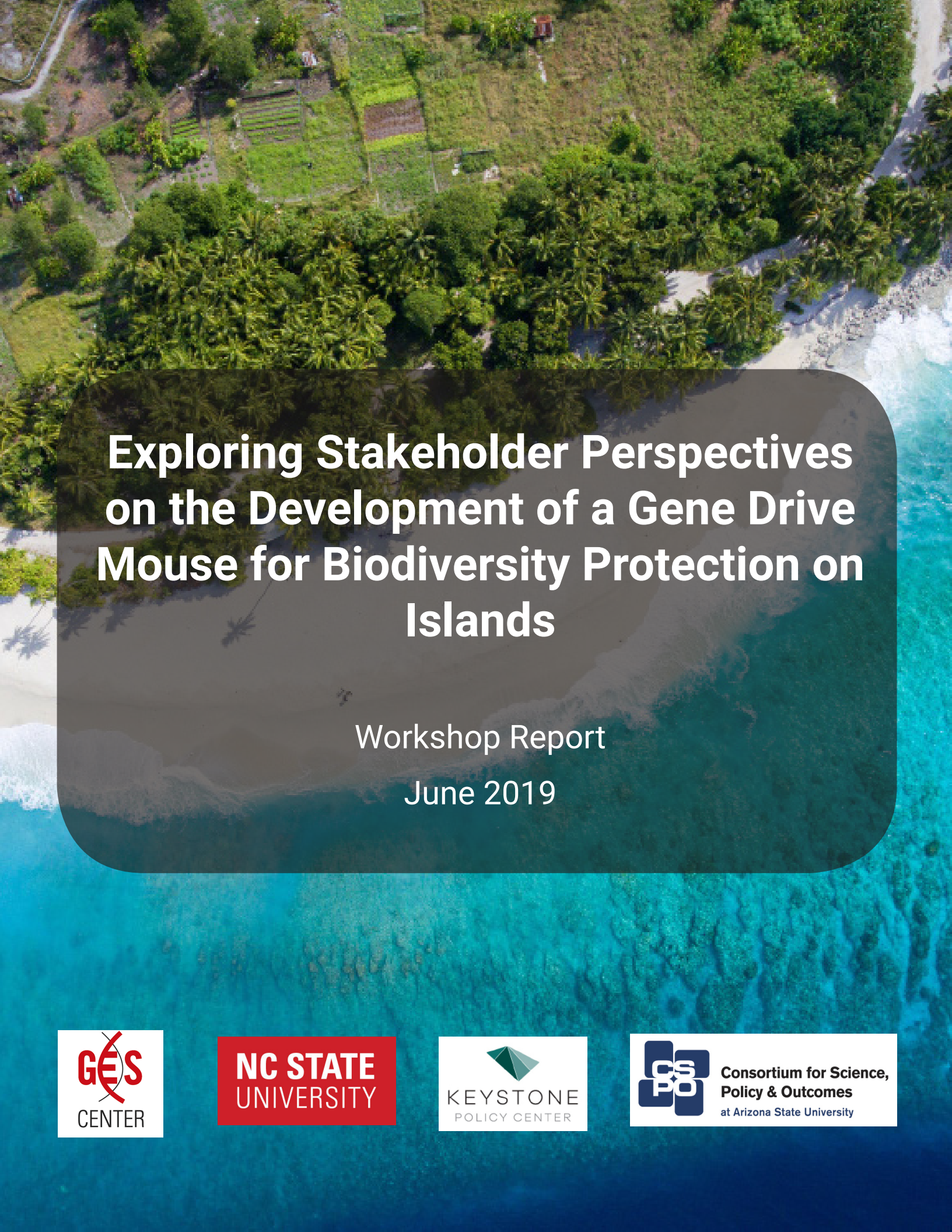

Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection on Islands

Workshop Report

June 2019

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CSPO Consortium for Science, Policy & Outcomes at Arizona State University

Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection on Islands: Workshop Report

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Available for download at the Genetic Engineering and Society Center website
http://go.ncsu.edu/ges-gene-drive-landscape

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Executive Summary

Workshop Purpose

The "Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection" workshop was held on the North Carolina State University campus in Raleigh, NC on March 7-8, 2019, aiming to convene a diverse group of stakeholders, scientists, funders, and leaders for an exploration of perspectives on the development of a gene drive mouse for restoring biodiversity on islands. Information collected at the workshop is presented in this report to inform upcoming decisions by the NCSU-Safe Genes research team about research, testing, and potential deployment of technologies (the Safe Genes program does not fund any environmental releases of gene drive modified organisms), as well as future engagement activities.

Project Background

House mice (*Mus musculus*) offer an ideal genetic model for exploring the possibility of developing a gene drive in invasive mammals. As pests, they pose challenges to human health (through disease transmission), agricultural yields and storage, and biodiversity, especially on islands where they are not native. The focal application for this workshop is the potential for developing and releasing a gene drive mouse on an island to suppress an invasive mouse population that has negative impacts to biodiversity endemic to that island (e.g., nesting seabirds, small reptiles).

This exploration of stakeholder perspectives is intended to inform laboratory research underway to develop a spatially-limited, gene drive mouse (through genetic engineering) to achieve invasive rodent population suppression or local eradication. Both the stakeholder analysis and laboratory research are funded through the United States Defense Advanced Research Projects Agency's (DARPA) Safe Genes program (SAFE-FP-005). The performer team led by NC State University was awarded support for a project entitled, "Restoring Ecosystems and Biodiversity through Development of Safe and Effective Gene Drive Technologies." Within that project, a stakeholder engagement team was tasked with qualitatively assessing the questions, should we create this gene drive organism, and, if so, under what conditions? The engagement team does not take a position regarding whether or how a gene drive mouse should be developed for biodiversity conservation.

This is a report to the Safe Genes project funders and researchers and the NC State-led performer team, exploring the potential to develop a gene drive mouse for protecting island biodiversity. For transparency, the report is publicly available on the website of NC State's Genetic Engineering and Society Center: https://go.ncsu.edu/report-gene-drive.

Workshop Objectives

- Summarize and discuss the findings of a recent landscape analysis, based on stakeholder interviews, including perspectives on *whether or not* a gene drive mouse should be developed (and someday potentially deployed) for biodiversity restoration (https://go.ncsu.edu/ges-gene-drive-landscape)
- Gather stakeholder perspectives on research design decisions and risk assessment related to the development of a gene drive mouse within a laboratory setting, as well as in biosecure simulated natural environments
- Gather stakeholder perspectives on the design and risk assessment of *hypothetical* field trials/environmental releases of a gene drive mouse (*note, no environmental releases are funded by the Safe Genes program*)
- Gather input into the design of future community-level and stakeholder engagement

Workshop Design

The workshop was designed to create a conversation between technical researchers working on developing and testing different gene drive mechanisms in mice and expert stakeholders interested in the

ecological and societal implications of a gene drive mouse in wild settings. The invitation list for the workshop included participants from organizations that are likely to engage on the issues but have not yet taken positions on the emerging technological options.

The researchers are still grappling with the feasibility and efficacy of several technical options for gene drive mechanisms. The workshop organizers therefore designed dialogues around key decision phases in the arc of the project. Each of the discussions began with an overview of the state of the science; key take-aways from each subsequent discussion are outlined below.

Discussions

In the Lab: Gene Drive Mechanisms

- Participants less familiar with gene drives appreciated the background presentation.
- Biasing gender (to suppress a population by attrition) may not be considered sufficiently humane: changes in competition or mating strategies could potentially lead to increased levels of starvation, fighting, cannibalism, cruelty, or aggression.
- Public support of gene drives may depend on high confidence of efficient and effective eradication. If only partial success is likely, support for the entire system of research may be in jeopardy.
- Public audiences may be less concerned with distinctions among specific gene drive mechanisms (t-Sry, Y-shredder, X-shredder).

In the Lab: Self-limiting Gene Drive Options

- Self-limiting strategies may address the major concern of biocontainment.
- Molecular control mechanisms are compelling, and many of their subsequent considerations of risks/benefits of gene drives were influenced by the potential use of locally-fixed alleles.
- Locally-fixed alleles are not useful for reinvasion management (of a new population of mice with different genetics.

Simulated Natural Environments for Testing Gene Drive Mice

- Discussions emphasized the importance of the first set of experiments going well; a breach of protocol or adverse effect could have a large impact on public perception.
- Following strict staff training protocols may be as important as testing and maintaining physical barriers for containment.
- Other initiatives, such as Target Malaria, may have lessons for engaging public audiences about early stages of research and testing, prior to a trial release of a new technology.
- Community engagement near and around the simulated natural environment facility may be important, but community debate could quickly come to be dominated by organizations focused on global implications.

Island Selection for Potential First Field Trial

- Fictional island scenarios enabled rich discussion about candidate island selection criteria that encouraged attention to a diversity of characteristics and potential trade-offs.
- Participants rated this activity very highly.
- While trends could be identified, the diversity of stakeholders in the room translated into a diversity of opinions regarding the most desirable island scenario.
- A point of consensus was that a candidate island must have a mature regulatory regime.
- Participants judged the presence of other rodent species to be the most ‘relaxable’ of the island selection criteria, which surprised the project team, who has always considered it to be an important criterion. This suggests the need for additional two-way dialogue between stakeholders and project personnel.

Lessons for Engagement

The workshop concluded with a focus on future community and stakeholder engagement. These discussions prompted reflection from both the workshop participants and organizers, described below. Overall, early engagement was viewed as important,

with particular support for beginning engagement processes 'upstream' from the full development of an emerging technology - gene drive mouse development is still in-progress. By organizing the workshop around different decision phases of technology development, participants were able to have productive discussions about current, near-term, and far-term research activities. Important to note here is the novelty of facilitating dialogue between stakeholders and an innovation team genuinely open to different perspectives. Participants communicated their appreciation for the innovation team being open to feedback and learning from a broad range of stakeholder input, and the innovation team communicated appreciation for the workshop participants' willingness to learn more about the project and provide this feedback.

One useful tool for soliciting feedback in the face of uncertainty about the project was the use of fictional scenarios. The development and evaluation of four scenarios allowed for complex integration of facts and values, encouraged tradeoff discussions, and revealed implicit and explicit priorities. Fictional scenarios also allowed organizers to include realistic island criteria, but avoid singling out particular island communities as possible sites of field trials. Using scenarios to explore meaningful tradeoffs integrated and brought to life many of the complex issues that had been discussed throughout the workshop until that point.

However, some participants also saw potential risks with early engagement. For example, discussions of technical options without safety studies and risk assessment may be counterproductive and raise undue alarm with some stakeholders and broader public audiences. Similarly, discussion of potential new tools may make it difficult for existing strategies (current invasive species eradication strategies use broad spectrum toxicants) to be maintained. Some concerns of early engagement centered on the inherent conflict between the intent to develop a workable mouse and hence work towards public acceptance and the intent to be an 'honest broker' of different options between the scientists and the public. In this light, these concerns are consistent with uncertainties about authority and responsibility -- particularly with respect to engagement -- at each of the phases of research outlined above.

Additionally, the stakeholders that attended the workshop were broadly supportive of gene drive research. The persons/organizations that argue for moratoria on gene drive research altogether were not present (but were invited). As such, the overall tone of the workshop and workshop report may reflect greater consensus than exists in the landscape of gene drive research and governance more broadly.

Even with these qualifiers in mind, feedback from the workshop participants and reflection from the organizers suggest relative success with respect to overall workshop goals. Moving forward, one of the next questions to grapple with is how to move from stakeholder engagement to community engagement, particularly with respect to the timing of community engagement.

Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection: Workshop Report

1.0 Workshop Purpose

The "Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection" workshop was held at Hunt Library on the North Carolina State University campus in Raleigh, NC on March 7-8, 2019. The aim was to convene a diverse group of stakeholders, scientists, funders, and leaders for an exploration of perspectives on the development of a gene drive mouse for restoring biodiversity on islands. While a prior landscape analysis based on stakeholder interviews investigated *whether* such a mouse should be researched and developed, among other issues (https://go.ncsu.edu/ges-gene-drive-landscape), this workshop focused on gathering feedback regarding societal issues associated with future research and design phases. Information collected at the workshop is presented in this report to inform upcoming decisions by the Safe Genes research team about research, testing, and potential deployment of technologies, as well as future engagement activities.

1.1 Project Background

House mice (*Mus musculus*) offer an ideal genetic model for exploring the possibility of developing a gene drive construct in invasive mammals. As pests, they pose challenges to human health (through disease transmission), agricultural yields and storage, and biodiversity, especially on islands where they are not native. In line with the guidance of the National Academies of Sciences, Engineering, and Medicine report on gene drive research (NASEM, 2016), if research on gene drives in mice were to progress to a field trial, an island ecosystem would offer an additional level of physical containment. This workshop (and the landscape analysis) explored stakeholder perspectives about the potential for developing and releasing a gene drive mouse on an island to suppress an invasive mouse population that poses a threat to biodiversity endemic to that island (e.g., nesting seabirds).

This exploration of stakeholder perspectives is intended to inform laboratory research currently underway to develop a gene drive mouse (through genetic engineering), creating an inheritance mechanism that biases future generations to be male (or female) only, thereby achieving invasive rodent population suppression by attrition. Both the stakeholder analysis and laboratory research are funded through the United States Defense Advanced Research Projects Agency's (DARPA) Safe Genes program (SAFE-FP-005). Safe Genes performer teams work across three primary technical focus areas to develop tools and methodologies to control, counter, and even reverse the effects of genome editing—including gene drives—in biological systems across scales. The performer team led by NC State University was awarded support for a project entitled, "Restoring Ecosystems and Biodiversity through Development of Safe and Effective Gene Drive Technologies."

Dr. Jason Delborne, a faculty member in Forestry and Environmental Resources and the Genetic Engineering and Society Center at NC State, is a Co-Principal Investigator of this Safe Genes award. He leads the stakeholder engagement team of experts tasked with qualitatively assessing the questions, should we create this gene drive organism, and, if so, under what conditions? Other members of the stakeholder engagement team included Dr. Katie Barnhill-Dilling, who was funded as a postdoctoral researcher at NC State, and the Keystone Policy Center (primarily represented by Julie Shapiro) and Dr. Mahmud Farooque, who received financial support as consultants through the Safe Genes award to NC State. This engagement team does not take a position regarding whether or how a gene drive mouse should be developed for biodiversity conservation.

This is a report to the Safe Genes project funders and researchers and the NC State-led performer team, exploring the potential to develop a gene drive mouse for protecting island biodiversity. The report is publicly available on the website of NC State's Genetic Engineering and Society Center: https://go.ncsu.edu/report-gene-drive.

1.2 Workshop Objectives

- Summarize and discuss the findings of a recent landscape analysis, based on stakeholder interviews, including perspectives on *whether or not* a gene drive mouse should be developed (and someday potentially deployed) for biodiversity restoration (https://go.ncsu.edu/ges-gene-drive-landscape)
- Gather stakeholder perspectives on research design decisions and risk assessment related to the development of a gene drive mouse within a laboratory setting, as well as in biosecure simulated natural environments
- Gather stakeholder perspectives on the design and risk assessment of *hypothetical* field trials/ environmental releases of a gene drive mouse (*note, no environmental releases are funded by the Safe Genes program*)
- Gather input into the design of future community-level and stakeholder engagement

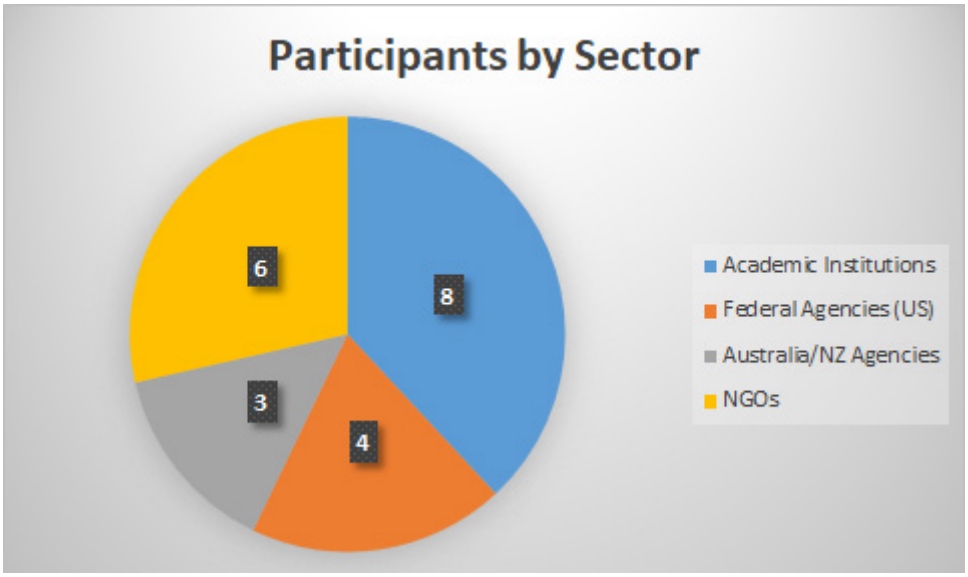
1.3 Workshop Design

The workshop was designed to create a conversation between technical researchers working on developing and testing different gene drive mechanisms in mice and expert stakeholders interested in the ecological and societal implications of the potential future deployment of a gene drive mouse to protect island biodiversity. This posed some challenges because the researchers are still grappling with the feasibility and efficacy of gene drive mechanisms. Uncertainties about the likelihood of success remain, and the risk profiles for each option are yet to be developed, making it difficult for expert stakeholders to express preferences, issues, and priorities. In addition, many expert stakeholders who might potentially be interested and engaged in issues related to gene drives and biodiversity conservation are not currently engaged due to the lack of an existing product. Hence, the invitation list for the workshop included participants from organizations that are likely to engage on the issues but have not yet taken positions on the emerging technological options.

Facilitating conversations between stakeholders with different kinds of prior knowledge required ensuring some basic level of understanding the advantages, disadvantages, and associated uncertainties related to laboratory research, testing, and potential field trials of gene drive mice. In that vein, the workshop began with a very basic overview of gene drive methods for population control and moved on to specific modeling approaches under consideration by the project team (sections 2 and 3). Next, attention shifted to a discussion of the issues related to testing gene drive mice inside a biosecure "simulated natural environment" (section 4), which could then lead to field trials in different island environments. Since there are no active set of test islands currently under consideration in the United States, fictional scenarios with different geographical, ecological, societal and regulatory characteristics were developed to spur conversation about how to select an island for a future field trial (section 5). The final segment of the workshop focused on future stakeholder and community engagement (section 6). These discussions were further informed by presentations of risk assessment models used in Australia (box 4.1) and social science research on public perceptions on invasive mammal control in New Zealand (box 4.2).

1.4 Participants

- Evolutionary biologists
- Invasive species experts
- Ethicists
- Mouse biologists
- Conservation experts
- Animal welfare experts
- Wildlife biologists
- Biotechnology policy experts
- Population geneticists
- Population modelers



1.4 Agenda

March 7, 2019

9:00 AM Introductions
- Participant introductions, agenda review

9:30 AM Background
- The NCSU Safe Genes project – *Jason Delborne, North Carolina State University*
- Summary of stakeholder interview report – *Julie Shapiro, Keystone Policy Center*
- Examples of relevant community engagement case studies – *Mahmud Farooque, Arizona State University*

10:15 AM Break

10:30 AM In the lab: Technological options for gene drive mouse
- Presentation on different gene drive mechanism options – *Paul Thomas, University of Adelaide* [recorded video] (Q&A by *John Godwin, North Carolina State University*)
- Small group discussion of pros, cons, and questions regarding the technological choices

12:00 PM Lunch

1:00 PM In the lab: Technological choices/options for self-limiting drives (private alleles)
- Presentation on different self-limiting drive options – *John Godwin, North Carolina State University*
- Small group discussion of pros, cons, and questions regarding the technological choices

2:30 PM Break

2:45 PM Simulated Natural Environment (SNE): Design and engagement
- Presentation on SNE design and plans – *Toni Piaggio, US Department of Agriculture*
- Small group discussion on SNE design

4:15 PM Field trials (*hypothetical* environmental release)
- Overview of risk assessment models and hazard analysis considerations – *Owain Edwards, CSIRO*

4:45 PM Open discussion and reflection

5:30 PM Dinner and presentation
- Public Perspectives on Invasive Species/Mammal Control with novel technologies in New Zealand – *Edy MacDonald, New Zealand Department of Conservation*

March 8, 2019

9:00 AM Field trials (*hypothetical* environmental release)
- Small group discussion of individual scenario islands (risks, benefits, concerns, trade-offs, etc.)
- Full group discussion to compare island scenarios

10:45 AM Break

11:00 AM Island selection
- Presentation of island selection criteria – *Royden Saah, Island Conservation*
- Discussion of island selection

12:00 PM Lunch

12:15 PM Design considerations for future stakeholder and community engagement

1:30 PM Final reflections and discussion

2:00 PM Adjourn

2.0 In the Lab: Basic Gene Drive Mechanisms

2.1 Background

The purpose of this section was to provide a basic overview of emerging gene drive strategies for invasive species control and the different methods to sex-bias a population (all male or all female) that are currently under consideration by the technical research team. Attention focused first on the technical methods of each strategy, followed by significant discussion about their potential ethical, legal, and societal implications. Three general strategies were discussed, as described below. Each of these technical options are in different stages of "in-development," and none of them has yet produced a gene drive mouse, or evidence that successful development is definitely achievable. Thus, the innovation team presented all options as characterized by some degree of uncertainty as reflected in the presentation of progress to date and remaining research questions.

2.1.1 t-Sry

- **What is it?** The t-complex is a naturally occurring feature in *Mus musculus* that biases inheritance; most offspring—upwards of 90%—inherit the t-complex (Kanavy & Serr, 2017). Capitalizing on this naturally occurring gene drive, researchers are attempting to insert the masculinizing gene (Sry) into the t-complex, making most offspring phenotypically male even if they are genetically female, which will result in substantial population decline if not eradication (Backus & Gross, 2016).
- **Advantages:** Relies on a naturally occurring gene drive, which the public may prefer to a synthetically-derived gene drive.
- **Disadvantages:** 90% inheritance rates may not be sufficient for invasive rodent management applications (i.e., suppressing populations but not eliminating them).

2.1.2 X-shredder

- **What is it?** X-shredder is a gene drive mechanism that targets and disrupts specific sequences on the X chromosome (in some cases cutting, or shredding, the X chromosome), and thus biasing against females in a population (see Galizi et al., 2016).
- **Advantages:** Because a single male can mate with multiple females, reducing the number of females is more effective than reducing the number of males.
- **Disadvantages:** Can only work if the targeted sequence is found only on the X chromosome.

2.1.3 Y-shredder

- **What is it?** Gene drive mechanism for biasing against males of in a population by disrupting, or shredding, the Y chromosome (see Prowse et al., 2019).
- **Advantages:** May not require homing, which has been elusive in all of the gene drive mechanism experiments in mice thus far.
- **Disadvantages:** When the mechanism fails, it creates a resistant allele. Relies on male mate selection, which does not generally confer selective pressure (males may mate with multiple females).

2.2 Stakeholder Views on Basic Gene Drive Mechanisms

While conversations covered many topics, the following themes arose as key considerations in comparing the three gene drive strategies described above.

2.2.1 Animal Welfare: Some of the participants questioned the premise that reducing the population of invasive species by biasing sex through genetic manipulation is more humane than existing eradication and control strategies, which are based on toxicant baits that cause internal hemorrhaging. Concerns centered on the issue of having more/less of one sex than the other during the transitional period (between introduction and eradication) and what kind of behavioral and psychological impact the sex imbalance would have on the populations of

invasive rodents. Issues such as starvation, fighting, cannibalism, cruelty, and aggression were raised; natural boom and bust cycles and the temporary increase in mouse populations with introductions of gene drive mice were considered. Some participants offered that the welfare of the invasive species needed to be weighed against the welfare of the threatened species. There appeared to be a potential ethical dilemma that depended on cultural and societal attitudes with respect to different species, invasive as well as endangered.

2.2.2 Efficacy and Efficiency: Approaching the technological choice question from the standpoint of animal welfare, some participants favored strategies that would be most efficient in getting to complete eradication of an invasive mouse in the shortest amount of time. They were of the opinion that technical efficiency took precedence over behavioral concerns. To these participants, the t-Sry approach, which could yield 90% reduction in the first generation of a treated population, appeared less favorable because they felt it was not any more effective than traditional rodenticides. However, other participants pointed out that from an integrated pest management standpoint, multiple strategies and tools will most likely be used to achieve suppression as quickly as possible. In other words, the t-Sry would not be the only pest control method used.

2.2.3 Technological Choice: Some stakeholders did not think that the appearance of being more "natural," as was the premise offered with the t-Sry option, would make a genetic population control strategy more appealing than others that were more "synthetic" or "transgenic." These stakeholders gave more weight to the likelihood of success factor. They found the X-shredder, based on current state of research, more desirable than others. Other concerns weighing on the technological choice considerations were (a) regulation, (b) reversibility, (c) off-target effects, (d) mutation and resistance development, (e) island specific impacts of temporary increases in mouse populations, (f) need for repeat applications, and (g) public acceptance.

2.2.4 Public Perception: It was unclear if the welfare of an invasive species, a concern among some of the participating stakeholders, would be as important to the broader public. Potential for spread beyond the targeted population, temporary increase of the invasive mouse population, and off-target effects may be of greater concern than choice of male vs. female bias or natural vs. synthetic technology. Some stakeholders also worried about misperception. For example, the public could view gene drive as a permanent, effective and efficient alternative to the integrated pest management approach, which would consider gene drive applications as another tool in the toolbox to consider. Some participants thought that initial public acceptance or rejection of genetic manipulation for biodiversity conservation could also change over time. Public perceptions may also vary between developed and developing countries, where there are greater threats and more dire impacts on lives and livelihoods. It may also depend on the "who" and "why"; for example, whether technological development is led by the government acting explicitly in the public interest or by large agricultural firms seeking to increase profits.

2.2.5 Public Engagement: In general, participating stakeholders did not think that it was too early to engage the public in the discussion of different technological choices, even though much uncertainty about the potential trade-offs still remained. Some stakeholders worried about word choice and wondered whether the use of the term "shredder" may negatively bias public views against those technological approaches. Some participants felt that instead of avoiding discussion of complex tradeoffs and worst-case scenarios, scientists should welcome dialogue with the public for greater transparency and the building of trust.

3.0 In the Lab: Self-limiting Gene Drive Options

3.1 Background

The purpose of this section was to present three specific options for self-limiting gene drives, which would spread through a population of mice to achieve population suppression or eradication, but have a low probability of spreading beyond the targeted geography or timeframe of intervention. Workshop presentations and discussions addressed three self-limiting options, respective of their theoretical advantages and disadvantages (e.g., reversibility and off-target impacts) as currently understood and potential stakeholder concerns.

3.1.1 Locally-Fixed Allele

- **What is it?** Because of "founder effects," there is generally lower genetic diversity on invaded islands than on mainlands. The effects of this genetic bottleneck are such that relatively quickly, island populations have drifted genetically from the source mainland populations. The locally-fixed allele approach takes advantage of this natural process, developing a gene drive that targets alleles that are found in each individual in an island population (i.e., not found or in very low frequency in mainland populations). This is considered to be a form of molecular control because were a gene drive mouse with locally-fixed alleles to move from the island to the mainland and mate, there would not be homing or minimal homing in mainland genotypes. In other words, the gene drive would not spread or have limited spread from which the mainland populations would fully recover (Sudweeks et al., 2019).
- **Advantages:** Allows for some measure of limitation over the spread of a gene drive; gene drive doesn't affect other populations.
- **Disadvantages:** If there is a new invasion of invasive mice on the island of concern, the drive with a locally-fixed allele is highly unlikely to be compatible with (or work on) the new population. Need to sample target population thoroughly to obtain representative genomic data to identify alleles and their frequency in the population. Target alleles must be fixed (a single allelic state found in each individual in the population).

3.1.2 Threshold Drive

- **What is it?** A threshold drive is designed to go to fixation in a breeding population only when the initial introduction of gene drive organisms exceeds a certain threshold. For example, if the threshold of the drive system is 50%, and the current invasive population is 1,000 mice, introducing more than 1,000 mice (50% of a population of 2,000) will drive the introduced trait throughout the population, while smaller introductions will eventually be eliminated. The molecular techniques rely on strategies such as "killer-rescue." Threshold drives are theoretically self-limiting because a small number of gene drive mice landing on a neighboring island or mainland will not drive the trait to fixation in those non-target populations because a threshold would not be achieved.
- **Advantages:** Does not depend on identifying locally-fixed alleles or collecting population genomic data. Also allows reversal of a drive by introducing a number of wild-type organisms that overwhelms the threshold required for driving a trait to fixation.
- **Disadvantages:** Requires large releases of gene drive modified mice, which likely exacerbate the threat to endangered species and biodiversity in the short term.

3.1.3 Daisy Chain

- **What is it?** A type of split drive, which is a multi-part CRISPR-based gene drive. Daisy chains are multi-part drive systems, where each transformation has to work for the next to be initiated. No element can drive itself, and one element is not driven at all, resulting in a gradual deceleration of the driven trait. This strategy represents a generational or temporal limitation

on the spread of a gene drive (see Noble et al., 2019).

- **Advantages:** Modeled to have a low threshold for fixation; one may only need to release a small number of gene drive organisms in order for the desired trait to effectively spread through a population.
- **Disadvantages:** Genetic rearrangement could result in a self-driving daisy chain, which would undermine its feature of deceleration.

3.2 Stakeholder Views

3.2.1 New invasion: While finding the self-limiting approaches appealing, some participating stakeholders were concerned about the issue of reinvasion – how to keep the mice from coming back or the appearance of new mice with a different genetic background than the previously identified, locally-fixed alleles. Some participants thought that the approach would be more attractive where biosecurity or biocontainment could be more effectively assured or enforced. An island's distance from the mainland, and whether inhabited or uninhabited, also seemed to matter with participants.

3.2.2 Cost and Time: Cost and time were a concern among some of the participants since the self-limiting approach with private alleles will require an understanding of the genomic population structure on the island and developing a new construct for every island. If true, this shortcoming may undermine the goal of creating an inexpensive and easily scalable technology to save threatened species.

3.2.3 Technological Choice: Participants felt that the tradeoffs between the different self-limiting technological options depended on the island and the invasive population in question. With locally-fixed alleles, since the choices are island specific, there is the possibility of needing to reevaluate the gene drive and non-gene drive options for each new endangered species situation. Some participants thought that if the gene drive does not work the first time, it could create resistant alleles, requiring a redevelopment of the mouse construct. The threshold drive was attractive to some participants because of its reversibility feature and the likelihood of decreased maintenance and management over time.

3.2.4 Public Engagement: Some stakeholders felt that the locally-fixed alleles strategy called for more and earlier public engagement because of concerns about reinvasion, high sunk costs, tradeoffs between varying technological choices, and hypothetical impact considerations. Some stakeholders expressed concerns over invasive species designation, asking at what point a mouse that has developed locally-fixed alleles becomes a part of the local ecosystem — and thus, no longer "invasive." This further identified the need for early engagement to determine any cultural or religious significance associated with the targeted species.

Box 3.1: Physical containment and genetic studies for GE biosecurity at the USDA/ APHIS/Wildlife Services National Wildlife Research Center (NWRC)

Purpose: Conduct trials with wild house mice (non-genetically engineered) to determine appropriate physical containment methods and biosecurity plans at NWRC. Such trials will prepare us more fully for the future ability to conduct gene drive rodent trials.

Research Questions:

1. What are effective & efficient materials & methods to contain free-ranging wild mice?
2. What are the primary, secondary, & tertiary physical-containment methods for wild mouse trials at NWRC?
3. If a mouse was to escape the building, what is its behavior (e.g., distance traveled from building, duration until exited NWRC campus, fate), and how does this inform our biosecurity plan?

Image 1. Photo of the NWRC

Spatial Limitation of Gene Drives by Targeting "Locally-fixed Alleles"

Research Objective: Synthetic gene drives rely on endonuclease-mediated cutting at specific genomic target sequences. The absence of such target sequences is sufficient to preclude genome-editing activity. A key goal of this project is to achieve spatial limitation of gene drives by targeting sequences present ubiquitously in island populations of interest, but not in adjacent populations. 'Locally-fixed alleles' (i.e., 'private alleles') are expected to arise through mutation and genetic drift when migration is limited, and

are commonly observed in rodent populations on oceanic islands (e.g., (Ozer et al. 2011, Savidge et al. 2012)), thereby providing unique genomic targets for designing synthetic gene drives. NWRC scientists have developed genomic approaches to identify locally-fixed alleles in any island population, which can then be used to inform design of genetic constructs tailored to affect specific island mouse populations only, but will not affect neighboring populations. Because this approach is based on well-studied population genetic principles of genetic drift and mutation, the outcomes can be readily modeled. Importantly, we have performed 'proof-of-concept' bioinformatics analyses using existing genomic resources for mice. It is important to note that the idea behind this gene drive target site approach is that it should be inherently "safe" as it could not self-replicate in wild mice outside the target population as they would lack the gene drive target sequence necessary for endonuclease activity.

Identify 'locally-fixed alleles' from six invasive mouse populations

Research Objective: To identify locally-fixed alleles in a target island rodent population, we will use a whole genome re-sequencing approach. To maximize analysis efficiency, genomic DNA from a sample of 40 individuals will be combined for each population prior to sequencing. Resulting sequences representing each population will then be surveyed using bioinformatic computational techniques to identify potential genome editing sites that harbor private alleles, and also facilitate additional genetic analyses of subject island mice populations, such as quantifying population differentiation, genetic diversity, and migration rates (Syring et al. 2016).

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4.0 Simulated Natural Environments

4.1 Background

The purpose of this section was twofold: (1) collect initial expert stakeholder feedback about some of the design considerations for gene drive mice trials in a simulated natural environment (SNE) using biosecurity preparedness plans at the USDA National Wildlife Research Center (NWRC) as a case study and (2) discuss stakeholder and community engagement strategies for such trials. NWRC is in the process of conducting trials with wild house mice to determine appropriate physical containment methods and biosecurity plans for envisioned SNE experiments. To be clear, NWRC has not yet conducted any trials with gene-edited or gene drive mice.

4.2 Stakeholder Views

4.2.1 SNE Design: Stakeholders were generally pleased with the different levels of physical containment. There were a few concerns expressed by some of the participants. First, in terms of **representation**, the test area did not appear to be representative of island geography, and the sample size seemed small and in need of more replication. Second, there were concerns about possible breaches through lapses in **human protocol**. Suggestions were made that staff training protocols be given the same level of priority as physical barriers. Third, some participants were interested in knowing more about the escape test using wild mice - how they escaped and when, which highlighted the importance of **communicating** details in the reporting of results.

4.2.2 Engagement Design: To meet the innovation team's overriding objective to get the first experiment, application, and engagement "right," the participants recommended maintaining a high degree of transparency. They suggested a focus on earning trust rather than seeking public approval: involving the local and broader stakeholder communities early in the containment and protocol design process; going beyond minimum National Environmental Policy Act (NEPA) requirements; involving media if necessary; and providing routine updates. Learning from the engagement experiences of the Target Malaria project was suggested (e.g., https://targetmalaria.org/how-the-stakeholder-engagement-teams-of-target-malaria-work-together).

4.2.3 Suggestion of locally-fixed allele Strategy: Stakeholders extended the discussion beyond the current SNE trials with wild house mice to contemplate some of the challenges and complications that would be posed by gene drive mice SNE trials, resulting from the interplay of regulatory mechanisms at the island, local, national and global scales. Some participants thought that the use of a locally-fixed allele strategy would offer biological containment in addition to the physical containment already envisioned. Essentially, the suggestion was to use a gene drive that would only target the experimental mouse population in the SNE and not affect surrounding mouse populations even if one were to escape.

4.2.4 Benefits and Risks: Some participants thought that an SNE experiment with gene drive mice might raise community concerns because it was not addressing a local problem (i.e., Ft. Collins does not have an invasive mouse that threatens local biodiversity). They worried that community engagement efforts for SNE experiments with gene drive mice may open the door for other interests to play an outsized and non-constructive role in the trial process. Some stakeholders also discussed the need to be attentive to non-physical harms and address community concerns related to religious beliefs and cultural values.

Box 4.1: Field Trials (*hypothetical* environmental release)

Presented by Owain Edwards, Commonwealth Scientific & Industrial Research Organisation (Australia)

There are currently no regulatory precedents for the design of a risk assessment framework for field trial releases of a synthetic gene drive. There are, however, design principles available from the literature, in particular those summarized in the *Gene Drives on the Horizon* report (NASEM 2016). This and other publications have favored the use of a quantitative risk assessment framework (QRAF) over a qualitative approach. A phased testing approach is also recommended, in which gene drive organisms move from laboratory testing to confined natural environments before any open release trials are considered. A previous QRAF for release of a *Wolbachia* gene drive mosquito (Murphy et al. 2010) can be used as a model for the development of an RA for gene drive mice. One key difference is the wealth of basic biological, ecological and genetic information that was already available in the literature for *Aedes aegypti*, including mosquitoes infected with the released *Wolbachia* strain. Much of this information will need to be collected for both wild type and gene drive mice. The standard QRAF involves identification of hazards, endpoint identification and prioritization, and risk quantitation, and involves extensive consultation with expert and non-expert stakeholders (Hayes et al 2018). Collection of baseline biological data for wild type mice can start immediately, but most of the information necessary for the QRAF can be collected only once the details of the technology and target island are known.

Box 4.2: New Zealanders' Attitudes Towards Emerging Pest-Control Technologies

Presented by Edy MacDonald, National Science Challenge (New Zealand)

The Biological Heritage National Science Challenge has funded a 2-year project (2017 – 2019) to explore New Zealanders' attitudes towards new and/or emerging pest-control technologies. This project aims to explore how New Zealanders' underlying values and beliefs shape their attitudes towards pest-control methods and technologies. This includes new ways to use familiar methods (i.e., development of a species-specific toxin) and the potential of new technologies (i.e., gene drive and trojan female techniques). Understanding public attitude formation towards novel technologies while the tools are being developed presents a positive and proactive opportunity for early and inclusive engagement with the nation.

This project has three research aims: 1) develop a model which segments the New Zealand population based on underlying worldviews and explore how these views influence opinion towards novel technology; 2) conduct focus groups to explore nuances of worldviews and delve deeper into opinions toward the novel technologies; 3) assess the impact of segment-aligned framed articles on affect, risk perception, and motivated reasoning.

5.0 Island Selection for Potential First Field Trial

5.1 Overview

If a gene drive mouse is able to clear laboratory testing hurdles, satisfy expectations in SNE experiments, and is deemed ready for a field trial, the most critical question for the research team will be selecting one or more candidate islands appropriate for the first environmental release trial. This workshop session thus explored stakeholder views with respect to different candidate island characteristics. In consultation with the research team, the engagement team developed four hypothetical island scenarios and presented them in a narrative format (Appendix A). Workshop participants worked as groups and rotated among four tables, each focused on one island scenario, to provide feedback about risks, benefits and concerns. After discussing all scenarios independently, they were then presented with a comparative chart (Table 5.1) of the island characteristics and asked about their first and second preferences for an imagined first field trial.

Table 5.1. Fictional Island Scenarios

Island Selection Criteria	Island A	Island B	Island C	Island D
Size	5 ha	10 ha	100 ha	400 ha
Distance from mainland	10 km	1000 km	1 km	100 km
Presence of native mice	No	Yes	No	Yes
Human activity on island	Small-scale Eco-tourism	Lighthouse	Research Station	Indigenous agriculture
Geography	Sandy beaches		Steep Cliffs	
Accessibility - Public	Yes	Yes	No	No
Accessibility - Research team	1 hr boat ride	flight to landing strip	10 min boat ride, with crane access	1 day boat ride
Regulatory Oversight	U.S.	AU	US	AU
Number of land managers involved	Wealthy Conservationist	Petrochemical Company	Government (Fish & Wildlife)	Tribal government, Federal government
Knowledge of invasive mouse population (behavior, genetics, ecology)	N/A	1 sampling event	20 years of studies	1 year of study
Livestock & other animals	None	feral goats	None	llamas, pigs, chickens
Prior eradication efforts	Succeeded in 2009	historical baiting around barracks	None	None
Non-targets of concern	None	native mouse	endangered raptor	None
Presence of M*us musculus*	No, would be introduced	Yes	Yes	Yes
Feasibility of eradication with toxicants	Highly feasible	Feasible	Unclear	Difficult
Organisms threatened by mice	bat spp that is rebounding	an extirpated lizard that could be reintroduced	several endangered birds	Mice spread human disease as a vector for tick-borne illness

5.2 Stakeholder Views

Given the small sample size (~20 stakeholders), absence of some critical stakeholder voices, and the fictional nature of the islands presented, the objective of the session was not to look for consensus but to explore general trends, identify some common areas of agreement and disagreement, and look for any important considerations that might have been missed in prior, internal conversations about criteria for island selection.

- The following benefit considerations made **Island C** the top choice (8/20) for first-release candidate island: proximity to a university, good understanding of population and genetic data, well controlled access, little human traffic, established research station, government buy-in, and no native mice. Concerns included proximity to a mainland location with strong environmental activism and accidental transport of the gene drive mice to the mainland by a predator.
- **Island B** received one fewer "vote" (7/20), with its tiny size, government oversight, controlled access, better biosecurity, longer distance from mainland, and good regulatory path. Expressed concerns included ownership by a foreign company, presence of native mice, and the movement of extraction equipment.
- **Island A** was third (5/20). Absence of people or endangered species, and record of previous successful eradication with toxicants were among the positives. Concerns centered around risk of escape to the mainland, knowingly introducing harm, and dire consequences if things went awry.
- **Island D** was not chosen by any of the participants as a first or second choice because of several knowledge and information gaps. Many participants were not clear about the need for the release. Some were also concerned about the implied lack of historical engagement with the indigenous community and not having enough information about that community's preferences and values. Other participants were concerned about risks to livestock and crops and the presence of a native mouse.

Reviewing the island selection criteria against participants' preferred choices, the following characteristics appear to be good predictors of support: demonstrated need, island size, remoteness from continents, knowledge of invasive mouse population, feasibility of eradication by toxicants, and public ownership. However, the criteria preferences might have been influenced by the exercise's focus on where to locate a first field trial, and we also note that none of the participating expert stakeholder were fundamentally opposed to the idea of developing and testing a gene drive mouse - an opinion that was expressed in our interviews of stakeholders for our landscape analysis. One area identified for future exploration is the potential value of additional fictional scenarios versus scenarios based on actual candidate islands. While the value in using fictional scenarios for this exercise has been made clear above, the engagement team suspects that using additional fictional scenarios would only be valuable if a novel characteristic needs exploring. Otherwise, continued reliance on fictional scenarios alone may provide a false sense of certainty about island characteristics that may ultimately mask the inevitable added complexity of real candidate islands.

6.0 Island Selection Criteria: Genetic Biocontrol of Invasive Rodents (GBIRd) Partnership

Following the discussion of island characteristics for a first field trial, participants were presented with the broader history of invasive species management on islands, followed by the island selection criteria developed by the GBIRd Partnership. Workshop participants were asked to reflect on which criteria were most important, discuss the potential for flexibility, and provide strategic advice to technical researchers regarding island research and selection.

6.1 Criteria for Island Selection

Box 6.1: Criteria for Selection of Islands

Presented by Royden Saah, Island Conservation

Invasive mice on islands cause extinctions through predation on native species. Toxicants are the current tools used to eradicate invasive rodents from islands. Efforts to prevent extinctions are limited to only 15% of islands with threatened species, the remainder are not considered feasible with current tools.

Our mission to prevent extinctions is limited to islands where invasive species threaten endangered species. Two tools (Threatened Island Biodiversity Database and Database of Invasive Island Eradications) are used to guide our efforts in protecting biodiversity. With approximately 1200 invasive mammal eradications from islands documented, the data shows overwhelming positive effects on the restoration of vulnerable populations and island ecosystems more widely.

To address the other 85% of islands where current toxicant use is not feasible, our program is developing gene drive technology in mice as an alternative or complement to current tools. Gene drive mouse development is still in early stages. These mice will cause inheritance of genetic traits, such as sex determination, from progenitor to offspring at greater than 50%. This will affect the population by, for example, creating a single sex population on the island. Gene drive mechanisms are spread exclusively via sexual reproduction. A deliberate step-wise process with safeguards and assessments considering efficacy, safety and social acceptance is being followed. It is currently envisioned that after development and testing in the laboratory, these technologies will be assessed for safety and efficacy in specialized, contained, simulated natural environments. Safety and efficacy will be demonstrated, and social and regulatory acceptance will be required before any field testing occurs on islands.

The progression of intentionally developed genetic traits to manage pest populations started in the middle of the 20th century. As documented in the USDA archives, mass insect rearing facilities and the use of radiation to induce sterility were applied by Edward Knipling and team to the screw-worm fly. Sterile males released in high numbers would outcompete fertile males and lead to the decline in pest populations. Initial tests were conducted on Sanibel Island, Florida using introduced goats, intentionally wounded/infested with the target organism. This successful test in 1951 led to the first field test of the Sterile Insect Technique on the island of Curacao, Netherlands Antilles in 1954. Progressive advancements quickly lead to the eradication of the screwworm from the United States in 1959.

Obligate Criteria

1. Island is within a country with a mature regulatory environment for genetically modified organisms
2. Island is within a country or overseas territory where house mice (*Mus musculus*) populations are present and non-native.
3. Island is biosecure based on two key criteria:
    a. Either closed to the public or has only infrequent and controlled visitation,
    b. Remote enough to avoid unassisted immigration or emigration of mice (i.e., >1km from other land masses).
4. *M. musculus* are the only rodent species present.

Desirable Criteria

1. Reasonably economical and feasible to visit the island year-round
2. No challenges exist to treatment using traditional, rodenticide-based methods to eradicate mice. Key characteristics include:
    a. uninhabited (besides research station or similar),
    b. no livestock present,
    c. no native rodents,
    d. no species endemic to that island that may be negatively impacted by a rodenticide application,
    e. no non-target species of concern,
    f. regulatory environment allows the use of brodifacoum bait products,
    g. small - island size <300 ha,
    h. single land managing entity.

The above ecological criteria are ideal and proposed as a primary filter. Ultimately, engagement with and acceptance from stakeholders, island associated communities, and regulators are requirements needed to consider an island as potential field trial site for future gene drive technology.

6.2 Stakeholder Views

- Participants felt very strongly that candidate islands needed to be (1) within the jurisdiction of a country that has a **mature regulatory regime** for genetically modified organisms and (2) is **biosecure** with respect to public access and unassisted migration.
- Some participants felt that the criteria of *Mus musculus* being the only rodent species present could be relaxed in some situations, as could the criteria about economic feasibility with respect to regular visits if an adequate monitoring plan could be put in place. Among additional criteria to consider, some participants recommended paying attention to the issues of weather, season, and timing; timing the release of a gene drive in terms of population cycles; attending to ecosystem consequences with respect to non-mouse and non-animal targets (e.g., could removal of mice lead to an explosion of weedy plants? Or are their relationships between mouse and rat populations?) With respect to regulatory regimes, an additional consideration was the different scales for approval and endorsement; people could be more in favor of local oversight and hesitant about larger international oversight. Some participants thought that generic criteria, while helpful, may need to be scrapped if no candidate island remained viable. Lastly, participants raised the possibility of looking beyond English-speaking countries.

7.0 Design Considerations for Future Stakeholder and Community Engagement

7.1 Overview

Having discussed various technological options, testing in simulated natural environment and island selection for a first (hypothetical) environmental release, the purpose of the concluding section was to collect feedback from the participating stakeholders to five questions about stakeholder and community engagement design: what to ask and when, where, who and how to engage stakeholders and community members. The participants did not spend equal time with each question; the discussion flowed among the questions.

At the end of the workshop, participants were asked to share their anonymous reflections about the stakeholder workshop design. Thus, in addition to drawing from the plenary discussion, the highlights below include relevant feedback from the participant reflections.

7.2 Stakeholder Views

7.2.1 When should engagement occur?

- Some of the participating stakeholders were in favor of **broader engagement prior to and during regulatory processes**, which may have their own requirements for incorporating public input. Others thought that early engagement could also reveal expert blind spots and explore community attitudes to inform different technical considerations (e.g., if there were a strong, community preference for a drive with "natural" origins, such as t-Sry).
- However, some participants saw **potential risks with early engagement** with the general public. They felt that discussions of technical options with the general public in absence of safety studies and risk assessments, which cannot be adequately performed at early stages of research, may be counterproductive and raise undue alarm. Some participants believed that discussion of potential new tools may make it difficult for existing strategies of rodent eradication (i.e., the use of toxicants) to be maintained. Other concerns about early engagement centered on the inherent ethical dilemma between the intent to develop a workable mouse (and hence work towards public acceptance) and the intent to be an 'honest broker' of different options between scientists and publics.
- Some participants were in favor of a **phased or sequential approach**. They thought that for the sake of transparency, there needed to be engagement at each go/no go decision point in the research trajectory. Others felt that engagement with gene drives for mice should coordinate with engagements carried out for gene drives in mosquitoes since the latter technology has advanced further in proof-of-concept.

7.2.2 Where should engagement occur?

- Some participants thought **national dialogues** would be helpful in familiarizing the problems and challenges of island conservation and publicizing the idea of gene drives. They felt that it was important to discuss the demand factor—why these technologies are needed—and increase public awareness about threats to biodiversity and problems with current management techniques.
- Other participants focused on the need to **engage at the local level**, especially with under-represented groups, and to partner with trusted boundary organizations to reach broader publics. They felt that factors at play at local levels were different from those at the national level: people have different attitudes when it is in their backyard. Some participants suggested learning from the experiences of other groups such as those working on the genetically engineered mosquitoes (without gene drive).
- Yet, participants pointed to the way that conservation problems often extend from local to national and global scales, implying the need for **engagement at the international level** with multilateral organizations and bodies.

7.2.3 With whom should engagement occur?

- **Experts:**
  - Conservationists/wildlife biologists who are against (though not vehemently so) use of gene drives for conservation,
  - Scientists working on gene drive research and development, but not focused on stakeholder engagement,
  - Bioethicists, Economists, Social Scientists, Humanities and Policy Scholars and Practitioners working on gene drive research and/or governance
- **Non-Governmental Organizations (NGO)**:
  - Working on conservation and biodiversity priorities,
  - Representing specific communities of interests such as hunters/anglers, indigenous peoples, health-care, and community development,
  - Opposed as well as neutral to research and/or development of gene drives,
  - Not otherwise engaged (e.g., Rotary Club, churches, schools), and
  - Involved in non-conservation application of gene drives (e.g., Malaria).
- **Governmental Organizations** representing local, state and national bodies,
- **Universities** local to the candidate island,
- **Funders**, current and potential,
- **Critical Communities of Interest:** Some participants referenced results from social science research studies such as those conducted in New Zealand to identify critical communities of interest (see Box 4.2).

7.2.4 What kind of engagement should occur?

- Some of the participants felt that **media partners and websites** should be used for broader communication, education, and outreach to publicize the problem and solution strategies.
- Other participants pointed to the need for **two-way, cross-disciplinary and multi-stakeholder engagement** and explicitly including those who opposed gene-drives.

7.2.5 What questions should be asked?

- **Stakeholder Engagement:**
  - Researchers and innovators might be concerned that public engagement could derail a project unnecessarily or prematurely. How can engagement design attend to these concerns and establish appropriate expectations regarding how public input will affect project decisions and progress?
  - What are the best mechanisms or engagement strategies to solicit questions from the public that can influence research meaningfully?
  - What are some of the barriers for individuals and groups to come to the table to discuss the topic?
  - How best to identify the potential expert blind spots with respect to publics and their concerns?
  - How to strategize on indigenous engagement - how were other projects successful, what to do and what to avoid?
- **Community Engagement:**
  - What are public views on and priorities for the ‘naturalness’ of different gene drive options?
  - How to unpack questions about problem identification and underlying assumptions (e.g., does the public agree on the importance of biodiversity)?
  - How do communities want to be engaged and informed about this project?
  - Are communities concerned about whether or not this is a platform technology for other applications?
  - What percentage of funding (relative to the scientific research) should be directed to stakeholder and public engagement, and Ethical, Legal, and Societal Implication (ELSI) research?
  - What are the values that underlie opposition (or support) for gene drives for island conservation?

8.0 Lessons for Engagement

The workshop concluded with a focus on future community and stakeholder engagement. These discussions prompted reflection from both the workshop participants and organizers, described below.

Overall, early engagement was viewed as important, with particular support for beginning engagement processes 'upstream' from the full development of an emerging technology - gene drive mouse development is still in-progress. By organizing the workshop around different decision phases of technology development, participants were able to have productive discussions about current, near-term, and far-term research activities. Important to note here is the novelty of facilitating dialogue between stakeholders and a relatively uncommitted innovation team. Participants communicated their appreciation for the innovation team being open to feedback and learning from a broad range of stakeholder input, and the innovation team communicated appreciation for the workshop participants' willingness to learn more about the project and provide this feedback.

One useful tool for soliciting feedback in the face of uncertainty about the project was the use of fictional scenarios. The development and evaluation of four scenarios allowed for complex integration of facts and values, encouraged tradeoff discussions, and revealed implicit and explicit priorities. Fictional scenarios also allowed organizers to include realistic island criteria, but avoid singling out particular island communities as possible sites of field trials. Using scenarios to explore meaningful tradeoffs integrated and brought to life many of the complex issues that had been discussed throughout the workshop until that point.

However, some participants also saw potential risks with early engagement. For example, discussions of technical options without safety studies and risk assessment may be counterproductive and raise undue alarm with some stakeholders and broader public audiences. Similarly, discussion of potential new tools may make it difficult for existing strategies (invasive species eradication with toxicants) to be maintained. Some concerns of early engagement centered on the inherent conflict between the intent to develop a workable mouse and hence work towards public acceptance and the intent to be an 'honest broker' of different options between the scientists and the public. In this light, these concerns are consistent with uncertainties about authority and responsibility — particularly with respect to engagement — at each of the phases of research outlined above.

Additionally, the stakeholders that attended the workshop were broadly supportive of gene drive research. The persons/organizations that argue for moratoria on gene drive research altogether were not present (but were invited). As such, the overall tone of the workshop and workshop report may reflect greater consensus than exists in the landscape of gene drive research and governance more broadly.

Even with these qualifiers in mind, feedback from the workshop participants and reflection from the organizers suggest relative success with respect to overall workshop goals. Moving forward, one of the next questions to grapple with is how to move from stakeholder engagement to community engagement, particularly with respect to the timing of community engagement.

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Appendix A: Island Narratives

Island A

With its orange sand beaches and unique flora and fauna, the tiny Island A has always had a trickle of intrepid tourists visiting from the larger US territory of Gotham Bay, located 10 km to the north. The allure comes from the pristine beaches surrounding the 5 hectare island. The terrain is easily accessible to most levels of hiking, allowing those who visit to view the whole island with an abundance of endemic lizards and snakes (non-venomous) and beautiful native seabirds. Early naturalists identified three species of mammals on Island A: the Gordon vole (Microtus gordonia), the Lesser Arkham bat (*Craseonycteris arkham)* and the invasive house mouse (Mus musculus). The Gordon vole is now extinct and the Lesser Arkham bat (smallest extant bat/mammal) is known to exist on two other small islands off of Gotham Bay. The decline in the native and endemic mammal species coincided with the arrival of *Mus musculus* brought to Island A by fishermen using the island as a fishing base. The ephemeral fishing village on the island was established sometime in the late 1700s and remained somewhat active until the mid-1800s.

When the wealthy philanthropist and conservationist Bru Swain purchased Island A in 2000, her intention was to clean up the island and tighten the process for visiting, thereby protecting the remaining threatened flora and fauna. Mindful of the extirpation of the Lesser Arkham Bat species and the extinction of the Gordon vole, Swain set up small cabins near the archeological remains of the fishing village and established a structured ecotourism system that benefits the island restoration programs and teaches the importance of islands and biodiversity. Small groups of ecotourists arrive on the island several times per week to participate in guided tours and small restoration projects. Swain facilitated a mouse eradication effort in 2007, which was declared successful in 2009, creating the conditions that would allow the reintroduction of the Arkham bat.

Before this action is taken, a field trial of gene drive mice could be conducted by introducing a small population of genetically engineered *Mus musculus* with unique alleles that would simulate the targets for a gene drive mouse. The resulting field trial would test the ability of a gene drive mouse to crash an invasive population, targeting genetic sequences that would not be found in mice in any wild environments.

Island B

Warbuck's Standard Oil corporation is 27 years into a 99-year lease of Island B from the Australian government. The petrochemical company has full responsibility for the island environment and must ensure the ecosystem is not impacted by their gas extraction activities. Island B sits 1000km northeast of Annieston Australia. During surveys in 2003, government ecologists sampled native and invasive rodents from Island B and published their findings in a review of rodents on Australian islands. To control for the invasive house mouse, regular baiting occurs around the hard knock barracks that house the workers.

Despite its modest land area (10 hectares), Island B is very profitable for company CEO Oliver Warbucks. The profitability is more impressive knowing that a landing strip takes up a considerable portion of the island. The other major infrastructure outside of the extraction equipment and barracks is a lighthouse to protect ships from the outlying rocks on the north end of the island. Typical for a Pacific island, the landing strip is sometimes used by private aviators to refuel when making journeys through the vicinity. On several occasions, the only other invasive mammal (goats) have interfered with aircraft landings on the air strip, but generally the goats are looked at as a curiosity by the oil workers.
Due to the mouse problem, Warbucks Standard Oil corporation has considered conducting an eradication of the house mouse from the island, if for

nothing else, to reduce the constant effort of baiting around human spaces. The feasibility study showed that a conventional eradication with rodenticides could be performed, but it would not be cost-effective. Oliver Warbucks has also showed interest in hosting a gene drive mouse field trial, mentioning scientific interest, potential positive publicity with environmental groups, and the advantage of eradicating house mice without needing to pay for a plan to protect the native mouse. If an eradication did occur, a critically endangered Southwest Pacific Goanna (*Varanus hanniganis*) found on several islands in proximity to Island B, could be translocated to Island B to expand what is thought to be its original range.

Island C

Though only 1 km off the coast of Nautilus, California, Island C has fewer than 10 human visitors per year due to the steep cliffs that surround the entire 100 hectare island. For the biologists, mostly associated with University of California, Nemo campus, who are lucky enough to get a permit to conduct research, the island is just a 20 min zodiac ride away from campus. The reason for the difficulty in obtaining permits is due to the US Bird & Forest Agency (US BFA) being very stringent with permits. The crane-controlled basket ride up the cliffside that allows humans and provisions to gain access to the island takes about the same amount of time as the boat ride.

Though sparsely equipped, the research station has carried out ecology work on the island over the last 60 years. 20 years of data have been collected on the invasive mouse population, which includes genetic sampling. Dr. Jules Verne has even published on the gene flow of mice through Island C. Dr. Verne is currently examining the genetic differences in mice that have started to prey on the endangered Arronax Booby. The only other endangered bird that inhabits the island is the Crespo owl - found only on Island C. The US BFA has shown interest in collaborating with researchers at UC Nemo to host a gene drive mouse trial for research purposes and the protection of the Crespo owl.

Island D

The 400 hectare island is inhabited by indigenous people who grow crops and raise livestock, including chicken, emu and pigs. Island D is 100 km from the mainland of Australia, so a full day boat ride is needed each way to gain access to or return from the island. Responsibility for the management is shared between the indigenous council of the island and the national government of AU. The AU government strictly controls access to the island due to the sensitivities associated with the indigenous people on the island. Not much scientific research has been published about Island D, but 10 rodent sampling events did occur over the course of 2012, during a rare ecosystem analysis of islands populated by indigenous peoples. The study team found both *Mus musculus* and a native mouse on the island.

A research team from an Australian university approached the tribal council about the possibility of using a gene drive mouse to eradicate the invasive house mouse. In the initial meeting, the indigenous representatives neither expressed enthusiasm nor opposition to the possibility, instead requesting an inquiry by their tribal environmental task force.

Appendix B: Participant List

Facilitation & Leadership Team	
Jason Delborne	North Carolina State University
Julie Shapiro	Keystone Policy Center
Mahmud Farooque	Center for Science Policy Outcomes
Katie Barnhill-Dilling	North Carolina State University

Stakeholders & Expert Participants	
Dimitri Blondel	North Carolina State University
Christie Boser	The Nature Conservancy
Stas Burgiel	National Invasive Species Council
Sumit Dhole	North Carolina State University
Owain Edwards	Commonwealth Scientific & Industrial Research Organisation
Joshua Fisher	US Fish & Wildlife Service Pacific Islands Fish & Wildlife Office
John Godwin	North Carolina State University
Doria Gordon	Environmental Defense Fund
Fred Gould	North Carolina State University
Stephanie Griffin	The Humane Society
Hannah Grunwald	University of California, San Diego
Elizabeth Heitman	University of Texas Southwestern Medical Center
Gregory Kaebnick	The Hastings Center
Jennifer Kuzma	North Carolina State University
Edy MacDonald	New Zealand's National Science Challenge
Aditi Mankad	Commonwealth Scientific & Industrial Research Organisation
Antoinette Piaggio	US Department of Agriculture National Wildlife Research Center

Holly Robertson	American Bird Conservancy
Royden Saah	Island Conservation
Megan Serr	North Carolina State University
Karen Tountas	Foundation for the National Institutes of Health