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EDITORIAL

Is there a future for genome-editing technologies in conservation?

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In a recent review, Pimm *et al.* (2015) highlight emerging technologies in protecting biodiversity. While their list is noteworthy, the authors' exclusion of innovations in genomic research, with the exception of single-species DNA barcoding methods, was surprising given recent advances in genome-editing technology and its potential application to conservation. Taylor & Gemmell (2016) address that deficiency in a subsequent commentary identifying three avenues where emerging genomic technologies have great potential for increasing our ability to conserve biodiversity. Those areas include the use of next-generation sequencing technologies and methods such as RADseq for monitoring genetic diversity, effective population size, and introgression (Andrews *et al.*, 2016); the use of environmental DNA (eDNA) and metabarcoding approaches to map species occurrence and interaction networks (Evans *et al.*, 2016); and the use of genomic data and gene-editing technology to identify and alter regions of the genome that may impact fitness and limit survival in endangered taxa (Taylor & Gemmell, 2016). Here, we extend that the theme with additional discussion on how genome-editing technologies can benefit the conservation of threatened and endangered species.

Genome-editing technologies as referenced herein include methods that can insert, delete or replace DNA within an organism's genome. One particular editing technique called CRISPR-Cas9 (Jinek *et al.*, 2012) has gained considerable momentum over the past three years achieving *Science*'s 2015 Breakthrough of the Year (Travis, 2015), largely due to its simplicity, relative low cost and precise genomic-editing capabilities (Mei *et al.*, 2016). The CRISPR-Cas9 technique was developed from the adaptive immune response of bacteria and archaea against invading viruses and plasmids (Jinek *et al.*, 2012; see also Lander, 2016). It is essentially an RNA-guided molecule that is programmed to identify a specific location within the genome and subsequently cut and replace target DNA (i.e. RNA-guided endonuclease; see Mei *et al.*, 2016 and Wright, Nuñez & Doudna, 2016, for specific details). The CRISPR-Cas9 technology has already been shown to have great potential to benefit humans in a variety of ways including improving crops (Kim *et al.*, 2015), eliminating disease (McLean & Jacobs-Lorena, 2016) and targeted medical therapies (Savić & Schwank, 2016). There is no reason why the technology could not be used as a tool to support biodiversity conservation.

We acknowledge that much needs to be done to increase awareness within the conservation community about how genome-editing technology can benefit conservation in practice. That is no easy task largely because of the widely held negative perception of genetically modified (GM) organisms used in agriculture, particularly by the for-profit commercial industry (Au, 2015; see also Redford *et al.*, 2014). However, the use of GM pharmaceuticals in human medicine has received less negative attention (Locwin, 2015). The conservation community can learn from this dichotomy, and identify tactful approaches for its advocacy in conservation.

How can genome-editing technology benefit conservation? First, most people agree that the prevention and mitigation of non-native invasive organisms is increasingly difficult and costly due to expanding global trade and travel (Banks *et al.*, 2015). Our ability to combat invasive species effectively is relevant for conserving biodiversity because non-native species are a significant contributor to recent vertebrate extinctions (Bellard, Cassey & Blackburn, 2016). Genomic-engineering technologies, and specifically those that utilize CRISPR-Cas9 *gene drive* methodologies to alter reproductive capacity (Esvelt

et al., 2014; Champer, Buchman & Akbari, 2016), can become a valuable tool to help prevent or eliminate invasive species with proper precautions in place (Oye *et al.*, 2014; Akbari *et al.*, 2015; Webber, Raghu & Edwards, 2015; Champer *et al.*, 2016).

For example, invasive rodents have impacted endemic fauna and flora of many remote island ecosystems (Harper & Bunbury, 2015; Jones *et al.*, 2016), and research is currently underway to develop genetic biocontrol methodologies to reduce that impact. A promising approach includes using genomic-editing techniques to alter the sex determination pathway of the invasive species by targeting the *Sry* gene (Larney, Bailey & Koopman, 2014) or using an X-chromosome shredder approach (*X-shredder*; Champer *et al.*, 2016) producing all-male offspring that would effectively eliminate reproduction without any need for pesticides or poisons that can negatively impact non-target species (e.g. Pitt *et al.*, 2015; see also Campbell *et al.*, 2015). The above applications have a strong potential for resulting in positive outcomes using a best practices framework already established from a long history of biological control applications addressing biosecurity concerns such as pre-release assessment of non-target effects and focused attention on preventing the spread of gene-edited organism into unintended areas (see Webber *et al.*, 2015). Additional options allowed by applying a genetic biocontrol approach include incorporating a 'kill-switch' in the modified organism that would then permit its intentional elimination from the environment or prevent undesired horizontal gene transfer to wild populations (e.g. Mandell *et al.*, 2015), yet more research is required to address their feasibility and associated risks in nature (Redford *et al.*, 2014; Schmidt & de Lorenzo, 2016).

Second, recent genomic research with domestic and wild canids highlights how severe bottleneck events can increase the frequency of deleterious genetic variants in the remaining population (Marsden *et al.*, 2016). These results have important implications for the management of species that have experienced a significant decline in abundance. Bottlenecked populations may experience an increase in disease susceptibility from pathogens (Hale & Briskie, 2007; Tompkins, 2007) or an increased frequency in genetic disorders that negatively impact survival within the remaining population (e.g. Räikkönen *et al.*, 2009). The founding population for the California condor *Gymnogyps californianus* captive breeding program, for example, is based on only 14 individuals among three genetic groups that were assumed to include half-siblings (Ralls & Ballou, 2004). A genetic disorder called chondrodystrophy increased in frequency within the founding population further restricting breeding pairs to avoid producing offspring with the condition (Ralls *et al.*, 2000; Romanov *et al.*, 2009). Despite a pessimistic outlook as presented by Shafer *et al.* (2015), gene-editing technology could be used to alter or remove the genetic disorder, or also a particular disease-causing pathogen, completely from the population, similar to methods proposed for human clinical applications (e.g. White, Hu & Khalili, 2015; Tabebordbar *et al.*, 2016).

Although more ambitious, CRISPR technologies can also be used to supplement genomic diversity of bottlenecked populations to increase pathogen resistance (e.g. Savage & Zamudio, 2011) or adaptive potential in a changing environment (*facilitated adaptation*; Thomas *et al.*, 2013; Harrisson *et al.*, 2014). The preservation of 'cryptic' genetic diversity is increasingly recognized as an important feature for allowing populations to adapt faster to environmental change (Hayden, Ferrada & Wagner, 2011; Paaby & Rockman, 2014). Similar to recent success using cryopreserved semen for supplementing genomic diversity of the black-footed ferret *Mustela nigripes* population (Howard *et al.*, 2016), CRISPR technology could be used for the same purpose, targeting genomic regions with reduced diversity, as identified from whole-genome sequences obtained from preserved tissues of extinct lineages (e.g. Hofman *et al.*, 2015; Holmes *et al.*, 2016).

CRISPR technologies have also been proposed to resurrect extinct species (e.g. Shapiro, 2015). While recent methods are not capable of altering the genome to the extent required to produce a living individual of an extinct species, research is currently underway using CRISPR-Cas9 to modify phenotypically relevant genes in an extant species to reflect what existed in the closely related extinct species (or *trait resurrection*). For example, researchers have identified and successfully altered genes from the wooly mammoth *Mammuthus primigenius* and its closest living relative the Asian elephant *Elephas maximus* that are associated with adaptations to a cold environment (Lynch *et al.*, 2015; see also Shapiro, 2015). CRISPR technologies could be used to modify those specific genes within critically endangered elephant species thereby decreasing habitat restrictions if necessary. So likely is this technology to impact on conservation science and practice that the International Union for Conservation of Nature (IUCN) Species Survival Commission has established a De-extinction Task Force for drafting a set of guiding principles on de-extinction for conservation benefit (P. Seddon, pers. comm.).

We would remiss to acknowledge, however, that targeting just a few genes or genomic regions for editing may not always be sufficient for phenotypic change, or at least in the way intended for conservation. An increasing number of studies have shown that the genetic architecture of many fitness-related traits is largely under the control of many genes of small effect, or polygenic, including the influence of genetic epistatic interactions and functional intergenic regions (Harrisson *et al.*, 2014; Taylor & Ehrenreich, 2015). Therefore, significant challenges do exist for altering the phenotype using genomic-editing techniques; yet, new genomic technologies such as CRISPR-Cas9 have great promise for also making it much easier to link genotypes with phenotypes and fitness in non-model species (Bono, Olesnicky & Matzkin, 2015). Notable advances using CRISPR technologies for human health and commercial agriculture have occurred

quickly over the past few years because a well-established foundation already existed linking many genomic variants with observed phenotypic traits (e.g. Ainsworth, 2015; Harper, Nayee & Topol, 2015; Tabebordbar *et al.*, 2016). As whole-genome sequencing technologies become more accessible allowing for the generation of genomic datasets for multiple individuals in species of conservation concern, our ability to decipher the genomic architecture of complex traits important for species persistence will undoubtedly improve (see also Bono *et al.*, 2015). More research, focused on this topic, is certainly warranted and necessary for advancing genomic-editing as a tool for conservation management.

Furthermore, significant concerns do exist that genome-editing technologies such as CRISPR-Cas9 may also cause harm to the individual or population and community due to uncertainties with altering genome processes and potential subsequent non-target effects (e.g. Lander, 2015; Webber *et al.*, 2015). Those concerns arise from the fact that much remains to be learned about how the information encoded in the genome is transcribed into function. We agree that much is left to be learned (e.g. Harrisson *et al.*, 2014), but think that the possibilities offered by this technique should not be ignored, certainly not in a crisis discipline such as conservation. In fact, support already exists for the use of CRISPR technology in human somatic cell-based gene therapies (e.g. National Academy of Sciences, 2015), and the British regulatory agency that oversees reproductive biology has recently allowed research to proceed using CRISPR-Cas9 to alter human embryos (i.e. germ-line manipulation) for developmental biology research (Siddique, 2016).

Undoubtedly, there are practical, ethical and legal considerations that need to be addressed before genomic-editing technologies are integrated into active conservation practice. Researchers, practitioners and policy makers must work together and identify the best approaches for utilizing this technology while also acknowledging that great care must be taken to avoid irreversible harm. The rapid adoption of CRISPR-Cas9 and similar genomic-editing technologies for addressing human health-related issues is unprecedented as reflected by the growing number of applications as described in the scientific literature and popular press over the past 2 years. A similar level of enthusiasm is needed to explore, develop and implement the same technology for biodiversity conservation.

Disclaimer

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