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Review Paper

Identifying knowledge gaps for gene drive research to control invasive animal species: The next CRISPR step

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ABSTRACT

Invasive animals have been linked to the extinctions of native wildlife, and to significant agricultural financial losses or impacts. Current approaches to control invasive species require ongoing resources and management over large geographic scales, and often result in the short-term suppression of populations. New and innovative approaches are warranted. Recently, the RNA guided gene drive system based on CRISPR/Cas9 is being proposed as a potential gene editing tool that could be used by wildlife managers as a non-lethal addition or alternative to help reduce pest animal populations. While regulatory control and social acceptance are crucial issues that must be addressed, there is an opportunity now to identify the knowledge and research gaps that exist for some important invasive species. Here we systematically determine the knowledge gaps for pest species for which gene drives could potentially be applied. We apply a conceptual ecological risk framework within the gene drive context within an Australian environment to identify key requirements for undertaking work on seven exemplar invasive species in Australia. This framework allows an evaluation of the potential research on an invasive species of interest and within a gene drive and risk context. We consider the currently available biological, genetic and ecological information for the house mouse, European red fox, feral cat, European rabbit, cane toad, black rat and European starling to evaluate knowledge gaps and identify candidate species for future research. We discuss these findings in the context of future thematic areas of research worth pursuing in preparation for a more formal assessment of the use of gene drives as a novel strategy for the control of these and other invasive species.

1. Introduction

Globally, the pressures that invasive animal species place on biodiversity and agriculture are clearly recognised (Bellard et al., 2016; Doherty et al., 2016). These impacts are exaggerated in landscapes such as islands, including large island

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nations like Australia and New Zealand, where introduced species that became invasive are now linked to the localised or widespread declines or extinctions of native wildlife, and to large economic losses (e.g. Medina et al., 2011; Cox et al., 2013). Islands are particularly important assets for many countries yet remain vulnerable to introduced species that are having a disproportionately large effect on island ecosystems: for example, islands make up 5% of the global landmass and host some 19% of bird species and 17% of rodent species, yet 61% of all extinct species and 37% of critically endangered species remain confined to islands (Tershy et al., 2015). New Zealand, for example, is now on an ambitious path to eradicate several introduced predators that are major threats to their native wildlife (Russell et al., 2015).

As an island nation, Australia has a vested interest in the management of invasive species that impact on both native fauna conservation and agricultural production. For example, predation by feral cats and the European red fox have collectively been scaled as the highest contributing threats in the decline of Australia's terrestrial mammal fauna (Woinarski et al., 2015). Further, an average $A620 million over 5-years is the estimated impact on agriculture by pest animals (Gong et al., 2009). Control techniques typically consist of integrated chemical and physical management practices (e.g. poison baiting combined with habitat removal, fencing), direct intervention (e.g. shooting, trapping), and biological control (for rabbits). While current efforts to manage invasive species are ongoing, these have varying levels of efficacy at low population densities, are often associated with undesirable welfare outcomes for target and non-target species, they may also have unintended ecological consequences, and are often limited to short-term results in population control (Fancourt et al., 2015; Doherty et al., 2016; Kinnear et al., 2016). These constraints are motivating scientists to look at alternative approaches that are more targeted, economical to implement, reduce animal welfare concerns, and are self-sustaining across large geographical scales (Campbell et al., 2015b). Practices that extend control to the landscape scale are particularly warranted for invasive species with wide distributions.

Alternatives to conventional control for reducing the population size of some invasive species have been considered (Campbell et al., 2015a). For example, techniques that aim to introduce sterile males into populations and across generations have been successfully used to reduce invertebrate pests (Dyck et al., 2005), and have been proposed for cane toads (Koopman, 2006) and carp (Gutierrez and Teem, 2006). However, these alternatives require massive releases of sterile males that models predict are labour-intensive and likely have little sustainable impact. It is also a challenge to explain to the public and other stakeholders why large numbers of an invasive pest are being released into a control area. Gene drives are now being discussed as tools to reduce invasive animal populations (Burt, 2003; Dearden et al., 2017). These genetic elements produce a biased form of inheritance and can spread through sexually-reproducing populations at a greater rate than genes with standard Mendelian inheritance (Esvelt et al., 2014). While ambitious and still in early stages of development, the gene drive concept offers a species-specific and potentially non-lethal alternative to conventional methods and other forms of genetic control for managing invasive species (Harvey-Samuel et al., 2017).

A genome editing technique known as Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) and the associated nuclease, CRISPR-associated protein 9 (Cas9) has been adapted to create a “driving mechanism” for a gene cassette to increase the chances of the cassette being passed on to the offspring (Esvelt et al., 2014; Gantz et al., 2015). This form of synthetic RNA-guided gene drive is actively being discussed as a tool to drive a genetic trait into a wild population (Thresher et al., 2014; Campbell et al., 2015a; Johnson et al., 2016). The CRISPR gene editing tool uses a nuclease, Cas9, that is directed with a high degree of specificity to cleave a target DNA sequence, and thus can be used to either disrupt, remove, edit, or insert genetic traits in an organisms’ genome with great precision (Doudna and Charpentier, 2014; Shigeta et al. 2016). Evidence from laboratory trials suggests that RNA guided gene drives based on the CRISPR/Cas9 system could spread a targeted gene through nearly 100% of individuals in populations of yeast, fruit flies, and mosquitoes (DiCarlo et al., 2015; Gantz et al., 2015; Hammond et al., 2016). While the functionality of the CRISPR/Cas9 gene editing tool remains limited to some taxa, there is now strong interest in developing this technology in the laboratory, and ultimately in field trials, for vertebrates that are pests in animal agriculture and conservation (Ni et al., 2014; Webber et al., 2015). Although offering great potential, this opportunity requires considered planning of the biological and social risks and barriers (Dearden et al., 2017), and to evaluate which invasive species may be appropriate for initial proof-of-concept efforts and to determine an appropriate approach to risk assessment.

RNA guided gene drives could be used to introduce a number of different gene traits to directly control the numbers of a pest species, or to reduce an environmental impact of a pest (e.g. interfering with the transmission of a targeted biological characteristic, or blocking a toxin-producing gene, Tingley et al., 2017). However, one application that is gaining interest for many pest species is the disruption of the sex-determination process to bias inheritance of one sex over another across generations leading to skewed sex ratios, decreased fertility and fecundity, and ultimately population suppression or extirpation (Deredec et al., 2008; Alphey, 2014; Esvelt et al., 2014; Gantz and Bier, 2015). Male transgenic progeny carrying an additional copy of the *SRY* gene (male phenotype control gene) on a gene drive on an autosomal chromosome will father offspring all of which will carry *SRY* regardless of their sex chromosome complement, and will all develop as phenotypic males, all of who will in turn father only male offspring, reducing the number of fertile females until few or none remain in the population. This concept becomes an attractive (albeit theoretical) consideration for sustainable landscape-level control programs. Although much of the established theory on genetically-assisted population suppression has been developed around the requirements of insects (e.g. Dowling et al., 2015), *SRY*-gene drives have been proposed as a promising approach for the control of invasive vertebrate pests whose impact is primarily direct interference with native species or agriculture (Burt, 2003).