

Title:

A mutually responsive approach to developing technologies that alter shared ecosystems

Key Personnel

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The bioethics problem to be addressed:

An emerging dilemma in bioethics concerns novel genome editing technologies capable of altering ecosystems. Such interventions, deployed in the shared space of the environment, should only be initiated if acceptable to the communities involved. But what does “acceptable” entail? By what process should scientists and communities jointly make decisions from the earliest stages of project planning? **This project will explore the suitability of the reciprocity-based concept of “Responsive Science” as a model for community consent and community decision-making during the development and real-world testing of novel ecological interventions.**

A powerful example of a novel technology for ecological interventions is the combination of CRISPR-based genome editing with a so-called ‘gene drive’. The latter enables genetic alterations made with CRISPR to pervasively spread to entire wild populations (Esvelt et al 2014). The many potential applications include combating vector-borne diseases such as malaria and dengue, replacing toxic pesticides and herbicides in agriculture, and curtailing invasive species.

Background

In early 2014, ahead of the publication of their work, the scientists who had first understood the potential of CRISPR gene drive consulted with outside experts from other disciplines. These consultations led to a call for broad public discussion prior to implementation in the laboratory (Esvelt et al 2014, Oye et al 2014, Esvelt, Church, & Lunshof 2014). Shortly thereafter, in 2015, CRISPR gene drive was demonstrated in four different species (DiCarlo et al 2015, Gantz and Bier 2015, Gantz et al 2015, Hammond et al 2015), underscoring the urgent need for a framework for responsible development. The need for regulatory reform to account for novel synthetic biology technologies, including gene drives, was addressed in a White Paper, on the Revision of the Coordinated Framework for the Regulation of Biotechnology co-authored by members of our team (<http://poet.mit.edu/>).

The arguments for proactively and publicly addressing questions concerning novel genomic technologies were highlighted in a Worldview essay in Nature (Lunshof 2015) and prompted an analysis of contrasting approaches to social responsibility among life scientists by Sankar and Cho who, in a contribution to the American Journal of Bioethics, asked

“how investigators will handle the possibility of disagreement among the public or the possibility that the public will conclude that the research should not proceed” (Sankar and Cho 2015).

We believe these questions can be best addressed in the context of a specific real-world intervention in which a bioethics study develops in parallel to the scientific project.

Scientific Approach

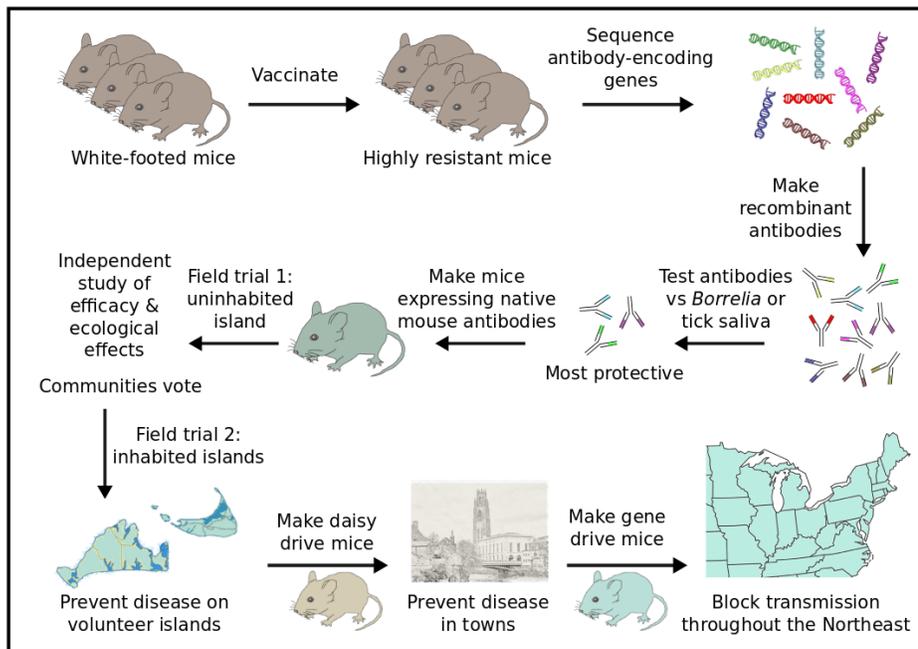
The Esvelt lab, at the Media Lab of the Massachusetts Institute of Technology, has begun preparations to conduct a scientific project aiming to control Lyme disease using recently developed genome engineering technologies. The planned intervention will block disease transmission by heritably immunizing wild populations of white-footed mice, the primary reservoir of the disease, which are responsible for infecting most ticks and therefore for most human Lyme disease cases east of the Mississippi. Immunizing all of the mice in an area would dramatically reduce the number of infected ticks and consequently the incidence of disease (Tsao and Barbour 2004). Releasing large numbers of genetically immunized mice on an island could permanently reduce the incidence of disease.

Nantucket and Martha’s Vineyard were chosen as possible second-round study sites due to their high disease burdens, well-educated populations, and history of local decision-making by New England town-hall democracy, as well as their proximity to numerous small uninhabited islands that could serve as first-round field trial sites. The relative geographic isolation of an island limits the extent of possible unintended environmental consequences. On an island, released altered mice can, if necessary, be replaced with wild-type equivalents, thereby restoring the original situation. The Esvelt lab has proposed to begin the scientific study by generating immune mice with no foreign DNA, and therefore without any form of gene drive system. Released in large numbers on a small uninhabited island, such mice can be used to test the efficacy of the approach and discover potential environmental side-effects without risking accidental spread.

If the approach is successful on the uninhabited island and then on either Nantucket or Martha's Vineyard, mainland communities could subsequently choose to alter their own mouse populations using “daisy drives”, a limited and local form of gene drive invented by the Esvelt laboratory as a means of safely testing effects and giving communities control of their own shared ecosystems without imposing those decisions on others (Noble et al 2016).

The project that we propose to the Greenwall Foundation aims to address questions of community consent and decision-making by the island population during the early development and later real-world testing of the novel ecological intervention of genetic immunization of white-footed mice. Ongoing consultations with the island communities through in-person and online fora, as part of our community consent and decision making study, will determine whether and how the scientific project proceeds.

The scientific work, including both lab-based and potential future field work, are being conducted independently with funding that is unrelated to the bioethics project that we here propose to the Greenwall Foundation.



Preliminary work and Progress

A preliminary workshop, held at MIT on December 11 2015, brought together citizens from Lyme-afflicted communities, educators and communicators, representatives of several NGOs, medical experts, laboratory and social scientists, ecologists, risk analysts, and ethicists to begin mapping a way forward. An inquiry we sent to the Greenwall Foundation in January 2016 incorporated our preliminary work on community engagement at that point in time.

Progress Report:

On Nantucket, a public meeting involving the local Board of Health and approximately 30 interested citizens was held on June 6, 2016. The outcome was a broad agreement to move forwards; all present indicated that they were willing to consider the possibility of eventually releasing more than a hundred thousand engineered mice on the island. The meeting and proposal were described in the *New York Times* and the *Boston Globe*. Two subsequent meetings with representatives from the various Boards of Health on Martha's Vineyard, and with a group of ~100 interested citizens, took place on July 20. Attendees indicated a strong desire to move forwards with at least one of the proposed scientific methods of generating Lyme resistant mice. As on Nantucket, all present indicated a willingness to consider a release on Martha's Vineyard. The public presentations and interactions with members of the community have been video recorded, providing a unique documentation of the very early phase of community deliberation.

The presentations on the scientific project led to the initiation of local regulation and governance activities: the Nantucket Board of Health has drafted a project oversight plan detailing governance, including a Data Safety and Monitoring Board to conduct independent assessments, report their findings, and issue a recommendation to the community. The representatives of Martha's Vineyard are interested in working with Nantucket's framework to create a uniform governance process.

Specific aims:

I. To identify and examine the relevant normative issues involved in the development and use of genomic technologies in the shared environment.

The project we propose to the Greenwall Foundation will work with residents of Martha's Vineyard and Nantucket. These islands are good candidates for genomic interventions for scientific reasons, but they also are an excellent setting for the study of community consent. The year-round island populations consist of closely-knit communities with a long democratic tradition, with income below the state median; they are joined in the summer by a more diverse and wealthy elite. The size, education level, history, and diverse socioeconomic characteristics of these two communities make them ideal environments in which to explore relevant normative questions. Starting from a unique experimental model, "Responsive Science", that tests intertwined community discourse and scientific research, we will assess issues of individual vs communal informed consent, the implications and adequacy of democratic deliberations in these communities, and the relevance of community decisions for next steps and larger-scale genomic interventions beyond the islands that are the focus of the proposed study.

The bioethics research will consist of a conceptual and normative inquiry, starting from an analysis of already established community engagement models, and also examine very recent examples of community reactions to proposed ecological interventions. In order to relate the findings from the existing community engagement models to the real-world situation of the communities we work with on Nantucket and Martha's Vineyard, we will seek the input from these communities through small-scale qualitative assessment. Direct interactions between our

team and the communities will be facilitated by our Research Assistant Joanna Buchtal, who also is a member of the scientific team as well as a Martha's Vineyard native and citizen. Details are below in the Methodology section. A Letter of Support from Martha's Vineyard and Nantucket's proposed governance plan for the project are attached.

II. To address the concrete problem of Lyme disease by informing the community-guided development of anti-Lyme disease interventions

Lyme disease cases have risen from negligible in the 1960s to an estimated 300,000 Americans per year by 2015 (CDC 2015) due to land-use changes favoring white-footed mice, deer, and ticks (Levy 2015). If not diagnosed and treated with antibiotics in a timely manner, it can lead to a protracted chronic disorder with substantial disability. Health care costs related to Lyme disease are an estimated \$710 million - \$1.3 billion per year and rising (Adrion 2015).

Immunizing white-footed mouse populations could permanently prevent most infections. By informing discussions with a careful analysis of the relevant normative issues, we will promote awareness of the options available and add to the quality of consent and communal decision-making.

III. To investigate the feasibility of addressing ethical concerns prior to and during technology development by informing what may become a guiding model for future community-supported ecological interventions.

We firmly believe that environmental genomic technologies demand a mutually responsive model of technology development emphasizing early discussion, transparency, and community guidance. To put this into practice, the Esvelt lab is committed to work according to the model of "Responsive Science", a notion that originates from the Harvey Mudd College's Hixon Forum (Hixon Forum 1990), which requires normative questions being investigated as they arise during the development of novel technologies, in this case ecological engineering in people's shared environment. In order to appropriately address the ethical questions, real-world data are needed to identify and examine the perceptions, values, and preferences concerning the potential ecological interventions of the individuals and communities involved. The online platform "Responsive Science" (under construction; to be located at www.responsivescience.org) will be an important tool for direct communication between scientists, stakeholders, and the community at large.

While societal accountability and transparency are increasingly recognized as key requirements in academic work across the disciplines, they are of particular importance in the life sciences and critical in any research that involves the shared environment. Through our project we will demonstrate the feasibility of early-stage collaborations between bioethicists and scientists and establish a new model for community engagement in applied ecological research.

IV. To develop and test a new model in normative ethics that may become a guiding model for future work in emerging ecological technologies

We aim to develop and test a model of community decision-making and consent based on reciprocity and mutuality, enabling responsive interaction between research scientists and the persons and communities that are involved in the scientific project that has been proposed to be conducted in their environment. The island communities of Nantucket and Martha's Vineyard that may eventually volunteer as second-round field trial sites will select the uninhabited islands for the first round, as well as the type of immunized mice to be released, ecological monitoring to be performed, and set the points at which communities must affirm support for the project to continue. The arguments, deliberations, and outcomes will in turn inform the further development of the bioethics model.

Because the communities were approached before experiments began, the heritable Lyme

immunization project is likely unique in the extent to which community concerns will drive the research, which in turn will be shared in an iterative cycle of mutually responsive deliberation and decisions about progress to next steps. This is the key concept of “Responsive Science”. While preliminary interactions with members of the community have shown that the concept of “Responsive Science” can indeed be translated into practice, the normative underpinnings so far have been lacking.

The bioethics project that we propose aims to fill that gap by developing a normative model for community decision-making and consent that can underlie a truly “Responsive Science”. The model shall be firmly based in ethical theory and build on the analysis of established models of community engagement and decisionmaking. Importantly, it will incorporate the real-world information relevant to the particular situation obtained through targeted interactions with community members and other stakeholders. Details are in the methodology section.

The proposed project is innovative and goes beyond the current work on the question of community consent, particularly in its potential to have a specific real-world impact that involves the shared ecosystem. Emerging genomics-based approaches to altering shared ecosystems are novel and potentially highly beneficial, but also raise concerns and create dilemmas that society has not faced previously. Further, as scientists and ethicists who have led the field from its inception, we believe the anti-Lyme intervention, as proposed in the scientific project, in this unique geographical and social setting is a most promising case study of possible gene drive applications. We will develop and test a novel bioethics-guided model of community decision-making in mutually responsive science that may inform current and future approaches to ecological engineering.

Methodology

Analysis

Our envisaged normative model stands in need of a solid foundation in ethics and through this project we will provide the necessary underpinnings. The project will begin by adapting a set of principles that were proposed by Knoppers and Chadwick (Knoppers, Chadwick 2005) as a new normative framework for genetics research following the completion of the Human Genome Project. These principles include reciprocity, mutuality, solidarity, citizenry and universality. At the start of our project we will investigate their suitability as guiding principles for our envisaged model of “Responsive Science”. In addition, we will address a fundamental question: how can the notion of ‘consent’, which was developed for use at the level of the individual, be applied to communities? How can community consent be reached? The question leads to the interface with political philosophy and political sciences, in particular to theories of deliberative democracy.

As our project addresses normative questions in community consent and decision-making through the lens of a real-world process, we will examine relevant ethics and philosophy literature on the relationship between normative models and the various concepts of empirical ethics. We will investigate the utility of applying different conceptions of philosophically-driven empirical ethics (Dunn et al 2012), identifying which variants are most applicable to our specific community-oriented study and delineating the novel approaches that will need to be developed.

We will then draw upon existing examples and analyses of previous community engagement cases.

For example, the Patient-Centered Outcomes Research Institute (PCORI) focused on the inclusion of patient stakeholders in research as partners and co-investigators (Robbins et al 2016)(Frank et al 2015).

Closer to the field of genomic engineering is the International HapMap Project. While the donors gave individual consent for their sample donation, complex community issues had to be addressed. Following the NIGMS /Coriell community consultation policy, Community Advisory Groups (CAG) were established at the sites of sample collection. The reports on the community engagement processes will be a most valuable resource.

A further relevant example is the Personal Genome Project (PGP), the normative underpinnings of which were developed by Jeantine Lunshof in collaboration with Daniel Vorhaus, Ruth Chadwick and George Church (Lunshof et al 2008). Reciprocity in the relationship between participants and researchers is a key feature of the PGP, as is Open Consent (Ball et al. 2014), although consent for DNA sample collection fundamentally differs from community consent for ecological interventions.

Most relevant to our normative model are two projects in which the release of engineered mosquitoes is intended to reduce the incidence of vector-borne disease. One project, an effort led by Oxitec Ltd. that seeks to release genetically altered sterile male mosquitoes in Key West Florida, is experiencing strong community pushback and likely rejection at the ballot box (Adalja et al 2016). In contrast, “Eliminate Dengue”, a project in Queensland, Australia, received a positive community response. This project releases mosquitoes deliberately infected with *Wolbachia*, a naturally occurring microbe that blocks the transmission of viruses (Kolopack et al 2015). A dedicated Community Engagement strategy has been a key component in “Eliminate Dengue”. While the communities did not play a role in guiding the early development of the technology, which involved introducing a naturally occurring virus-blocking bacterium into a species that did not previously harbor it, this effort is nonetheless the most suitable foundation on which to build a more comprehensive normative model of mutually responsive science.

Phase I

We will begin by researching the above examples and contacting the research teams involved. We will use the insights from these previous experiences to build a model for community consent and decision-making that is relevant to emerging ecological technologies.

Phase 2

We will inform our model by examining the preliminary and ongoing community engagement efforts on Nantucket and Martha's Vineyard. On-site work is critical for any type of ecological intervention research (Lavery et al 2008), and many aspects of the project, particularly the extent of community direction of research, are unique. Joanna Buchthal, a resident of Martha's Vineyard, will be our dedicated Research Assistant. As Project Manager of the scientific effort, she has already been successful in facilitating community interactions during the preliminary work. In the first year, the public meetings and other interactions between the scientific teams, elected officials, and local citizens will be recorded. We will catalog discussions on the online Responsive Science platform and in the comments sections of articles in the local press. This database will enrich our understanding of the interactions between scientists and communities to better inform our normative framework for Responsive Science. Once our framework is in near-final form, we will again seek input from the communities at the public meetings and on the Responsive Science online platform to identify missing areas and those requiring refinement.

Phase 3

We will evaluate the real-world utility of our newly developed model through interactions with the communities, the scientific team, and stakeholders from the governance arena. This will play a key role in guiding the scientific project. A report on this evaluation, our findings and conclusions, as well as an evaluation of flaws and mistakes in how the scientific project was handled, will be presented in the form of a peer reviewed open-access publication. The outcomes of our 2-year project, in advance of the implementation of ecological engineering interventions, will show the strength of our proposed model as well as the points that need further work in view of applicability to future ecological research by others.

Community interaction

In order to relate the findings from the existing community engagement models to the real-world situation of the communities we work with on Nantucket and Martha's Vineyard, we will seek, in the second phase of our project, the input from these communities through small-scale qualitative assessment. Direct interactions between our team and the communities will be facilitated by our Research_Assistant Joanna Buchthal, who also is a member of the scientific team as well as a Martha's Vineyard native and citizen.

The online platform "Responsive Science" will be an important tool for direct communication with the community at large, including formal representatives, as e.g. the Boards of Health, and other stakeholders. We may occasionally seek advice from external experts on emerging issues outside our field of expertise.

Dissemination of Results

The nature of peer-reviewed publication(s) expected from the project and how the target journal's audience includes key individuals who can change practice or policy:

We will describe the research and our bioethics model in open-access peer-reviewed publications in bioethics, public policy, and ecological journals. To reach scientists and policymakers, we will seek to publish high-visibility papers describing the process and policy implications in leading scientific journals. Given its potential importance for shaping future interactions between science, ethicists, and society, we will seek to publicize our model in venues intended for broad audiences, for example leading newspapers, *Project Syndicate*, *the Atlantic*, and *Scientific American*.

Human Subjects Research approval

We have sought Institutional Review Board approval for the project. COUHES (MIT's IRB) has determined the project's status as exempt.