North Carolina State University
Quarterly Progress Report

Period Covered by the Report: 6 July 2017 through 5 October, 2017

Date of Report: 11/10/2017

Project Title: Restoring Ecosystems and Biodiversity through Development of Safe and Effective Gene Drive Technologies
Contract Number: HR00111720046
Total Dollar Value: $5,036,289.00
Subcontractors: Texas A&M University, Island Conservation, University of Adelaide, Commonwealth Scientific and Industrial Research Organization
Program Manager: Dr. Renee Wegrzyn, Defense Advanced Research Projects Agency, Biological Technologies Office

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1 High-Level Project Progress

1.1 Big Wins

The key accomplishments in this most recent quarter relate directly to developing a functional vertebrate gene drive in the mouse model system and thus moving towards an *in vivo* proof of concept. Towards this end, mouse lines containing i) a synthetic target sequence to be used for gene drive homing and ii) a guide RNA (gRNA) have been successfully created. Together with a Cas9 endonuclease-carrying line obtained through a vendor, we have the components of a functional gene drive in a vertebrate animal and have since generated the first proof-of-concept evidence (post 9/30/2017, but included in November 2017 technical update materials). Gene drives need to influence a cellular mechanism to produce a desired phenotype and, as one task, we will induce female development through destruction of the Y chromosome *in vitro* (the Y chromosome is critical to functional male development in eutherian mammals). Importantly, the Thomas Laboratory has also demonstrated the effectiveness of this mechanism *in vitro* using embryonic stem cells and published these results. These developments are ahead of schedule overall, although key studies and developments certainly remain to be achieved.

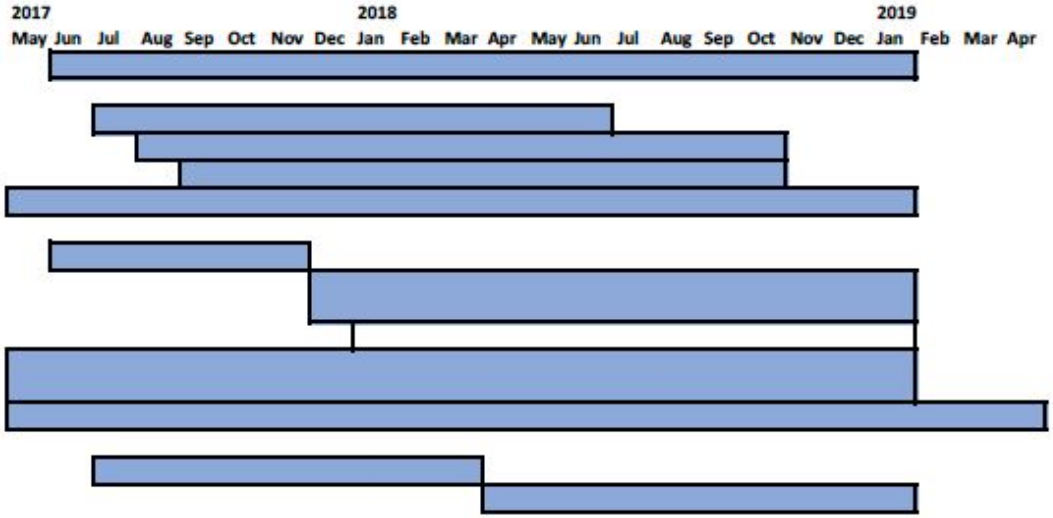
1.2 Go/no-go Progress

Accomplishment *Why is this significant? ID TA.*	**Month** *From Kick-off Presentation*	**Update** *What is the current status? Explain any discrepancies (behind/ahead of schedule). What is the next step?*
Target Founder mice generated	3	
Efficient Y-chromosome shredding demonstrated in embryonic stem cells (TA1)	3	This is a key proof-of-concept for one approach to modifying mouse offspring sex ratios (female-biased) using a gene drive mechanism that will be tested in this project.
Multinational MOU signed for GBIRd partnership (US, Australian, New Zealand partners - includes but not exclusive to Safe Genes team	3	This MOU is in place and represents an important formalization of the GBIRd partnership among the participant organizations, which strongly benefits the Safe Genes project efforts.
Cas9 guide RNA (gRNA) founder mouse generated (TA1)	3	This mouse has since been used to produce the first demonstration of gene drive function in a vertebrate animal

Transmission of synthetic 'Target' allele confirmed from breeding of founder mice (TA1)		This success provides a homing target for the gene drives being developed while also enhancing safety since this target does not occur in mice naturally (which would prevent drive function in other mice)

2 Schedule – Milestones and Deliverables

Task Name	Duration	Start	Finish
3.1.1.1 - Engineer t-Sry mice	24 mos	6/1/17	
3.1.1.2 - Engineering Generation 1 Drives	24 most		
3.1.1.2.1 - Generation of transgenic mice	12 mos	7/1/17	
3.1.1.2.2 - Assess Cas9 drives	15 mos	9/1/17	
3.1.1.2.3 - Assess Cpf1 drives	14 mos	9/1/17	
3.1.1.3 - Develop Y-shredder drive	21 mos	5/1/17	
3.1.1.4 - Spatial limitation of gene drives			
3.1.1.4.1 - Selection of Islands	6 mos	5/1/17	
3.1.1.4.2 - Identification of population-specific alleles	14 mos	12/1/17	
3.1.2 - Risk Assessment of Genome Editors	13 mos	1/1/18	
3.1.3 - Mathematical Modeling of Genome Editors	21 mos	5/1/17	
3.1.4 - Regulatory Engagement	24 mos	5/1/17	
3.1.5 - Engagement			
3.1.5.1 - Stakeholder Landscape Analysis	9 mos	7/1/17	
3.1.5.2 - Stakeholder Workshop	10 mos	4/1/18	



Milestone/ Deliverable Description	Responsible team members	Start Date	Due Date	Actual State Date	Actual End Date	Status	Dependencies *Across tasks and teams(if applicable)*
Engineer t-Sry mice (Task 3.1.1.1)	Threadgill	5/1/17	2/1/19	6/1/2017		On-schedule: t-allele established in pluripotent stem cell platform for engineering	

Generation 1 drive mice (Task 3.1.1.2.1)	Thomas	5/1/17	4/30/18	7/1/17		On-schedule: Target and gRNA mouse lines for Cas9 editing established, first successful editing demonstrated	Tasks 3.1.1.2.1, 3.1.1.2.2, 3.1.1.3, and 3.1.1.5 depend on success in this task. Tasks 3.1.2 and 3.1.3 will utilize data from 3.1.1.2 and 3.1.1.3
Identify Population-specific alleles (Task 3.1.1.4)	Piaggio, Godwin, Campbell	5/1/17	2/28/19	6/30/17		Behind-schedule*: Two US islands identified, Six Australian islands tenatively identified (need 4)	Task 3.1.1.5 will utilize data from this task
Risk Assessment (Task 3.1.2)	Hayes	1/1/18	1/30/19			On-schedule: Not yet initiated - will utilize data from other tasks that are underway	This task will utilize data from Tasks 3.1.1.2, 3.1.1.3, 3.1.1.5
Mathematical modeling of performance of genome editors (Task 3.1.3)	Lloyd, Cassey	5/1/2017	2/28/19	6/30/17		On-schedule: Refinement of individual based models underway, initial modeling of locally-fixed alleles indicates this approach is promising	Progress in this task will inform Task 3.1.2
Regulatory Engagement (3.1.4)	Howald, Saah, Edwards	5/1/17	4/30/19	5/3/17		On-schedule: Multiple engagements with US and Australian regulators, Development of US regulatory ‘toolkit’ initiated	Although not a strict dependency, accomplishment of this task will be facilitated by technical advances in other tasks.
Stakeholder Engagement (3.1.5)	Delborne, Farooque, Shapiro	5/1/17	2/28/19	9/1/17		On-schedule: Initial list of key stakeholders identified for interviews, Draft interview protocol developed	No strict dependencies, but further clarity on potential island targets will facilitate completion of this task

- Behind-schedule for Task 3.1.1.4: Hurricane damage in USVI and slight delays in partnership with Dept Parks and Wildlife, Western Australia have put the island selection part of this task behind schedule, but this should not delay completion of this task overall.

3 Task Progress, Accomplishments, and Plans

Task #/Title	Brief Description	% Complete	Total for Task	Total Spent	Remaining to Spend	Explain Deviations between Planned vs. Actual Expenditures
3.1.1.1 - Engineer t-Sry mice	t-Sry mice should develop as males, skewing sex ratios and reducing population sizes based on previous modeling.	10	$276,273	$0	$276,273	Some delays in subcontracting and ACURO approvals have let to delays in spending on this subcontract
3.1.1.2 - Generation 1 drive mice	This task will produce, characterize, and compare approaches for the first vertebrate gene drives	15	$542,744	$177,111	$859,732	Spending for this task is approximately on the anticipated pace.
3.1.1.3 - Develop an efficient Y-shredder	This task is intended to develop the best performing drive to be used in efficient sex biasing through Y-chromosome shredding	15	$417,744	$0	$417,744	Proof of principle was provided for this aim *in vitro*, but the bulk of expenditures will follow development of effective drives in Task 3.1.1.2

3.1.1.4 - Identify Population-specific alleles	This task is aimed at achieving spatial limitation of gene drive function by identifying island-specific genetic features for targeting	**10**	**$443,876**	**$12,227**	**$431,649**	Hiring staff at NCSU has taken some time and the first part of this task involves selection of islands for sampling, which does not involve significant costs.
3.1.1.5 - Develop efficient PAM-sensitive gene drive	This task will develop gene drives characterized by spatial limitation of drive function through dependence on specific population-specific sequences	**0**	**$288,585**	**$0**	**$288,585**	This task depends on Tasks 3.1.1.2-4
3.1.2 - Risk Assessment	This task will conduct systematic and structured hazard analysis for a Y-shredding gene drive	**0**	**$262,609**	**$0**	**$262,609**	Activities for this task draw on results from tasks 3.1.1 and 3.1.3 and are slated to begin in January 2018
3.1.3 - Mathematical modeling of performance of Genome editors	This task uses mathematical modeling to understand and predict gene drive function in both biosecure experimental contexts and for a potential future environmental release (not part of this project)	**10**	**$240,363**	**$11,020**	**$229,343**	This task is approximately on-schedule with postdocs being added in early 2018
3.1.4 - Regulatory Engagement	This task addresses and facilitates development of regulations for governing use of gene drive technologies.	**12**	**$61,864**	**$12,596**	**$49,268**	Expenditures are approximately following planned expenditures
3.1.5 - Stakeholder Engagement	This task will develop detailed information regarding stakeholders relevant to potential deployment of gene drive technology	**10**	**$210,504**	**$3325**	**$207,179**	Expenditures are approximately following planned expenditures

Task 3.1.1.1 - Engineer t-Sry mice

Progress

Work prior to initiation of this Safe Genes project established that the tw2 variant of the t-allele exhibits high levels of transmission ratio distortion with both laboratory strain sires and dams (C57Bl6 x sv129; >95% t-allele inheritance in 2000+ offspring in Threadgill lab) and in matings with wild-derived females from the Farallon Islands and sires who were the laboratory strain, F1 hybrids (lab x wild-derived) or F2 hybrid backcrosses (75% wild-derived; 98%, 98% and 96% t-allele transmission in each set of matings and 101-133 offspring in each). These results established that the tw2 variant transmits at high rates in both a laboratory and wild-derived genetic background.

Due to greater-than-expected challenges encountered with insertion of a large t-Sry construct (approximately 10 Kb) using CRISPR-based gene editing approaches, it was determined that induced pluripotent stem cells (iPSCs) would provide a favorable platform in which to experiment with and optimize approaches (Figure 1). These iPSCs were generated and were in the third passage at the end of the reporting quarter. Genotyping and sexing of these cells was initiated, but not completed by the end of the quarter.

Not all gRNAs tested proved effective in cutting either wild-type or tw2 targets in the t-allele region. However, two effective gRNAs for editing were identified by testing multiple designs in a mouse embryonic fibroblast system (Figure 2 below).

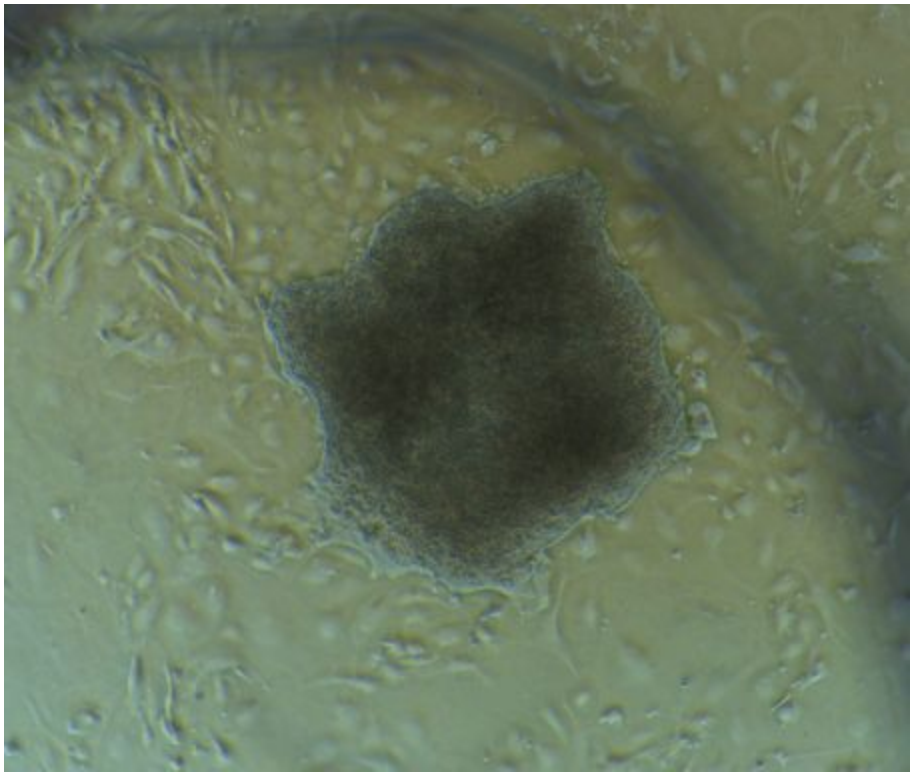


Figure 1. iPSC colony carrying t-allele following second passage (one of 12 subcloned colonies).

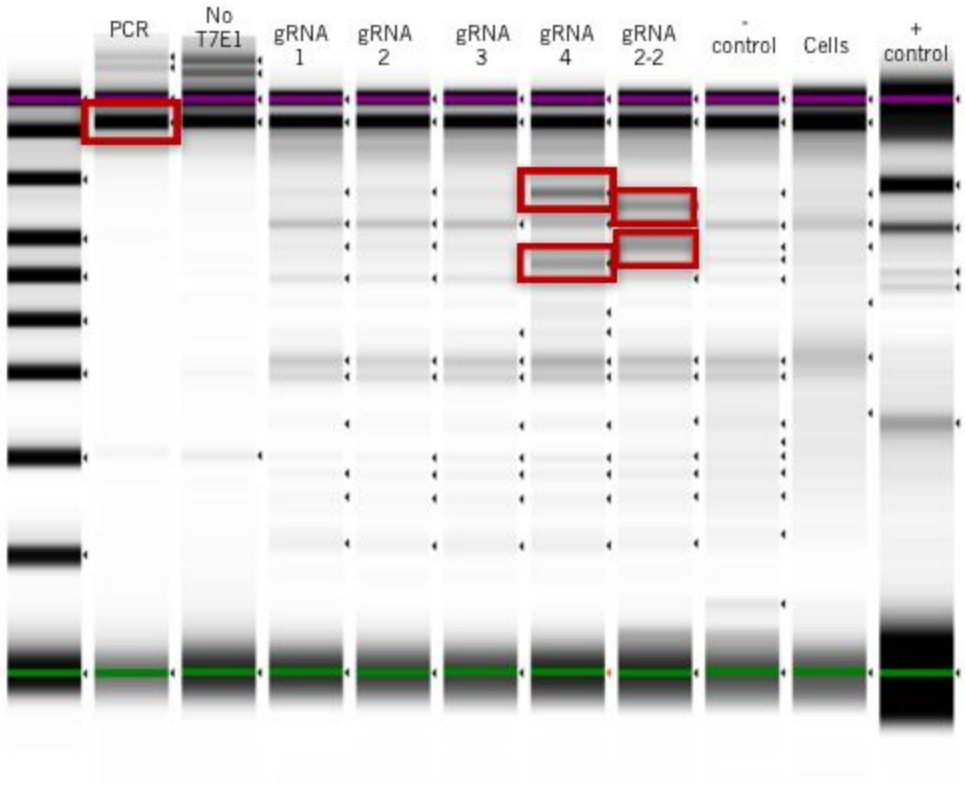
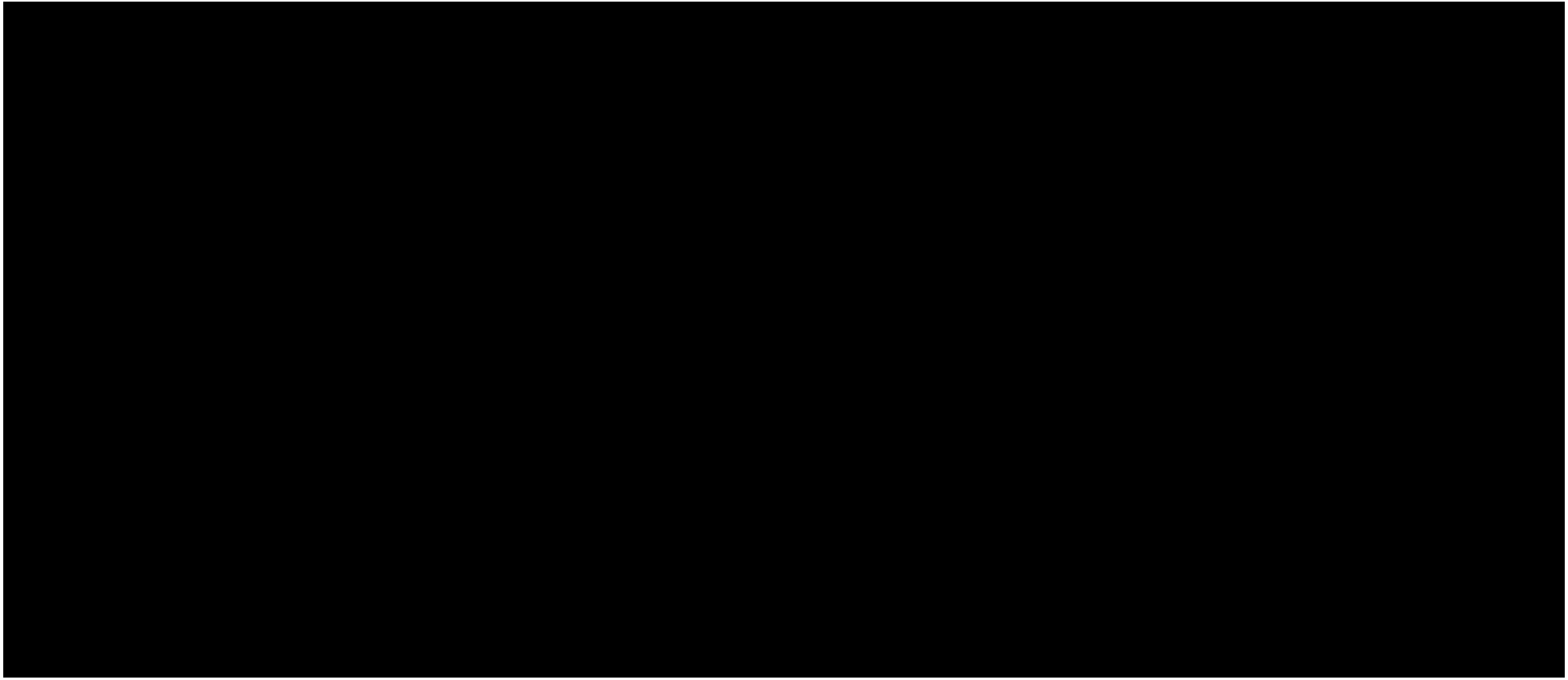


Figure 2. Tape station characterization of effectiveness of gRNAs for endonuclease cutting in the T7 endonuclease assay. gRNAs 4 and 2.2 show effective cutting in this figure (note that these gRNAs target different sequences and the predicted band sizes are therefore different).

Task 3.1.1.2 - Generation 1 Drive Mice

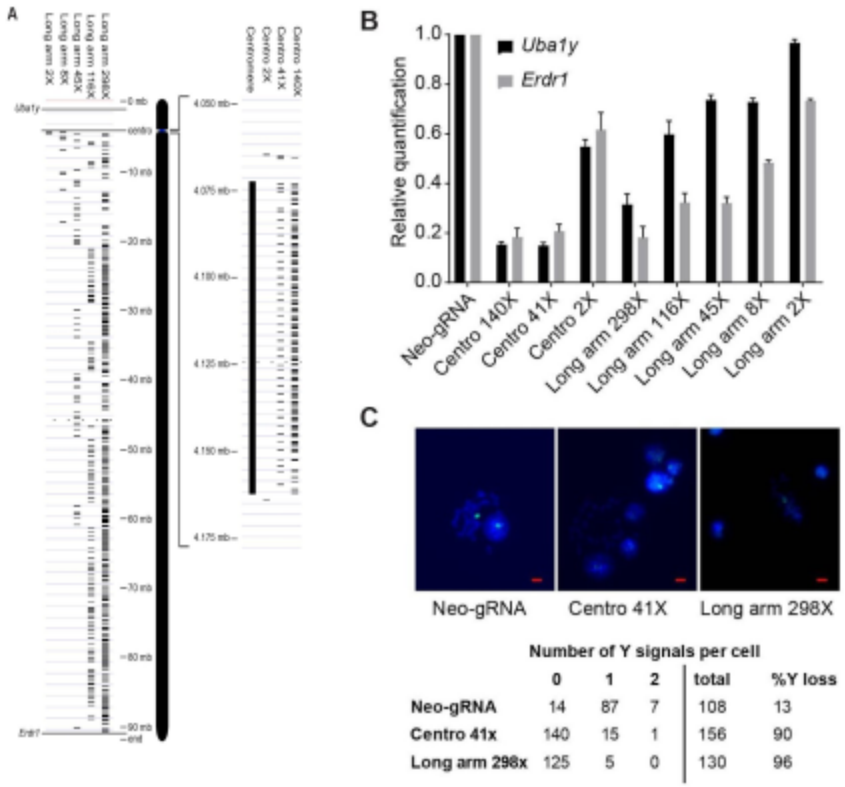
The first goal in the development of synthetic gene drives is the i) purchase and establishment or ii) production and development of mouse lines carrying key components of these drives. During the initial reporting period, three mouse lines were either obtained or developed:

- A mouse line carrying the Cas9 endonuclease under the control of the CMV promoter was purchased from the Jackson Labs and established in the Thomas laboratory at the University of Adelaide (Figure 3).
- A mouse line carrying a synthetic target allele to be used in testing gene drive homing was developed and transmission was confirmed by breeding from the founder mice of this line.
- A mouse line carrying a gRNA targeting homing to this target allele and a mTomato fluorescent reporter was developed. This construct cassette was inserted into the tyrosinase gene (*Tyr*), which is necessary for developing the normal dark coat color. This construct therefore provides both an external phenotypic marker (white coat color) and also fluorescent marker useful with either tissue samples (e.g., ear punch) or in gametes. The generation of a successful founder was confirmed by both sequencing and tissue flourescence (Figures 4-7).



Task 3.1.1.3 - Feminizing Y-shredder drive

The synthetic gene drives under development in Task 3.1.1.2 are to be used in producing a 'Y-shredder' gene drive system that should bias offspring sex ratios effective towards females through production of XX- and XO- genotype offspring, both of which are predicted to develop as reproductively capable females. Progress was made towards this goal by demonstrating the efficacy of the proposed Y-shredder mechanism in embryonic stem cells (Figure 8a-c). Specifically, different gRNAs targeting repetitive sequences on the Y chromosome were tested and were effective in reducing genomic DNA amplication of Y-specific sequences (UBA1y and Erdr1; Figure 8b). Fluorescent *in situ* hybridization (FISH) for Y-chromosome sequences also indicated effective disruption of Y chromosomes (Figure 8c). These results were published in the journal *Molecular Therapy* (2017: Vol 25(8): 1736-8).



Number of Y signals per cell

	0	1	2	total	%Y loss
Neo-gRNA	14	87	7	108	13
Centro 41x	140	15	1	156	90
Long arm 298x	125	5	0	130	96

Figure 8. (A) Schematic showing position of gRNA target sites in the long arm and centromere of the Y chromosome. (**B**) qPCR of genomic DNA to quantify Y chromosome dosage. *Sox1* qPCR was used as the internal reference control. Data were presented as mean ± SEM from n ≥ 3 biological replicates. (**C**) FISH analysis detection of Y chromosome loss. Y chromosome and DAPI staining was indicated by green and blue signals, respectively. Scale bar = 5 µm. Published in Molecular Therapy (Mol Ther. 2017 Aug 2;25(8):1736-1738.)

Task 3.1.1.4- Identify Population-specific alleles

This task is aimed at achieving spatial limitation of gene drive function by identifying island-specific and locally-fixed genetic features that can serve as targets for gene drive homing. If present and possible to target effectively, this should allow a gene drive to function in the target population, but not if a gene drive carrier were to escape to a different population (presumably an adjacent island or mainland population).

The SOW for this project specifies six island and adjacent mainland populations will be sampled and characterized. Islands are being selected based on criteria listed in the SOW. During the reporting period, we identified two US islands for sampling - Southeast Farallon Island (offshore from San Francisco) and Sand Island at Midway Atoll, both sites of highly invasive and abundant mouse populations where sampling is also very feasible. Southeast Farallon Island was specified in the SOW and was the origin of a colony of wild-derived progenitor mice in the Godwin Laboratory at NCSU that will support the project. Four other islands in US territory were considered, specifically Buck is., Capella Is., Saba Is., and Dutchcap Cay, all in the U.S. Virgin Islands in close proximity to St. Thomas. Collaborative contacts were established with local USDA and USVI government personnel and these islands looked very promising. Unfortunately, the devastating effects of hurricanes Irma and Maria in the early fall of 2017 on St. Thomas have made working on these islands logistically impossible until at least early 2018 and possibly beyond (they are not anticipated to have electrical service until at least 2018 at last report). We consider the project risk for US island sampling to be very low.

Our group has identified a number of promising islands in Western Australia and established a collaborative relationship with the Department of Parks and Wildlife of the Western Australia state government to facilitate collections there. Importantly, the government of Western Australia has significant interest in this project, particularly because they have islands where invasive mice present a serious biodiversity threat and the presence of other native mammals makes more traditional toxicant-based eradication approaches very challenging. In collaboration with DPAW personnel (Director Dr. Margaret Byrne and Mr. Keith Morris), we identified the following islands as fitting our criteria: Browse, Thevenard, Direction, Boullanger, Whitlock, and Figure of Eight island. Although arrangements are still being finalized, we have the basis of an agreement for experienced DPAW personnel to sample these mouse populations for the project and at no personnel cost to the project. Mouse presence does need to be confirmed on some of these islands (recent historical records do support presence), but as there are more options than needed (six possible, four needed) we consider the risk to be low.

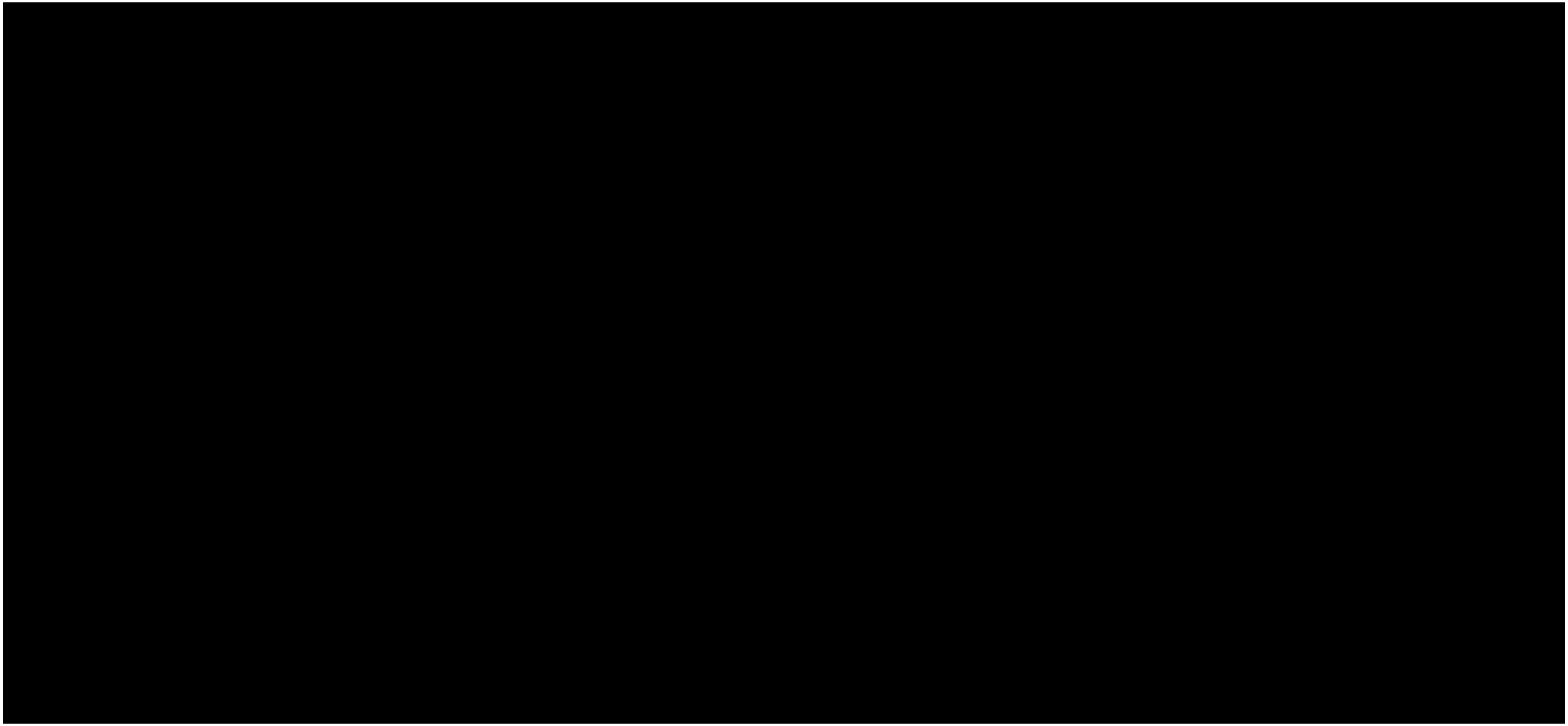
Once samples are obtained, analysis will primarily occur in the laboratory of Dr. Antoinette Piaggio at the USDA National Wildlife Research Center (NWRC). The NWRC group is part of this overall project, but is funded under a separate Interagency Agreement and is providing a separate quarterly report.

Task 3.1.2 - Risk Assessment

Phase I activities for this task will begin in 2018 and draw on findings from tasks 3.1.1.2-5.

Task 3.1.3 - Mathematical modeling of performance of Genome editors

This task uses mathematical modeling to understand and predict gene drive function in both biosecure experimental contexts and for a potential future environmental release (field releases are not part of this project). Modeling efforts are being pursued collaboratively by personnel at NCSU and the University of Adelaide. Progress to date includes an important paper by the Adelaide group that was not supported by the Safe Genes program (Prowse et al., 2017, Proc. Royal Society B 284: 20170799, http://dx.doi.org/10.1098/rspb.2017.0799), but is very relevant to the goals of developing safe and effective gene drives. This paper modeled four different gene drive approaches (different phenotypes induced in carriers) and also the likelihood of resistance to gene drive function developing under these different mechanisms and by employing different parameters and approaches to gene drive function (varying numbers of gRNAs from single to multiplexed). Preliminary models have also addressed the potential efficacy of the Y-shredder approach. This approach appears promising based on results to date (Figure 9), but predicted efficacy does depend heavily on the number of mates per male with this female-biasing sex ratio strategy. Efforts in the first quarter of this project initiated expansion of these models with the goal of developing spatially-explicit, stochastic, individual-based models.



Modeling efforts at NCSU in the reporting quarter focused on the efficacy of achieving spatial restriction of gene drive function through targeting of locally-fixed alleles. While quite preliminary overall, the modeling results thus far suggest even a relatively small proportion of individuals carrying alleles not susceptible to a gene drive in a mainland population (i.e., possessing a base sequence at the target site different from that of the island population) would result in a rapid rebound of that population even if a gene drive that targeted the majority of the population was introduced (Figure 10). This general result is quite consistent with the findings of a number of groups regarding the population impacts on drive function of resistance alleles.

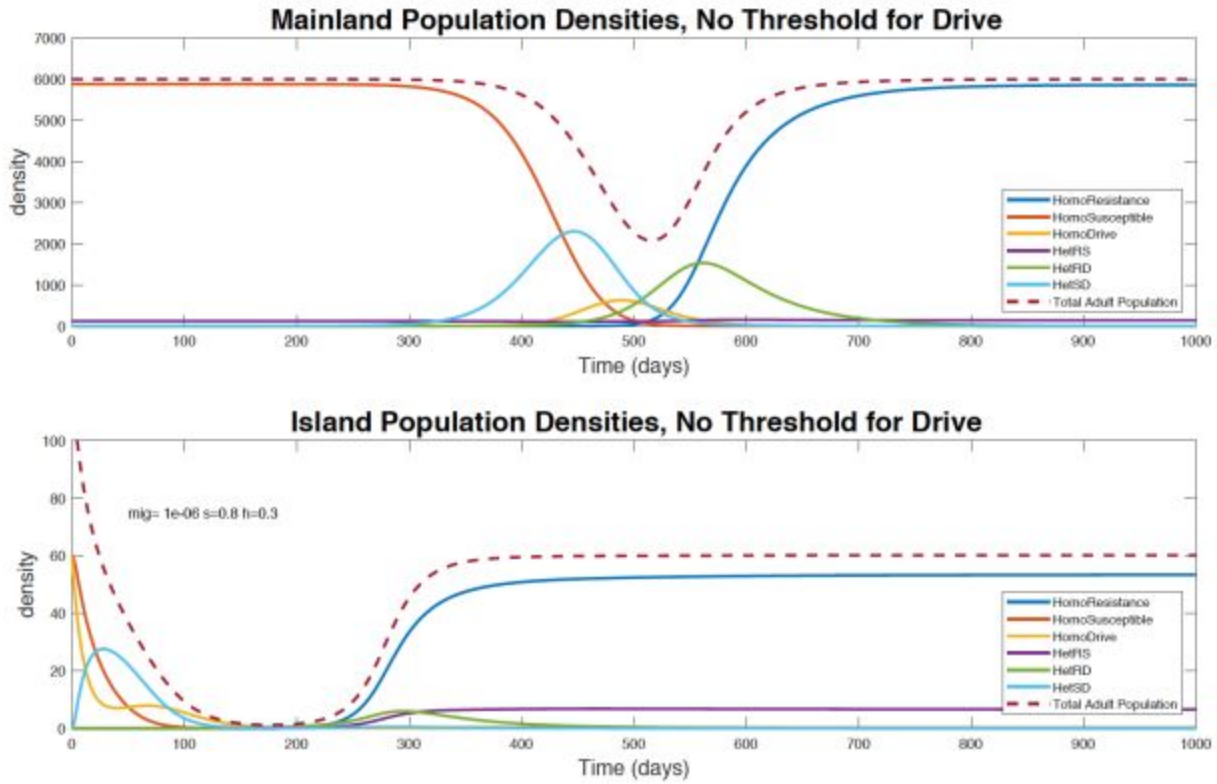


Figure 10. Modeling of an island and adjacent mainland population with resistance alleles to drive function present at even low levels (dark blue and dashed red lines; note that the presence of resistance alleles would also prevent long term population suppression in the island population as well).

Task 3.1.4 - Regulatory Engagement

Members of our team are working with regulators in the US and Australia as the regulatory framework for this very new technology develops. This entails early and sustained engagement, a commitment to keep the relevant regulatory personnel informed about developments as our project progresses, and endeavoring to collect data in a manner that is informed by and complementary to the anticipated needs of regulatory processes as these develop. Towards this end, our team: i) initiated a dialogue with the US FDA and

EPA prior to the Safe Genes project beginning (4/2017), ii) held a simultaneous engagement with regulatory personnel from the FDA, EPA, and USDA (5/2017), iii) made significant efforts towards the development of a 'regulatory toolkit' in cooperation with and funded by the US National Invasive Species Council (8/2017), and iv) have had an ongoing effort to characterize regulatory requirements that are relevant to our Safe Genes project (particularly team members John Eisemann and Emily Ruell of USDA-NWRC). A complementary effort (not funded by DARPA) towards regulatory engagement is occurring in Australia through the efforts of Owain Edwards (of CSIRO). Figure 11 illustrates our overall conception of the regulatory pathway for this technology and how activities in this Safe Genes project fit into this pathway.

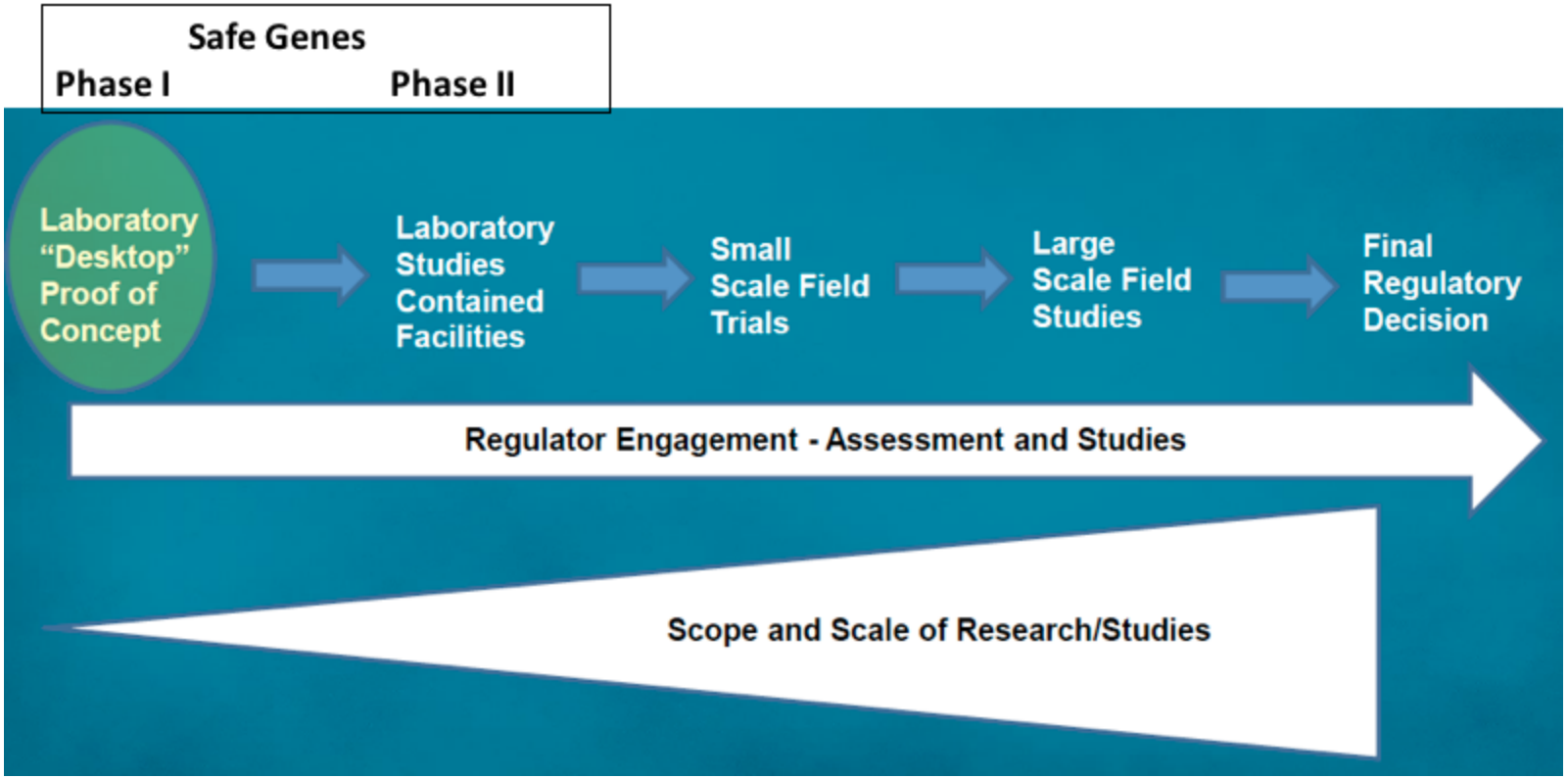


Figure 11. Regulatory pathway envisioned for gene drive technologies designed to reduce invasive rodent populations on islands.

Task 3.1.5 - Stakeholder Engagement

This task aimed at developing detailed information regarding stakeholders relevant to potential deployment of gene drive technologies, specifically a landscape analysis and workshop leading to the development of a report focused on stakeholder input regarding technology development. The landscape analysis is intended to define interests, positions, and influences. The workshop will focus on technology scenarios and receiving technical feedback on these scenarios and more generally.

Activities in the first quarter focused on development of a set of key questions driving the landscape analysis (listed below) and initiating identification of key stakeholders. The next steps for this task will be finalizing the list of key organizations, interest groups, and spokespersons. A related activity to better define the stakeholder landscape will be analyzing the public comments submitted in response to a revised Environmental Impact Statement (2013) developed for a proposed eradication on the Farallon islands.

Key Questions for Landscape Analysis

- What is the status of public debate around conventional invasive species eradication on islands?
- What are the mix of interests, and who represents those interests, attending to global, national, regional, and local scales?
- Are there “silent stakeholders” or “dormant stakeholders”?
- What are the design characteristics most valued by stakeholders in terms of a technology/method for eradication?
- What “endpoints” of risk assessment matter most?
- Acknowledging existing opposition to killing any animal, how might GBIRDs’ technology impact that debate (positively and negatively)?
- How might cultural and political diversity impact debates over GBIRD?

3.1 Project Coordination

- **GBIRd Steering Committee; On-Line Meeting with coverage of Safe Genes goals**
  - Attendees: Safe Genes team - Toni Piaggio & John Eisemann (NWRC), Karl Campbell/Gregg Howald/Royden Saah (IC); John Godwin (NCSU), David Threadgill (Texas A&M), Peter Brown (CSIRO); Other members: Fred Gould (NCSU), Dan Tompkins (Predator Free New Zealand)
  - Dates: 5/18, 6/20, 7/18, 8/15, 9/19

- **Engagement team conference calls: Aug 23, Sep 20, Oct 4, Oct 26, Nov 9**.
  - Participants: Jason Delborne (NCSU), Mahmud Farooque (ASU), Julie Shapiro (Keystone)

- **Coordinating Efforts on Advanced Biotech, Invasive Species and Policy Support, July 14, 2017, Online Meeting**
  - Attendees: Burgiel, Stanley (NISC), Abrahams, Leslie S (SPTI); Simon, Ian D (STPI); Chretien, JP (EOP/OSTP)

3.2 Dissemination and Translation (if applicable)

Island Invasives Conference, Dundee, Scotland, July 10-14, 2017

- John Godwin (NCSU), Karl Campbell, Gregg Howald (IC)
- This conference is focused on the issue of invasive species on island, which is also the central focus of our Safe Genes project
- Campbell presented an overview of broader concept and project to an audience of specialists and practitioners in invasive species management and exploration of this approach was broadly supported. Godwin lab member doctoral student [redacted] presented her work on t-allele transmission, reproduction, and mate choice in island mice. Manuscripts based on these presentations are in review.

Science Cafe public engagement presentation, September 27, 2017

- John Godwin and Jason Delborne led this presentation, Royden Saah attended
- This was a science outreach event at the North Carolina Museum of Natural Sciences as part of their 'Science Cafe' series. These events consist of a short presentation (~25 minutes) followed by 30+ minutes for questions from attendees.
- This event was well attended by the public with approximately 115 individuals taking part. The presentation by both a natural scientist (Godwin) and social scientist (Delborne) was perceived as particularly effective by the coordinating team for the museum. A recording of this event is also available for wide dissemination from the museum website and on YouTube.

Annual Meetings of the Society for Social Studies of Science: "Envisioning Responsible Innovation in Biotechnology: Engagement, GM Chestnut Trees, and Gene Drive Mice."

- Jason Delborne gave this presentation in Boston, MA. August 31, 2017
- Presenting key questions and progress to the social science community focused on science is valuable for input and dissemination

Partnership with the Department of Parks and Wildlife (DPAW), state of Western Australia

- Perth, Western Australia, 8/2017
- Karl Campbell, Owain Edwards (Dr. Margaret Byrne from DPAW)
- Develop partnership for obtaining mouse samples from Western Australian Islands and adjacent mainland areas for assessing the presence of locally-fixed alleles on islands
- The specific meaningful output is that DPAW will make a key contribution to our Safe Genes project by providing these samples and is contributing staff time and some direct costs for this effort. The more general meaningful output is the involvement of a critical stakeholder in conservation efforts in Western Australia that is very interested in the potential of the genetically-based approach we are investigating.

4 Publications and Presentations

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Title, Authors	Description/Type	Status
A Potential New Tool For The Toolbox: Assessing Gene Drives For Eradicating Invasive rodent Populations, K.J. Campbell, J. R. Saah, P.R. Brown, J. Godwin, F. Gould, G.R. Howald, A. Piaggio, P. Thomas, D.M. Tompkins, D. Threadgill, J. Delborne, D.M. Kanavy, T. Kuiken, H. Packard, M. Serr, A. Shiels	Island Invasives Conference, Dundee, Scotland, July 10-14, 2017	Under review for publication in conference proceedings
Towards a genetic approach to invasive rodent eradications: Assessing reproductive competitiveness between wild and laboratory mice, M. Serr and J. Godwin	Island Invasives Conference, Dundee, Scotland, July 10-14, 2017	Under review for publication in conference proceedings
Relevant papers from group where effort began before Safe Genes		
Dodging silver bullets: good CRISPR gene-drive design is critical for eradicating exotic vertebrates, Prowse, T.A.A., P. Cassey, J.V. Ross, C. Pfitzner, T.A. Wittmann, P. Thomas	Proc. Royal Society B 284: 20170799, http://dx.doi.org/10.1098/rspb.2017.0799	Published

Evaluating strategies for reversing CRISPR-Cas9 gene drives. Vella, M.R., Gunning, C.E., Lloyd, A.L. & Gould, F. (2017)	*Scientific Reports. 7: 11038. doi:10.1038/s41598-017-10633-2*	Published
Targeted Deletion of an Entire Chromosome Using CRISPR/Cas9, Adikusuma F, Williams N, Grutzner F, Hughes J, Thomas P	*Molecular Therapy*, Vol 25(8): 1736-8	Published

Popular Press articles – relevant to project, but interviews preceded Safe Genes

•How Genetically Modified Mice Could One Day Save Island Birds, Brooke Borel, Summer 2017. Features various members of Safe Genes team and others with focus on Farallon Islands.

http://www.audubon.org/magazine/summer-2017/how-genetically-modified-mice-could-one-day-save

- "Should Genetic Engineering Be Used as a Tool for Conservation?", Richard Conniff, July 2017,

http://e360.yale.edu/features/should-new-genetic-engineering-be-used-as-a-conservation-tool

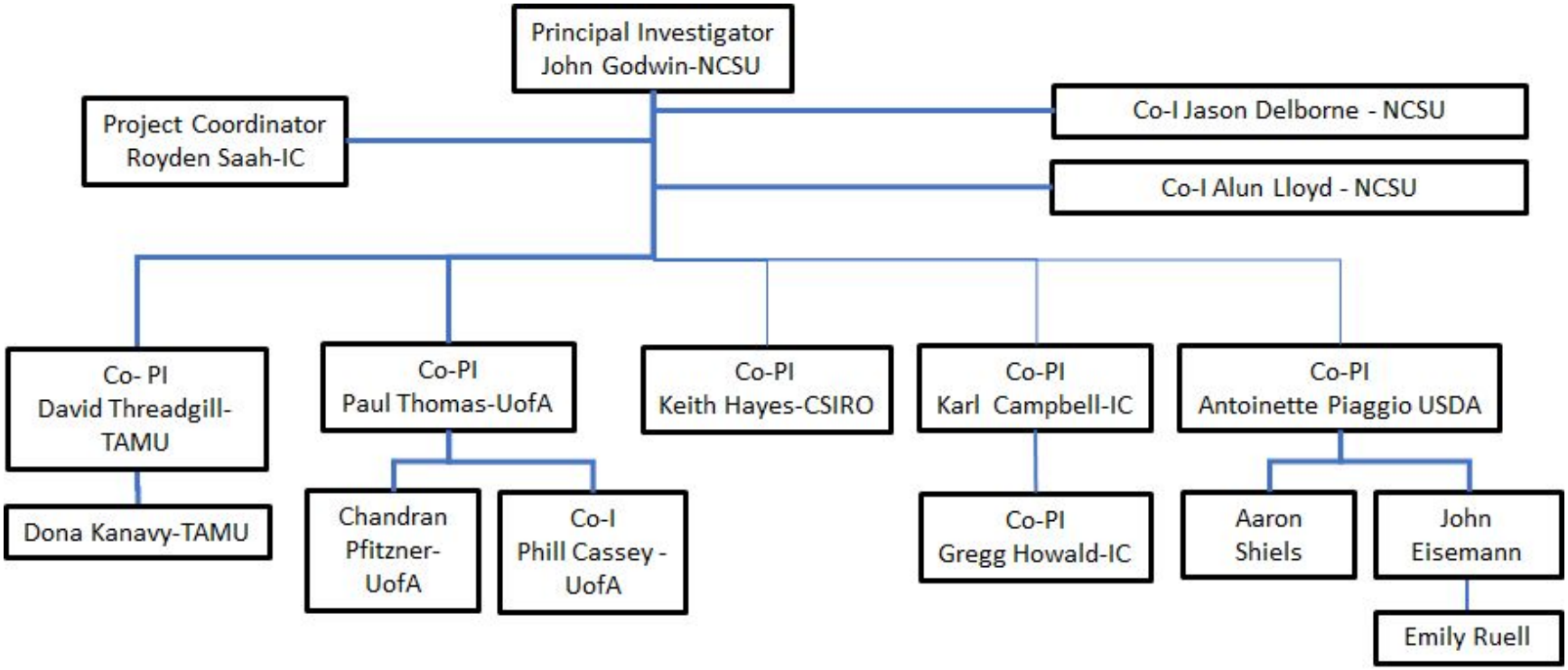
5 Patents, Invention Disclosures, IDEs, etc…

None to report.

Appendix I – Project Context

Teaming and Personnel

Organizational Chart



Contact Information

Prime Team Members and Contact Information: North Carolina State University

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Work Breakdown Structure