Horizon Scanning Series
The Future of Precision Medicine in Australia

Environment and Gene Drives

This input paper was prepared by Dr Mark Tizard (CSIRO)

Suggested Citation
Tizard, M (2017). The Future of Precision Medicine in Australia: Environment and Gene Drives. Input paper for the Horizon Scanning Project "The Future of Precision Medicine in Australia" on behalf of the Australian Council of Learned Academies, www.acola.org.au.

Gene Drives

This paper was prepared by Professor Mark Tizard

1. Abstract

The CRISPR gene editing tool can be customised to form the engine of a synthetic genetic cassette known as *gene drive* that can duplicate itself during the course of sexual reproduction such that all offspring from a reproductive event will carry the drive system. Theoretically the gene drive cassette, including a bioactive payload, will spread through a population over the course of several generations until it is present in all surviving individuals of the target species that are connected biogeographically. Gene drive has therefore been proposed as a tool to introduce genetic payloads that could be used to control or extirpate an invasive or pest species. Alternative applications of gene editing that do not involve gene drive may arise as more is understood about the biology of pest species in the context of affected environments.

2. Gene technology and the environment

The Australian environment represents a unique world heritage resource as a result of the evolutionary isolation of the majority of the species on the continent, following separation from Gondwana and other continental masses between 100 and 50 million years ago (Veevers & McElhinny, 1976). In more recent times the arrival of Europeans, following the first landing by Willem Janszoon in 1606, has led to a steady introduction of non-native animals and plants, starting with the accidental escape of stowaway rodents from ships. Eventually there were deliberate introductions of animals and plants by Acclimatization Societies, farmers and other land holders. In the last century a significant impact has come through the accidental and deliberate release, by the general public, of domestic pets that have not been neutered, leading to feral populations of cats and dogs. Between the effects of invasive animals and plants there have been significant, sometimes catastrophic impacts on the unique native fauna and flora of Australia.

Traditional methods to deal with these invasive pests involve the use of chemical poisons (through local or broadcast use of baits) and trapping and shooting of larger animals. For plants the use of insects as biocontrol systems has had some successes, with the alternative being broad spectrum herbicides. The use of chemicals inevitably leads to off-target impacts on native species that are also killed. For rabbits there has need some success with the use of viruses as biocontrol agents, specifically myxomatosis and calicivirus. However the emergence of resistant individuals eventually leads to a re-emergence of pest populations.

It is widely recognised that there is a need for innovative control measures for invasive species of animal and plant in Australian in order to ensure the preservation of many of the unique ecologies on this continent and retain many of the threatened species within those biological niches. The postulation of a synthetic engineered RNA guided gene drive systems (based on CRISPR), which can be customised to target any organism (provided it relies on sexual reproduction) presented bold new opportunity to control pest species (Esvelt K, et al. 2014, p. 03401).

3. Gene drive, the environment and impacts on human health

Development of the synthetic gene drive concept has opened up new opportunities but it has also triggered worldwide debate with regard to whether it can be developed into a form that can safely be deployed into a wild environment t (Webber, Raghu & Edwards, 2015, p. 10565; http://nas-sites.org/gene-drives/). One of the first organisms considered aa a priority target was the mosquito species that is responsible for the transmission and human health impact of the malaria parasite. It has been shown that a gene drive cassette can be transmitted through a laboratory contained population of mosquitos with high efficiency (Gantz et al. 2015, p. 6736). Since the female mosquitos are the gender that bite and transmit the disease (the males do not) one suggestion was to interrupt the female development pathway (Hammond et al. 2016, p. 78). This has been met with some concern since unchecked the spread of a gene drive that forces all male development in the population could ultimately lead not just to local reproductive collapse for the population but potential a global extinction of the species. Nonetheless new technological developments of gene drives are being conceived to control the potential for global spread (https://www.media.mit.edu/posts/daisy-drive-a-local-open-and-community-responsive-approach-to-solving-ecological-problems/). Such approaches are the focus of a major international collaboration, Target Malaria (http://targetmalaria.org). An alternative approach is to use the gene drive to push into the population a genetic trait that blocks the ability of the mosquito to carry the parasite and thus break the cycle of disease spread. This principle could be useful in Australia where a different mosquito species, Aedes, is both invasive and a vector for the Dengue fever virus. Early developments of systems to exclude viruses from the Aedes mosquito vector that could be coupled to a gene drive are showing promise (Omar Akbari & Prasad Paradkar, personal communication).

4. Gene drive for the control of vertebrate pests

Gene drive has been proposed as a technique to control vertebrate pests such as mice, rats and rabbits, with modelling showing that in the case of the mouse this may be feasible (Prowse et al. 2017, p.). There is an international consortium, Genetic Biocontrol of Invasive Rodents (GBIRd http://www.geneticbiocontrol.org/), that involves the University of Adelaide and CSIRO, led by Island Conservation (https://www.islandconservation.org/) which receives funding from the US Defence Advanced Research Projects Agency as part of their Safe Genes initiative (https://www.darpa.mil/program/safe-genes). The objectives are to develop a gene drive system to eradicate rodents (initially mice) from islands around the world where their predation threatens to cause extinction of rare bird species. This technology have public health implications since rodents also spread disease to the human population, a noteworthy example being Lyme disease in the US for which a gene drive solution is being considered (http://www.newyorker.com/magazine/2017/01/02/rewriting-the-code-of-life). The mouse is an ideal model system for the study of gene drive in vertebrate animals since the genome information necessary to develop a gene drive and the genetic systems needed to construct the transgenic animals are all well established. Though the technology has potential applications in other important pest species such as rats, rabbit, cats, foxes, dogs, carp and cane toads, there are many important considerations and knowledge gaps to be filled before the technology could be considered for their control. This will be the focus of research debate and planning for the next few of years. Selection of the optimal target species, public engagement activities to ensure these approaches are acceptable and the necessary technical developments will occupy the next 10 years of activity in what could be a very valuable area of research.

5. Environmental application of gene editing that is not gene drive

Since the 1930s the cane toad been marching across northern Australian damaging ecosystems and causing dramatic declines of key predator populations due to a defensive lethal toxin it carries. An attempt to mitigate these impacts has revealed that the key predators affected (including the northern quoll, fresh water crocodiles, monitors, lizards and constrictor snakes) can be trained not to eat cane toads through an approach known as conditioned taste aversion (CTA) which works best with small live toads (Ward-Fear et al, 2017, p. 112). CRISPR gene editing could be used to knockout the enzyme needed for the activation of the pro-toxin that the toad stores to the fully lethal toxin that kills the attacking predator. The resulting non-lethal cane toad should still be distasteful could potentially be used in a wild release as a tool for CTA to protect threatened predator populations (Tingley et al, 2017, p. 123). It is likely that the process of development would take at least five years to move from concept, laboratory validation and finally out to field trials.

As more is understood about the biology of specific pests in particular environments it may be possible that other direct applications of gene editing that do not involve the necessity for a gene drive function could come to light.

References

Akbari, OS, Bellen, HJ, Bier, E, Bullock, SL, Burt, A, Church, GM, Cook, KR, Duchek, P, Edwards, OR, Esvelt, KM, Gantz, VM, Golic, KG, Gratz, SJ, Harrison, MM, Hayes, KR, James, AA, Kaufman, TC, Knoblich, J, Malik, HS, Matthews, KA, O'Connor-Giles, KM, Parks, AL, Perrimon, N, Port, F, Russell, S, Ueda, R & Wildonger, J 2015 'BIOSAFETY. Safeguarding gene drive experiments in the laboratory.' *Science*, vol. 349, pp. 927-9

Esvelt, KM, Smidler, AL, Catteruccia, F, Church, GM 2014 'Concerning RNA-guided gene drives for the alteration of wild populations.' *Elife*, vol. 3, pii: e03401.

Gantz, VM, Jasinskiene, N, Tatarenkova, O, Fazekas, A, Macias, VM, Bier, E, James, AA 2015 'Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi.' *Proceedings of the National Academy of Science U S A*, vol. 112, no. 49, pp. 6736-43.

Hammond, A, Galizi, R, Kyrou, K, Simoni, A, Siniscalchi, C, Katsanos, D, Gribble, M, Baker, D, Marois, E, Russell, S, Burt, A, Windbichler, N, Crisanti, A & Nolan, T 2016 'A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae.' *Nature Biotechnology*,vol. 34, no. 1, pp. 78-83.

Oye, KA, Esvelt, K, Appleton, E, Catteruccia, F, Church, G, Kuiken, T, Lightfoot, SB, McNamara, J, Smidler, A & Collins, JP 2014 'Biotechnology. Regulating gene drives.' *Science*, Vol. 345, pp. 626-8.

Prowse, TAA, Cassey, P, Ross, JV, Pfitzner, C, Wittmann, TA & Thomas P 2017 'Dodging silver bullets: good CRISPR gene-drive design is critical for eradicating exotic vertebrates.' *Proceedings in Biological Science*, vol. 284, pp. 1860.

Tingley, R, Ward-Fear, G, Schwarzkopf, L, Greenlees, MJ, Phillips, BL, Brown, G, Clulow, S, Webb, J, Capon, R, Sheppard, A, Strive, T, Tizard, M & Shine, R 2017 'New Weapons in the Toad Toolkit: A Review of Methods to Control and Mitigate the Biodiversity Impacts of Invasive Cane Toads (Rhinella Marina' *Quarterly Reviews of Biology*, vol. 92, no. 2, pp. 123–149.

Veevers, JJ & McElhinny, MW 1976, 'The separation of Australia from other continents.' *Earth-Science Reviews*, vol. 12, no. 2-3, pp. 139-143.

Ward-Fear, G, Thomas, J, Webb, JK, Pearson, DJ & Shine, R 2017 'Eliciting conditioned taste aversion in lizards: Live toxic prey are more effective than scent and taste cues alone.' *Integrative Zoology*, vol. 12, no. 2, pp. 112-120.

Webber, BL, Raghu, S & Edwards, OR 2015 'Opinion: Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat?' *Proceedings of the National Academy of Science U S A,* vol. 112, no. 34, pp. 10565-7.