ISAC
INVASIVE SPECIES ADVISORY COMMITTEE

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Advanced Biotechnology Tools for Invasive Species Management

Submitted for consideration by the Invasive Species Advisory Committee (ISAC) Advanced Biotechnology Task Team

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Increasingly, genetic tools are being used to detect and solve pressing environmental, social, and health-related challenges. It is clear that investments in technology innovation can be game changing, as advances in biotechnology may provide new methods to protect the Nation's resources from the negative impacts of invasive species. The current toolbox of management options is recognizably insufficient to deal with many of the high-impact species that have been introduced. However, "surrendering" to these species is generally not a viable option from ecological, health, economic, socio-cultural, or political perspectives. Cost-efficient solutions to these "grand invasive species challenges" need to be found. Through processes that strategically alter an organism's genetic blueprint (aka genome), advanced biotechnologies may substantially improve our capacities to eradicate and/or control populations of invasive species.

Interest in the application of advanced genetic technologies is growing rapidly on national and international scales, across disciplines, and for parties affected by the impact of invasive species. As this interest grows, genetic technologies are quickly evolving with some raising questions over whether the potential risks are too high to warrant their use. Policy makers worldwide have expressed concern about the capacity of regulatory systems to keep pace with these technological advances and effectively address the societal concerns (known as "social license") that are inherent in the application of advanced genetic technologies, particularly when modified organisms are to be released. It is also important to note that the exploration of advanced genetic technologies is occurring in the midst of growing skepticism over both scientific and regulatory institutions. A single misstep in the development and application of advanced biotechnologies could fundamentally compromise social and political support for highly beneficial applications across a wide range of environmental, human health, and biodefense goals.

Clearly, there is a need to carefully explore the potential ecological, socio-economic, and political ramifications of using advanced genetic technologies to address invasive species. The National Invasive Species Council (NISC) has expressed this need through Action 6.3.1 of the *2016-18 NISC Management Plan*, which specifically calls for "an assessment of the potential ecological, socio-economic, and political benefits and costs of gene editing technology in the context of invasive species prevention, eradication, and control" (NISC 2016). The objective of this paper is to support this assessment by providing recommendations to NISC on the further development and application of advanced biotechnologies for invasive species eradication and control.

POTENTIAL APPLICATIONS

The rapid pace of technology advancement in the field of genetics is giving rise to approaches for the eradication and control of invasive species. Work is already underway to investigate advanced biotechnology applications for public health, pest management, and biodiversity conservation, all of which show a range of possibilities for addressing invasive species (Harvey-Samuel et al. 2017, Piaggio et al. 2017). Some examples of current explorations include:

Genome Editing: Genome editing is a technique that allows researchers to insert, delete, or modify DNA to silence, activate, or otherwise modify an organism's specific genetic characteristics. While the practice is not new (zinc finger nucleases [ZFNs] and transcription activator-like effector nucleases [TALENs] have been used since the late-1990s), the development and refinement of clustered regularly interspaced short palindromic repeats (CRISPR) combined with the Cas9 enzyme (CRISPR/Cas9) has rapidly transformed the field by increasing the specificity and efficiency of gene editing and decreasing costs by orders of magnitude (Vasiliou et al. 2016, Wang et al. 2016). Genome editing has a suite of potential uses and is currently being applied to human health and crop protection (e.g., vector-borne disease, crop pests). Future uses of genetic editing for invasive species management could include modifying:

- invertebrate pests for Sterile Insect Technique releases (e.g., mosquito eradication in Hawaii for eliminating avian malaria that is driving extinctions of Hawaiian endemic birds, Piaggio et al. 2017);
- introduced invertebrate pests so that they are unable to carry certain diseases, coupled with large scale releases

of those modified pests to increase the proportion of the population carrying the trait (Sampath et al. 2015, Piaggio et al. 2017);
- native species to be resistant to disease (e.g., bats for white-nose syndrome, amphibians for the fungal disease chytridiomycosis, Thomas et al. 2013, Adams 2016); and
- crops and other valuable plants to confer disease resistance, or to produce insecticide variants for invertebrate pests (e.g., American chestnut and chestnut blight, Jacobs et al. 2013).

Gene Drives: Gene drives further advance the use of genome editing by introducing a mechanism that promotes the inheritance of a particular gene to increase its prevalence in a population (Esvelt et al. 2014). Essentially, the process "drives" the desired genetic trait through subsequent generations of offspring from the modified individual(s). Gene drives occur naturally, but can now also be synthesized with CRISPR/Cas9. The use of gene drives provides the potential to modify sexually reproducing wild populations by design. Gene drives allow specific genes to be inserted, modified or deleted. For example, they can be used to modify populations to no longer carry a disease or to alter the sex ratio of all offspring to all male. Significant concern exists over the potential for gene drives to move beyond (or be moved beyond) their targeted population of an invasive species to affect that species where it is native (Noble et al. 2017).

To date, CRISPR gene drives have been synthesized in yeast, fruit flies and two species of mosquito (Di Carlo et al. 2015, NAS 2016). Specific potential applications include mosquito control to limit the transmission of malaria and other vector borne diseases, or to eradicate invasive rodents on islands.

RNA Interference: Ribonucleic acid interference (RNAi) is a naturally occurring intracellular mechanism, which effectively "silences" targeted genes (Fire et al. 1998, EPA 2013). The process involves the introduction of double-stranded RNA into the cell, which results in the destruction of single stranded messenger RNA with the same nucleotide sequence. This type of targeted gene silencing can be used to provide resistance to pests and diseases, eliminate production of specific hormones, or can be a taxa-specific toxicant (Huvenne and Smagghe 2010, Xue et al. 2012, Casacuberta et al. 2015). As such, these new technologies have significant potential to improve targeted pest and invasive species control and replace certain use patterns of conventional and organic chemistries used for broad-spectrum pest control. Future uses for invasive species control could include:

taxa-specific pesticides for use in baits and foliage sprays, or in applications to marine or freshwater systems to control invasive mollusks, fish, and introduced parasites of native fish (Heath et al. 2014, Owens and Malham 2015, Saleh et al. 2016);

taxa-specific hormone suppressants in baits that would disrupt social dynamics or turn workers against queens, leading to colony collapse in invasive social invertebrates like ants; and

modified invasive scale insects, such that invasive ants who share a symbiotic relationship with the scale are affected, but other scale predators or parasites are not affected.

ISSUES AND CONCERNS

As these advanced biotechnologies are developed, it is critical to have adequate decision support tools and methods that can identify, assess, and mitigate their potential risks in the research and development phase (e.g., laboratory conditions and field trials), as well as in their full-scale applications. A 2016 National Academy of Sciences (NAS) study included a number of recommendations relevant to the research phase and overall biosecurity, but increased attention is needed given ongoing evolution in the technology and regulatory requirements for assessing potential field-based applications (NAS 2016, Akbari et al. 2015). While this requires the development of new decision support tools, lessons learned and practices can also be derived from other fields of application.

Biosecurity: The 2016 NAS study included a significant focus on biosecurity, as well as recommendations for establishing confinement and containment protocols for laboratory and field-testing and release. The report outlines a step-wise approach similar to that used in the development of biocontrol agents. The steps include: preparation for research (phase 0); laboratory-based research (phase 1); field-based research (phase 2); staged environmental release (phase 3); and post-release surveillance (phase 4) (NAS 2016).

Risk Analysis: Research on advanced genetic technologies needs to proceed in a manner that identifies and assesses the relative risks at each stage of development (e.g., laboratory containment, clinical field trials) (Kuiken et al. 2014). Work is underway to strengthen risk identification, risk assessments, and population modeling capacities (Hayes et al. 2014, Casacuberta et al. 2015). This includes projects being undertaken by the U.S. Army Corps of Engineers (USACE) and Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO). Ideally, this work will inform the development of standardized risk analysis procedures and guidelines for prioritizing advanced biotechnology applications to invasive species eradication and control.

Risk Mitigation: There is also a need to develop risk mitigation techniques, for example by making the advanced biotechnologies self-limiting. The inclusion of reversal drives or daisy chain drives into gene drives are possibilities that are currently being explored (Noble et al. 2016). Additionally, the Department of Defense's Defense Advanced Research Projects Agency (DARPA) is funding the Safe Genes research program, which includes examination of controls for gene editing, application technologies, countermeasures and prophylaxis, and genetic remediation.

Governance: Policies and legal processes are shifting as regulators work to identify potential future technological applications and update existing rules accordingly (Marchant et al. 2013). The evolution of this regulatory process, most specifically associated with the Coordinated Framework for the Regulation of Biotechnology (Coordinated Framework), coincides with both an increase in the rate of technological change as well as an additional focus on the release of advanced biotechnologies for broader scale environmental applications (OSTP 1986, Oye et al. 2014). The movement be-

yond applications for medicines, food safety, and agriculture/livestock has raised questions as to whether the three current regulatory agencies have the requisite studies, data and risk assessment methodologies necessary to evaluate applications for broader ecological purposes, such as invasive species control.

The Coordinated Framework is designed to balance regulation adequate to protect consumer health and the environment with regulatory flexibility to avoid impeding innovation, and it outlines oversight responsibilities given existing legal authorities exercised by the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and USDA's Animal and Plant Health Inspection Service (APHIS). (OSTP 1986). A 1992 update and another initiated in 2015 have endeavored to maintain flexibility as biotechnology has advanced in scope and application (OSTP 1992, Holdren et al. 2015).[1] Within these regulatory processes, there are triggers for engaging assessments related to the National Environmental Policy Act (NEPA) and the Endangered Species Act (ESA), however invasive species applications represent a divergence from the types of products and private sector applicants with which the regulatory agencies have traditionally dealt. There are also arguments that the United States regulatory system itself is overly complicated. For example, the company Oxitec submitted two similar applications for trials of genetically modified *Aedes aegyptii* mosquitoes and to diamondback moths. Despite the similarity of the technology used, the mosquito application was reviewed by the Food and Drug Administration (FDA) given its focus on human health, whereas the diamondback moth was reviewed by APHIS given the focus on plant health. This has prompted a request from some developers of advanced biotechnologies for more clarity on how those regulatory regimes apply to invasive species applications.

Public Engagement and Social License: The most important long-term component for the successful use of advanced genetic technologies for invasive species eradication and control is public acceptance of the technology (Kuiken 2016). Failure to engage the public and foster support for real-world applications could leave these technologies sitting on the shelf despite their potential and significant investments in their development. Key questions include: Who is responsible for public outreach and engagement, particularly for issues that extend beyond the scope of public input into federal regulatory approval processes? At what stage should engagement take place? How should public dialogue be structured? How should competing interests be addressed (e.g., greater public good vs. local interests; transparency vs. proprietary commercial information)?

It is also important to recognize the need for and benefits of public discourse over a range of ethical and social issues including: how values inform notions of benefits and costs, what constitutes socially acceptable thresholds of risk, linkages to social justice, environmental justice and intergenerational equity, and how to maintain public trust in both science as well as government (Hart Research Associates 2013, Pauwels 2013, Meghani 2014, Sharpe 2014, Sankar and Cho 2015, NAS 2016). There will not be a single answer to these questions, but the mechanism for dialogue and public engagement is still critical for vetting the development and potential application of these advanced technologies.

Classical Biological Control: Classical biological control (biocontrol) is the use of an invasive species' natural enemies from its native range to control that invasive species in the new habitat that it has invaded (ISAC 2015, ISAC 2016). Parallels have been drawn between biocontrol and the use of genetically modified species as a control technique (the term genetic biocontrol has been used by some experts), given questions on any unintended impacts that the introduced organism could potentially have on non-target species and their ecosystems (Webber et al. 2015, NAS 2016, Piaggio et al. 2017). The identification, testing, and risk assessment of potential biocontrol agents is a rigorous regulatory process designed to ensure minimal to no non-target effects. Lessons can readily be applied from the long history of practice with classical biological controls. For example, biocontrol agents undergo an extensive process for risk analysis (Carruthers and D'Antonio 2005) and often include cost/benefit analyses as well (Jetter et al. 1997, de Lange 2010, McFadyen 2007). Of particular note is the use of a Technical Advisory Group for Biological Control Agents of Weeds (TAG) to provide guidance and serve as an interface between researchers and regulatory community (APHIS 2017).[2]

RECOMMENDATIONS TO NISC

We recommend that relevant NISC members work together to:

1. Foster the development of decision support tools and updated guidance for federal activities related to advanced biotechnology applications and invasive species, including:
   - prioritization frameworks to identify optimal targets (species and sites) for the application of advanced bio-

1 The 2015 update resulted in three documents relevant to potential future regulations:
- Modernizing the Regulatory System for Biotechnology Products: a draft update to the Coordinated Framework to clarify how the current authorities and responsibilities of EPA, FDA and USDA apply to different product (OSTP 2016a);
- National Strategy for Modernizing the Regulatory System for Biotechnology Products: A draft long-term strategy to ensure that the Federal regulatory system can efficiently assess any risks associated with future products of biotechnology. (OSTP 2016b); and
- Preparing for the Future Products of Biotechnology: an independent analysis of the future landscape of biotechnology products by the National Academy of Sciences, Engineering, and Medicine (NAS 2017)

In tandem with the development of these products, the EPA, FDA, and USDA are issuing guidance on how the update affects their own responsibilities and internal processes (see also Appendix I: Agencies and Statutes Regulating Biotechnology Products relevant to Invasive Species).

2 The TAG includes representation from USDA, DOI, EPA, DOD/USACE as well as the National Plant Board, the Weed Science Society of America and the ARS Biological Control Documentation Center.

technologies, and assessments of available and potential biotechnologies and their suitability for specific taxa/species in specific environments or under specific conditions (including climatic changes);
- updated guidance on confinement and containment protocols for laboratory and field testing and release;
- standardized risk analysis frameworks addressing aspects of risk assessment, management and communications appropriate to the full R&D cycles (i.e., project conceptualization, problem formulation, laboratory testing, field trials, scaled environmental releases); and
- evaluation of risk minimization and mitigation measures including physical, biogeographic, and temporal containment and application technologies.

2. Establish a multi-stakeholder technical advisory group under FACA focused on intentional environmental releases of advanced biotechnology applications. Modeled after the Technical Advisory Group for Biological Control Agents of Weeds, the group would identify emerging technical, social and environmental issues with their use and to help facilitate communication across the research, conservation and regulatory communities.
3. Call for relevant federal agencies to undertake a periodic horizon-scanning exercise to identify anticipated developments in advanced biotechnologies and their applications to invasive species prevention, detection, eradication, and control and report their findings to NISC via its Secretariat. This would include identification of implications for social license, policy and regulatory reviews, and resources needed for stewardship.
4. Direct the development and publication of guidance/best practices for developers of advanced biotechnology applications to invasive species to facilitate regulatory reviews, including clarity on regulatory jurisdictions, information/data necessary for reviews, and processes to interface with other relevant agencies where necessary and appropriate. The FDA, EPA, and USDA, as well as the Departments of Defense and the Interior have critically important roles in this process.
5. Direct relevant agencies to develop and publish a process to assess the ethical, social and interjurisdictional (i.e., federal, state, tribal, territorial) dimensions of emerging advanced biotechnologies and their deployment. This could include best practices, public engagement and securing social license.
6. Enable relevant federal research and development agencies to support research into new platform-providing advanced biotechnologies that can be applied widely to different invasive species and incentivize the development of novel approaches for invasive species management including the use of grand challenges as mechanisms to drive the development of new technologies.

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APPENDIX I

Agencies and Statutes Regulating Biotechnology Products relevant to Invasive Species

AGENCY	STATUTE	OBJECTIVE	APPLICATION
EPA	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)	Preventing unreasonable adverse impacts on the environment	Insect applications designed as a pesticide
EPA	Toxic Substances Control Act (TSCA)	Prevent the manufacture, processing, distribution in commerce, use, or disposal of chemical substances from presenting an unreasonable risk of injury to health or the environment	Catchall for applications not covered by other agencies or under other statutes
FDA	Federal Food, Drug, and Cosmetic Act (FD&CA)	Ensure human and animal drugs are safe and effective	Applications on rodents, fish and other animals, as well as on insects for health purposes
USDA	Plant Health Protection Act	Protect agricultural plants and agriculturally important natural resources from damage caused by organisms that pose plant pest or noxious weed risks	Plant applications that include a pest or noxious weed component

Derived from OSTP 2016b, which reviews statutes relevant to the full range of biotechnology products.