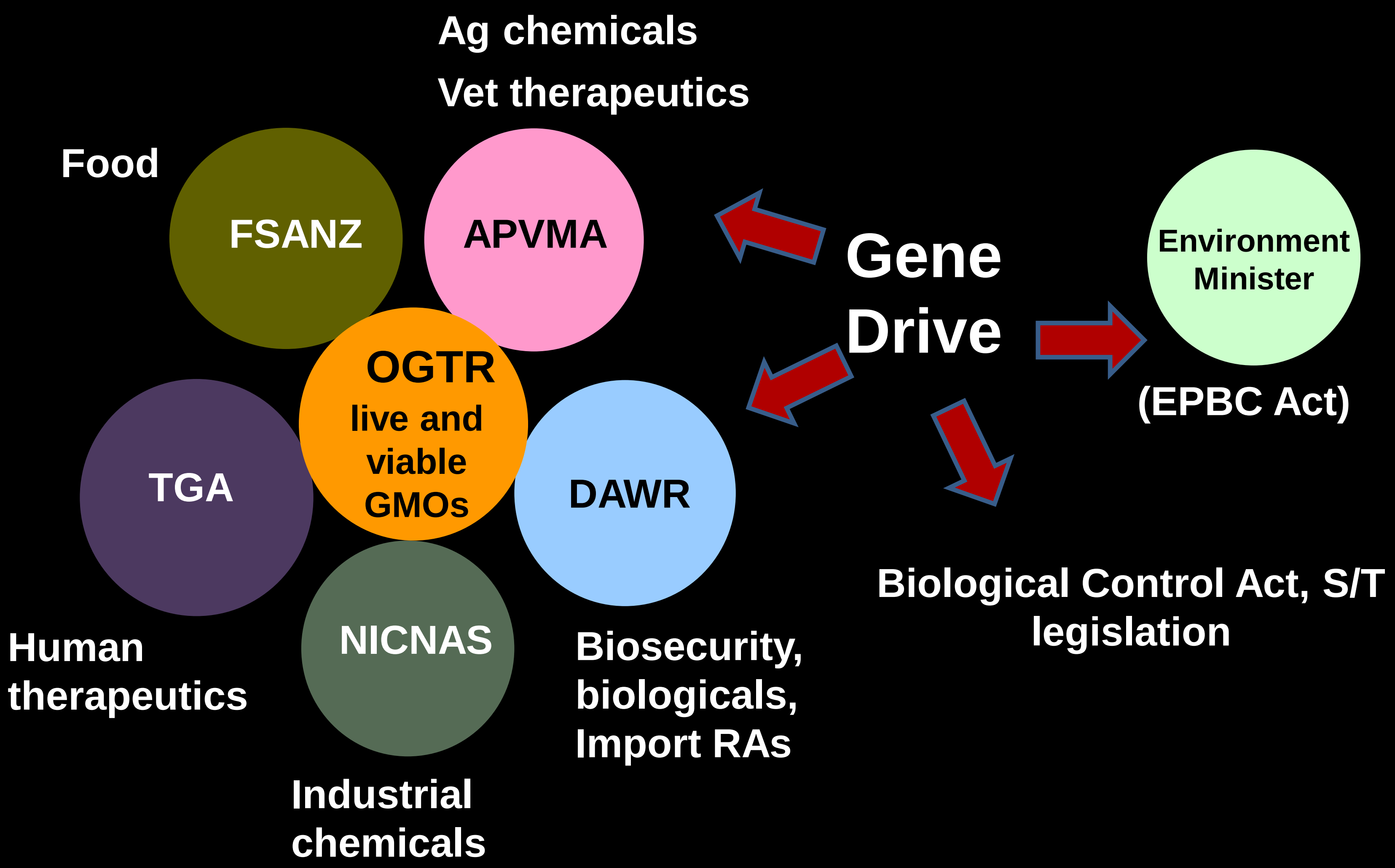
CSIRO

Australian Government
Australian Pesticides and Veterinary Medicines Authority

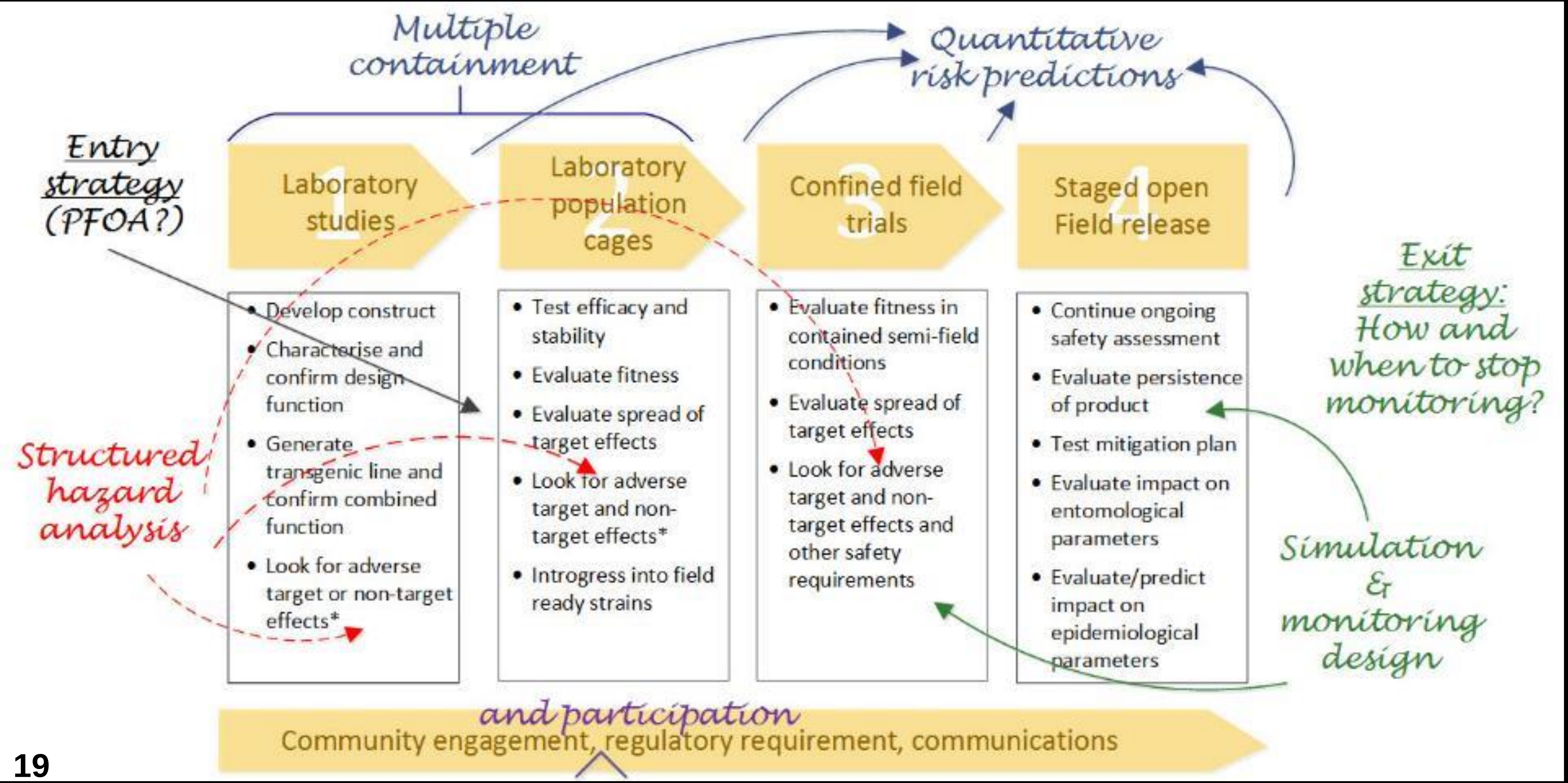
CSIRO-RSN Roundtable

June 30th 2016, Boardroom, Discovery Centre, Black Mountain, Canberra

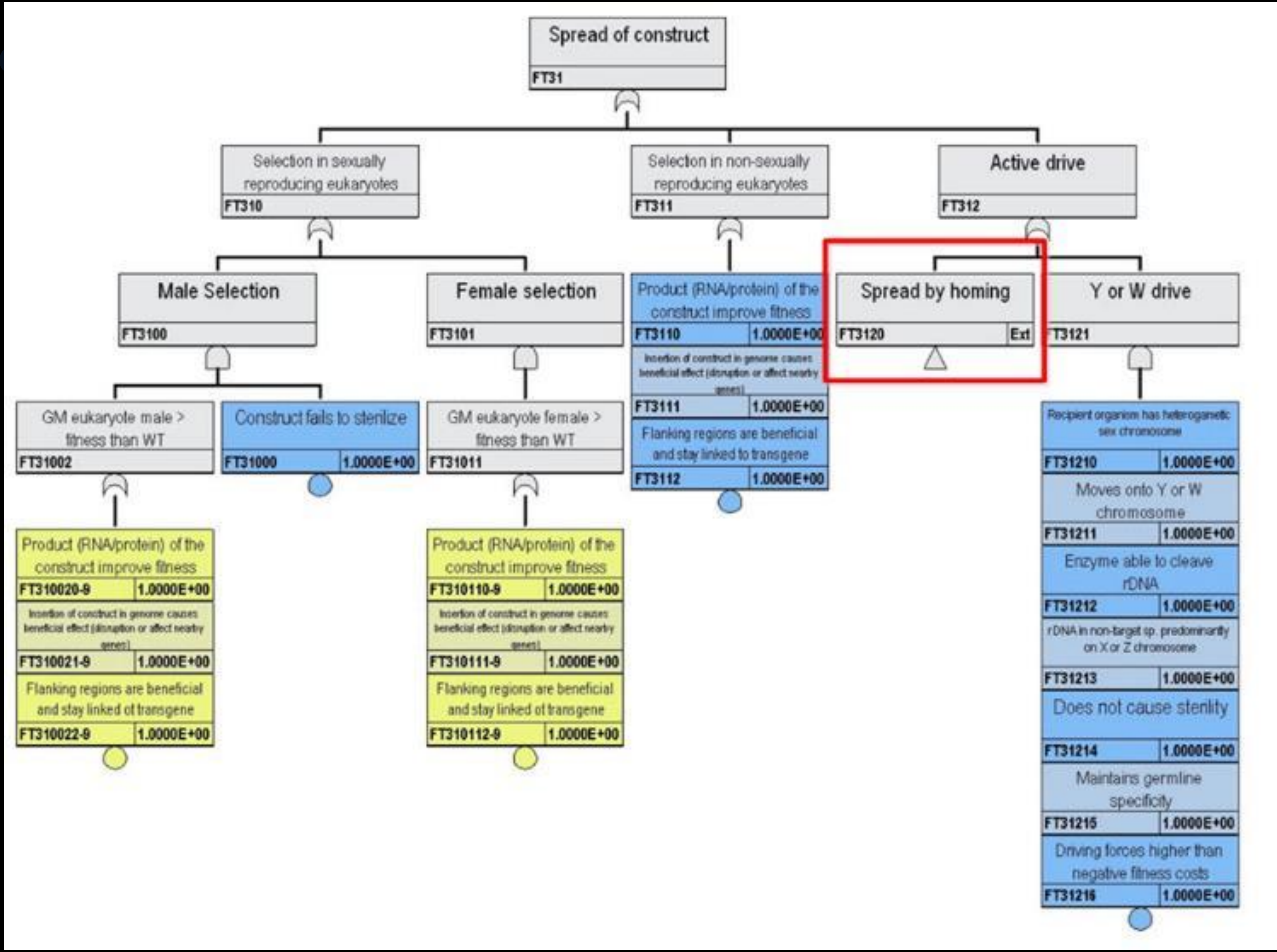
Gene drive regulation in Australia



Risk Assessment (led by Keith Hayes)



Risk Ass


Spread of construct
FT31
Selection in sexually reproducing eukaryotes
FT310
Selection in non-sexually reproducing eukaryotes
FT311
Active drive
FT312
Male Selection
FT3100
Female selection
FT3101
Product (RNA/protein) of the construct improve fitness
FT3110
1.0000E+00
Insertion of construct in genome causes beneficial effect (disruption or affect nearby genes)
FT3111
1.0000E+00
Flanking regions are beneficial and stay linked to transgene
FT3112
1.0000E+00
Spread by homing
FT3120
Ext
Y or W drive
FT3121
GM eukaryote male > fitness than WT
FT31002
Construct fails to sterilize
FT31000
1.0000E+00
GM eukaryote female > fitness than WT
FT31011
Product (RNA/protein) of the construct improve fitness
FT310020-9
1.0000E+00
Insertion of construct in genome causes beneficial effect (disruption or affect nearby genes)
FT310021-9
1.0000E+00
Flanking regions are beneficial and stay linked of transgene
FT310022-9
1.0000E+00
Product (RNA/protein) of the construct improve fitness
FT310110-9
1.0000E+00
Insertion of construct in genome causes beneficial effect (disruption or affect nearby genes)
FT310111-9
1.0000E+00
Flanking regions are beneficial and stay linked of transgene
FT310112-9
1.0000E+00
Recipient organism has heterogametic sex chromosome
FT31210
1.0000E+00
Moves onto Y or W chromosome
FT31211
1.0000E+00
Enzyme able to cleave rDNA
FT31212
1.0000E+00
rDNA in non-target sp. predominantly on X or Z chromosome
FT31213
1.0000E+00
Does not cause sterility
FT31214
1.0000E+00
Maintains germline specificity
FT31215
1.0000E+00
Driving forces higher than negative fitness costs
FT31216
1.0000E+00

Community Engagement

- To assist with community engagement, we are building on what we learned from previous experience with the Eliminate Dengue project

PLOS | NEGLECTED TROPICAL DISEASES

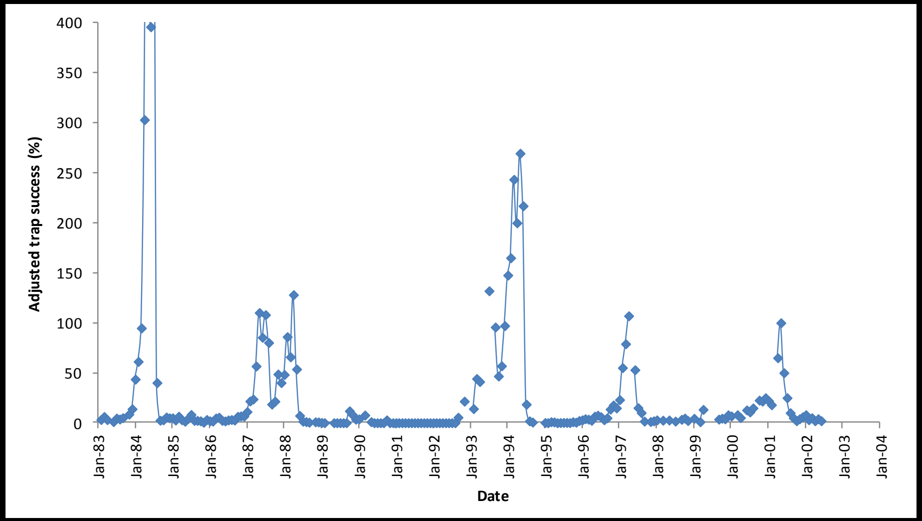
RESEARCH ARTICLE

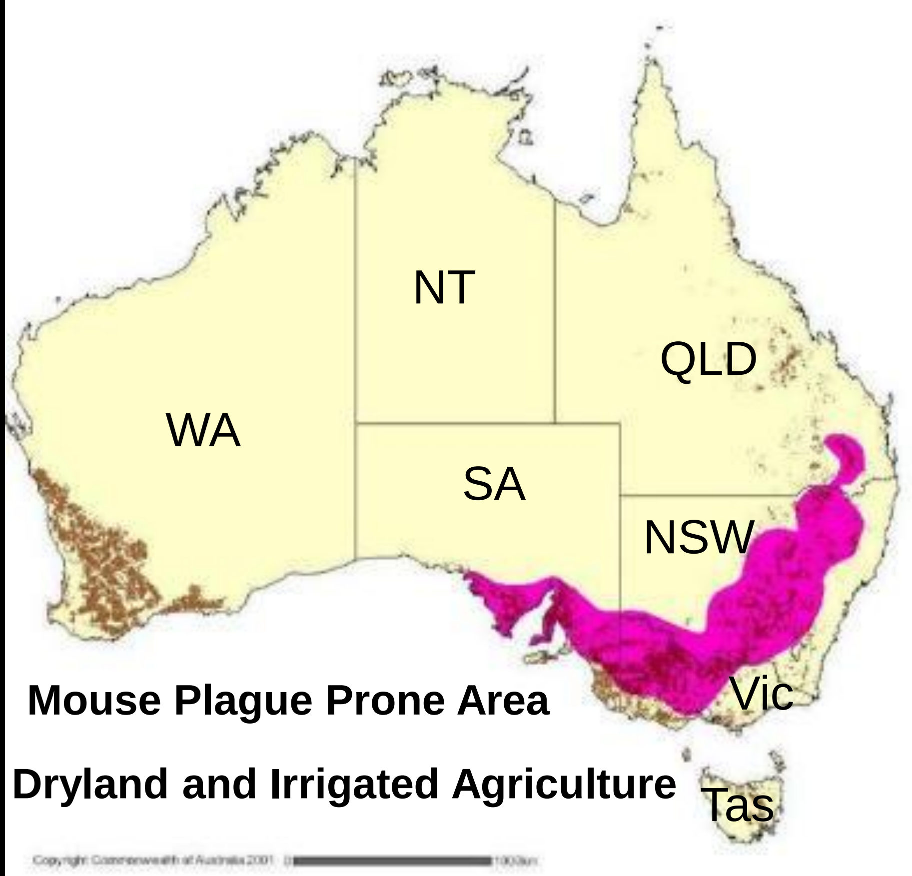
What Makes Community Engagement Effective?: Lessons from the *Eliminate Dengue* Program in Queensland Australia

Pamela A. Kolopack[1,2,3], Janet A. Parsons[2,4,5], James V. Lavery[1,2,3]*

Mouse plagues in Australia

- Cause significant damage ($M100s per plague)
- Occur in grain-growing regions of Australia (since 1904)
- Occur irregularly (1 year in 2 in Qld)
- Concurrent, widespread increase in densities (>1000 mice/ha)
- After crash, very low densities (< 5 mice/ha)





Modelling unexpected ecological consequences

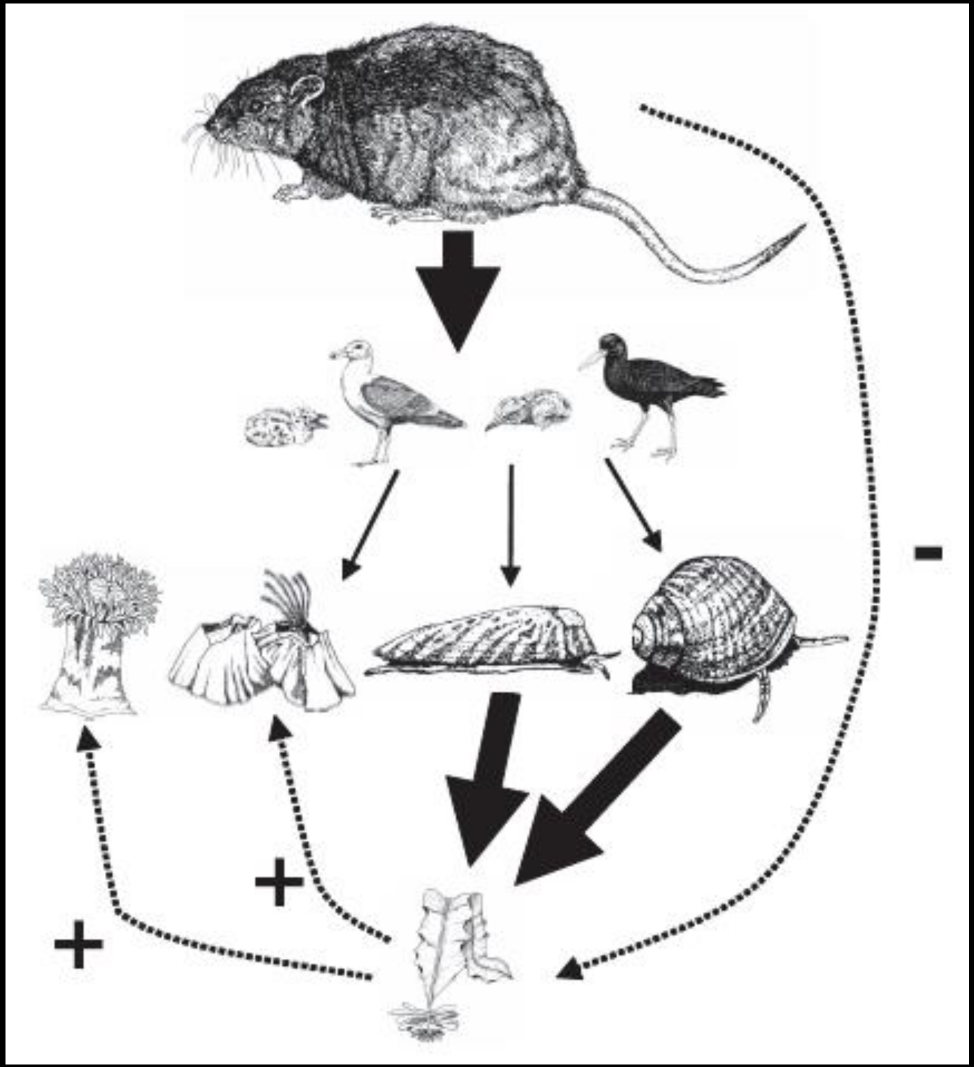
PNAS

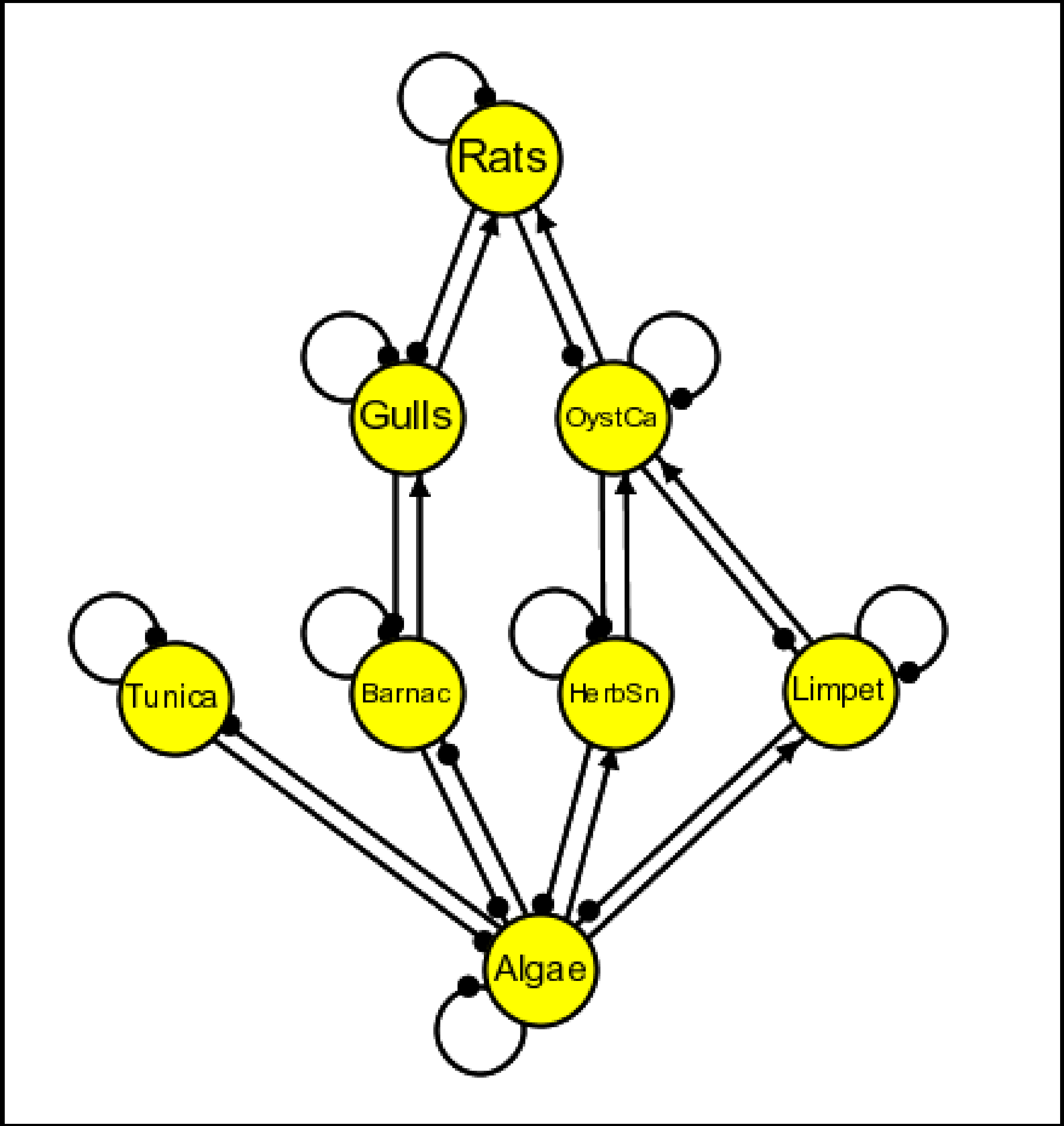
Introduced rats indirectly change marine rocky intertidal communities from algae- to invertebrate-dominated

Carolyn M. Kurle*, Donald A. Croll, and Bernie R. Tershy†

Department of Ecology and Evolutionary Biology, University of California, 100 Shaffer Road, Santa Cruz, CA 95060

Communicated by Donald Kennedy, Stanford University, Stanford, CA, January 22, 2008 (received for review September 10, 2007)





"adjoint (-A)"

11	−6	−6	−11	−9	5	2	−7
4	0	−3	−4	−3	1	1	−2
4	−3	0	−4	−3	1	1	−2
−11	6	6	14	9	−5	−2	7
−5	3	3	5	6	−2	−2	4
7	−3	−3	−7	−6	4	1	−5
−6	3	3	6	6	−3	0	3
1	0	0	−1	0	1	1	1

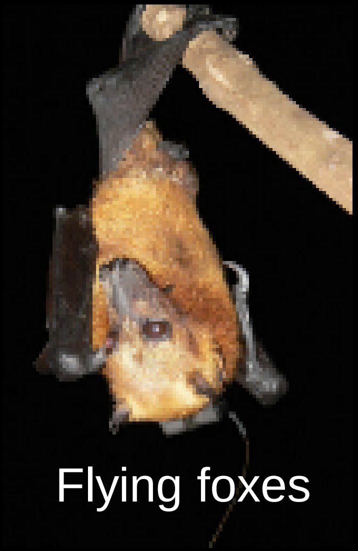
"Based on average proportion of correct sign"

1.0	0.88	0.88	1.0	1.0	0.94	0.79	1.0
0.79	0.50	0.69	0.79	0.73	0.57	0.60	0.67
0.79	0.69	0.50	0.79	0.73	0.57	0.60	0.67
1.0	0.88	0.88	0.83	1.0	0.94	0.79	1.0
0.90	0.73	0.73	0.90	0.72	0.72	0.62	0.75
1.0	0.69	0.69	1.0	0.94	0.75	0.63	0.86
1.0	0.79	0.79	1.0	0.80	0.83	0.50	0.68
0.63	0.50	0.50	0.63	0.50	0.58	0.57	0.55

Targets for gene drive in Australia?

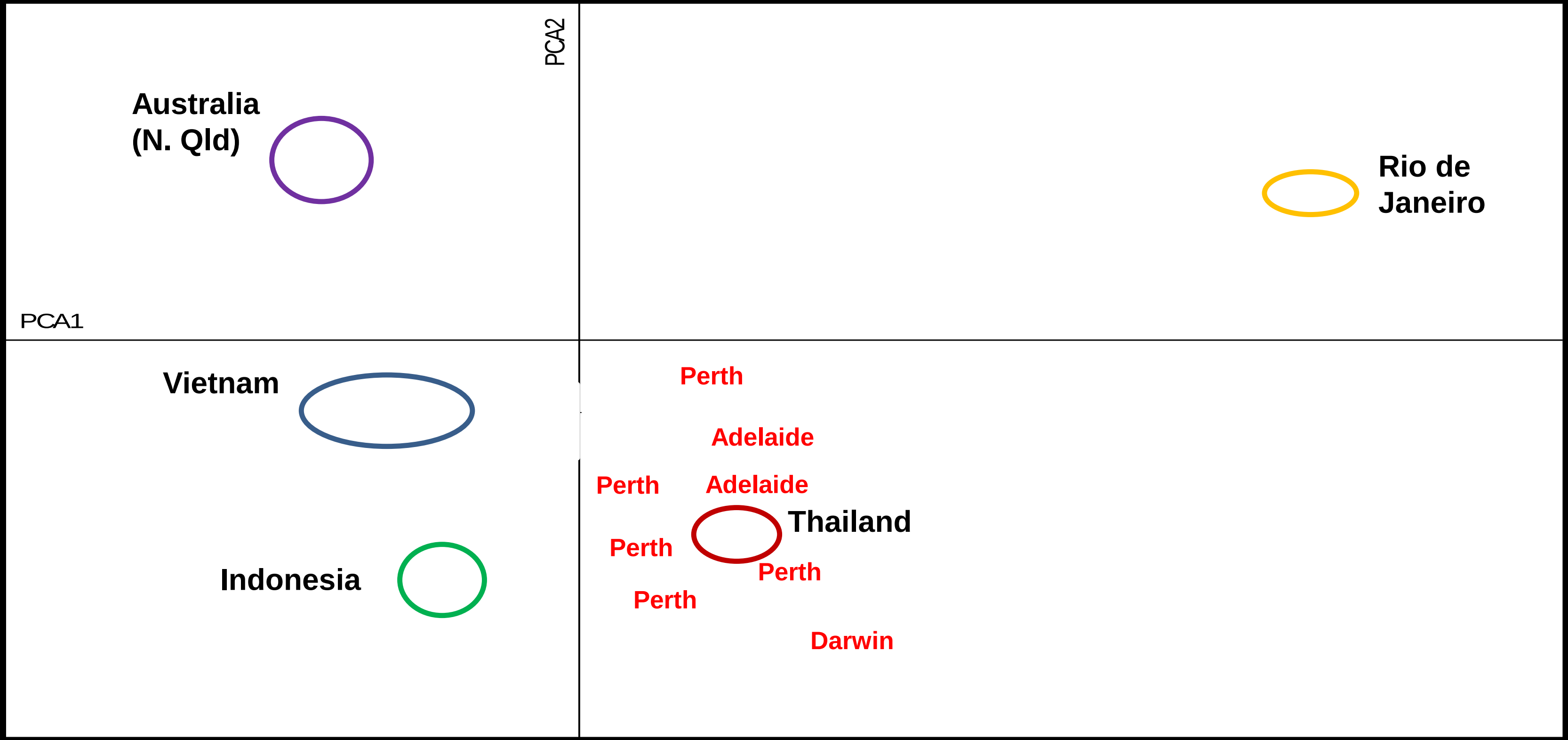
Invasive Species

Agricultural Pests



Arboviruses / Emerging Infectious Diseases

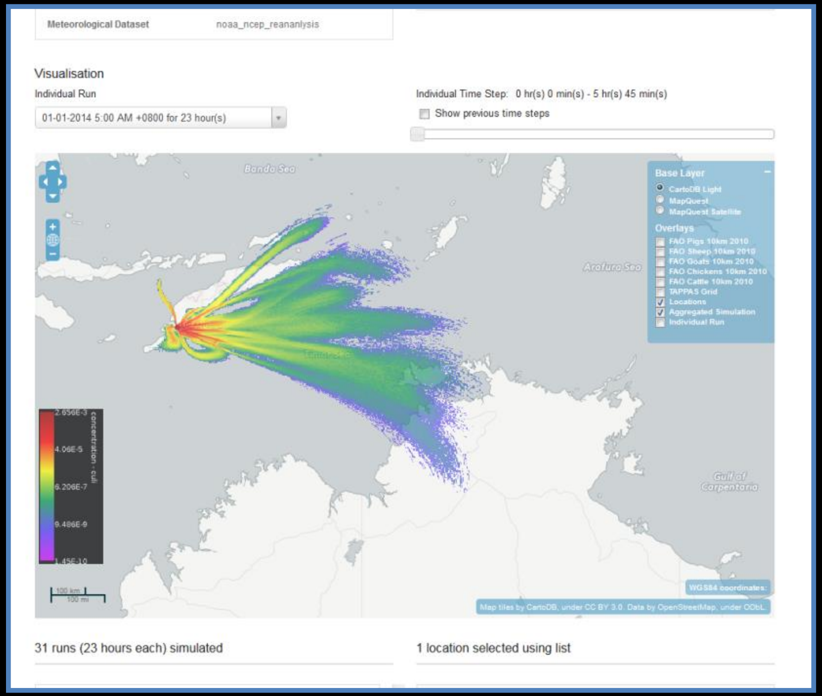
Genome SNP analyses on *Aedes* mosquito interceptions at Australian airports

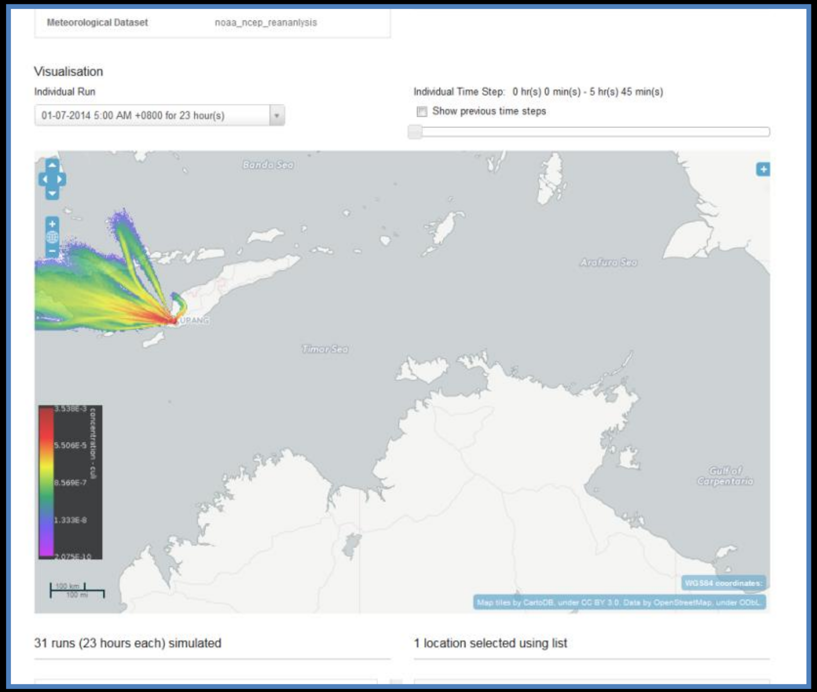


https://research.csiro.au/tappas/

TAPPAS – Tool for Assessing Pest and Pathogen Aerial Spread

An online software tool for modelling the dispersal of living organisms.


Meteorological Dataset
noaa_ncep_reananlysis
Visualisation
Individual Run
01-01-2014 5:00 AM +0800 for 23 hour(s)
Individual Time Step: 0 hr(s) 0 min(s) - 5 hr(s) 45 min(s)
Show previous time steps
Banda Sea
Arafura Sea
Gulf of Carpentaria
Base Layer
Overlays
31 runs (23 hours each) simulated
1 location selected using list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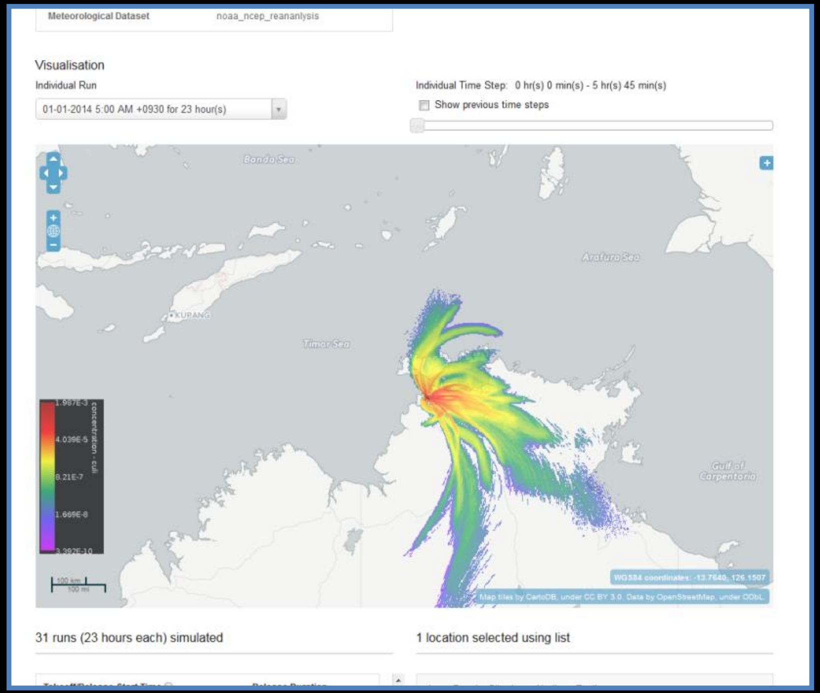
noaa_ncep_reananlysis
Visualisation
Individual Run
01-07-2014 5:00 AM +0800 for 23 hour(s)
Individual Time Step: 0 hr(s) 0 min(s) - 5 hr(s) 45 min(s)
Show previous time steps
Banda Sea
Arafura Sea
Timor Sea
Gulf of Carpentaria
31 runs (23 hours each) simulated
1 location selected using list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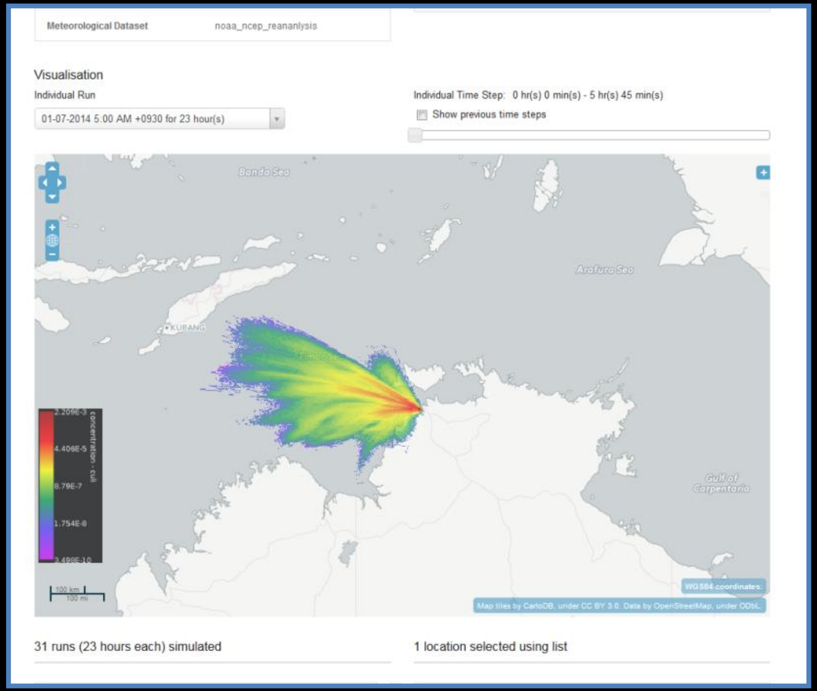
Visualisation
Individual Run
01-01-2014 5:00 AM +0930 for 23 hour(s)
Individual Time Step: 0 hr(s) 0 min(s) - 5 hr(s) 45 min(s)
Show previous time steps
Banda Sea
Arafura Sea
KUPANG
Timor Sea
Gulf of Carpentaria
31 runs (23 hours each) simulated
1 location selected using list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Banda Sea
Arafura Sea
KUPANG
Gulf of Carpentaria
31 runs (23 hours each) simulated
1 location selected using list

Terrestrial mammals in New Zealand

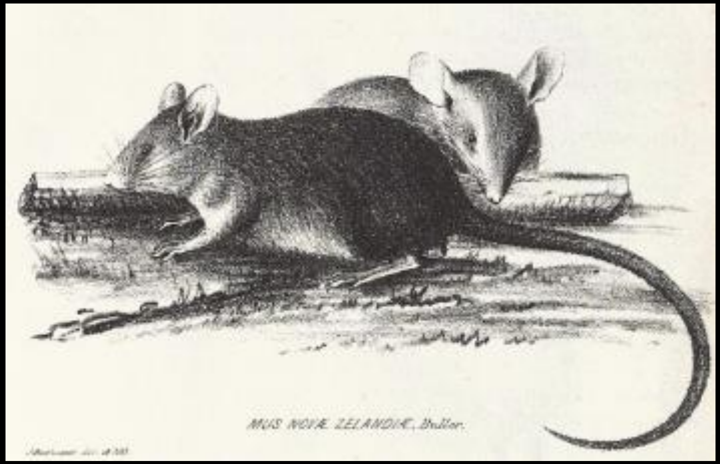
Pre-human settlement

- only 3 native mammals

Terrestrial mammals in New Zealand

Polynesian settlers
(10th century AD onwards)

- 2 mammals introduced



Terrestrial mammals in New Zealand

Captain Cook / whalers
(18th century AD)

- 5 more mammals introduced






Terrestrial mammals in New Zealand

European settlers
(19th century AD onwards)

- 25 more mammals introduced (and accompanying diseases)

FIRST SCOTTISH
COLONY for
New Zealand

That Fine
FAST
SAILING

TEAK-BUIL
SHIP

BENGAL MERCHANT,
501 *Tons Register*—JOHN HEMERY, COMMANDER,
WILL POSITIVELY
SAIL FROM PORT-GLASGOW
For NEW ZEALAND,
With the first Body of Settlers
FROM SCOTLAND.
On FRIDAY, Oct. 25.

SINGLE WOMEN, going out as Servants to Cabin Passengers, or in charge of Married Emigrants, will receive a *Free Passage* on board of this Ship.

All Goods and Luggage must be forwarded by the 20th instant *at latest*, on which day the Ship will clear out.

For *Freight* (having room for dead Weight and Measurement Goods) and *Passage*, apply to

JOHN CRAWFORD,
24, QUEEN STREET.

NEW ZEALAND LAND CO.'S OFFICE,

Cost of invasive mammals in New Zealand

Most ‘extinction-prone’ avifauna in the world

Primary reservoir for bovine TB and other diseases

Susceptibility to incursions e.g. FMD, theileriosis

The government estimates the cost of introduced species to the New Zealand economy and primary sector to be NZ$3.3bn a year (or US$2.4bn)

PREDATOR FREE 2050

ORIGINAL PRESS RELEASE 25 JULY, 2016: New Zealand to be Predator Free by 2050

"Prime Minister John Key has today announced the Government has adopted the goal of New Zealand becoming Predator Free by 2050."

Four interim 2025 goals:

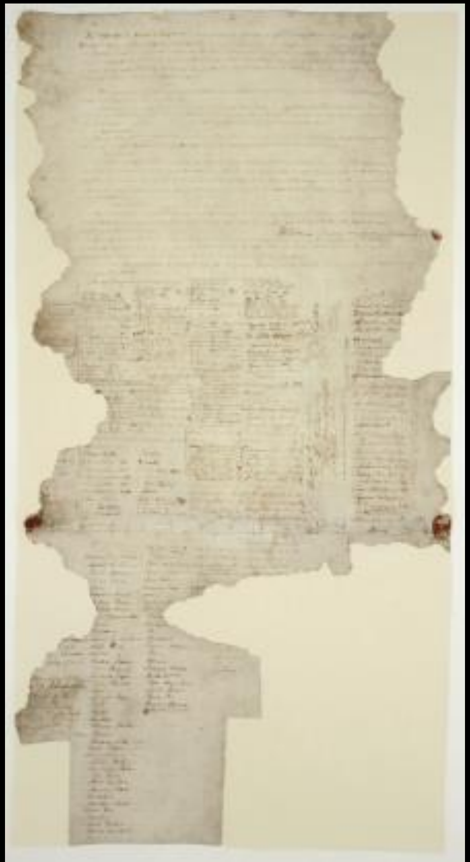
1. Suppress predators on a further 1 million hectares
2. Eradicate predators from at least 20,000 hectares without the use of fences
3. Eradicate predators from island nature reserves
4. Achieve a breakthrough science solution capable of eradicating at least one small mammal predator.

HONOLULU CHALLENGE

BOLD ACTION ON INVASIVE ALIEN SPECIES

Social licence to operate in NZ

- The New Zealand public is historically anti-GMO
- The Treaty of Waitangi recognizes Māori ownership of lands and forests, and their kaitiakitanga (guardianship)

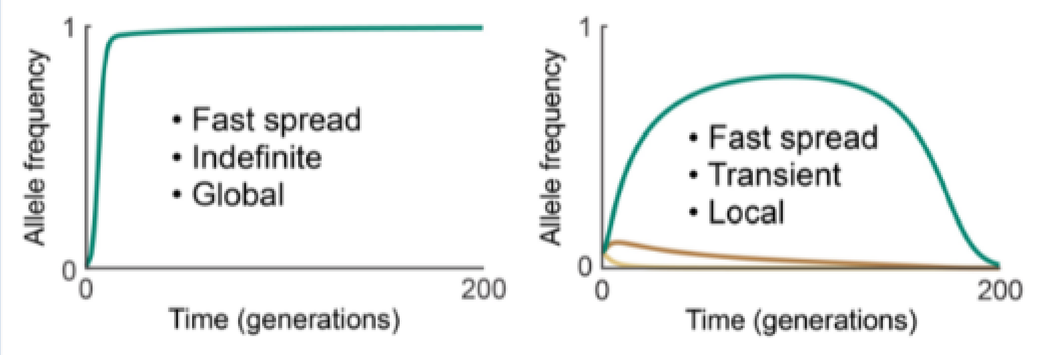


- 2012 national survey – 50% believed not enough is being done (increased since)
- 2014 focus groups – general support for research into new tools (including genetic)
- Ngā Matapopore (The Watchful Ones) – keen for international discussion of gene drives
- COP13 / COP-MOP8 / COP-MOP2 – New Zealand took a firm stand on opposing the global moratorium on gene drives and the attempt to equate gene drives with synthetic biology

Gene drive modelling needs

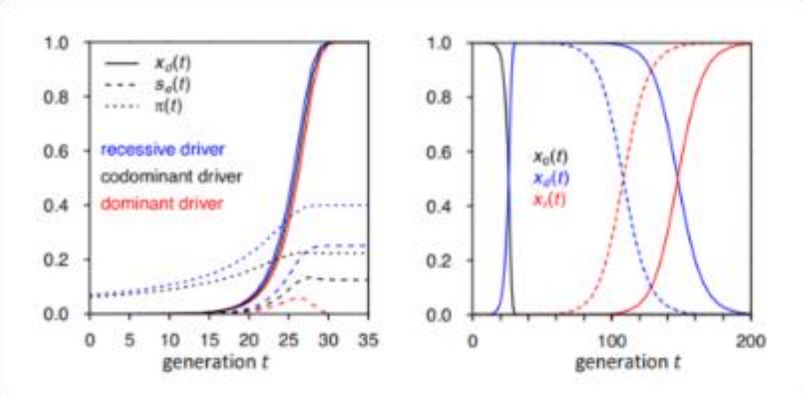
Blues skies fundamental (proof of concept)

- relatively simple; very conceptual
- deterministic or simulation



Identifying risks and hurdles

- more complexity (evolutionary dynamics, spatial, stochastic, biotic interactions)



Product specifications (guide R&D)

- complex simulation models
- combined genetic, evolutionary and ecological factors
- multiple scale
- scenario exploration
- non-spatial, quasi-spatial (e.g. meta-population) and fully spatial models
- increasing intensity of computing

Application strategies

- complex simulation models (including individual-based models)
- fully spatial and location/context tailored (integration with GIS layers)
- realistic target species life-history dynamics (including compensatory effects) and dispersal dynamics
- very computer intensive

Genetic Biocontrol of Invasive Rodents Program

Thanks to:
Fred Gould - NCSU
John Godwin – NCSU
David Threadgill – Texas A&M Univ.
Toni Piaggio – USDA, NWRC
Aaron Shiels - USDA, NWRC
John Eisemann – USDA, NWRC
Paul Thomas – Univ. of Adelaide
Gregg Howald – Island Conservation

GBIRd Program Contact:

royden.saah@islandconservation.org

Presenter Contacts:

karl.campbell@islandconservation.org
owain.edwards@csiro.au
tompkinsd@landcareresearch.co.nz

CSIRO
ISLAND CONSERVATION
Preventing Extinctions
LANDCARE RESEARCH
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