Preventing Tick-Borne Disease

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The proposal

To permanently break the transmission cycle between white-footed mice (the primary reservoir of Lyme disease) and ticks in order to reduce the number of infected ticks and consequently prevent new human infections.

Controlled releases of Lyme-resistant mice would introduce immunity to most or all of the native mouse population.

*Released mice would be genetically altered, but 100% mouse*

*A percentage of the Vineyard’s white-footed mice naturally express antibodies against the Lyme-causing spirochete Borrelia burgdorferi*
Open, Community-Driven Science

- Clear benefits to citizens
- Discussions before experiments
- Safeguards agreed upon early
- Developed/run as a nonprofit
- Independent monitoring and analysis
- Open and responsive science

This project will only move forward if embraced by the community
It could supplement, *not replace*, existing control efforts
Thoughtful, Measured Approach

- The Steering Committee must secure federal, state and local approval
- All efforts will be guided and monitored by local and national ecologists
- Trials will be sequential: uninhabited islands first, then inhabited

Changes are not anticipated to spread beyond the island. No gene drive!

Guiding principles for eco-engineering:
- Rule 1: Make the smallest possible change capable of solving the problem
- Rule 2: Start local and only scale up if warranted
Tick-borne disease is an ecological problem

The spirochetes that cause Lyme disease persist by moving between mice and ticks.
Tick-borne disease is an ecological problem

Ticks pass the spirochetes to humans, causing Lyme disease.
Tick-borne disease is an ecological problem

What if white-footed mice could not become infected?
Breaking the cycle

If *every mouse* produced antibodies conferring effective immunity from birth, the reservoir of *B. burgdorferi* would likely collapse.

No infected mice → No infected ticks → No infected people

**Important note:**
Some ticks could become infected from residual secondary reservoirs, but the rate should be *far* lower than today.
Ecological Vaccination

White-footed mice

Option 1: Immunize mice against Lyme spirochete only
Should not impact other species, but would not prevent other tick-borne diseases.

Option 2: Immunize mice against ticks
Should also prevent babesiosis, anaplasmosis, and ehrlichiosis. It would reduce the tick population, which may have side-effects.

Option 3: Do both!

Option 4: Do nothing
Timeline

Build heritably immune mice

~2 years to engineer immune mice

~3 years to generate enough mice for a small island

Release on an uninhabited island

Release on an inhabited island

2+ years to evaluate effects and raise enough mice for a large island
Implementation

Release immune mice in early spring, or over 1-2 years

• Introduced mice would increase the local mouse population to at most 200% of ‘normal’

• For context, mouse populations often fluctuate by >400% over the course of a year

• Bait stations could be used to reduce populations near commercial and residential areas

Local reductions will not impact the spread of resistance
Project Status

Local Presentations
• Jun 2016: Nantucket Board of Health meeting
• Jul 2016: Martha’s Vineyard health agents meeting
• Jul 2016: Edgartown Library presentation with Professor Sam Telford and Dr. Michael Jacobs
• Oct 2016: Martha’s Vineyard All-island Board of Health meeting
• Jan 2017: Nantucket Board of Health and community meeting

Project Management
• Jul 2016: Nantucket BOH agrees to jointly develop project management plan
• Dec 2016: Nantucket confirms Dr. Emily Goldstein Murphy to join the Steering Committee
• Jan 2017: 4/6 MV towns have agreed to send nominees to the Steering Committee

Project Milestones
• Our collaborators have finished vaccinating white-footed mice
• Animal protocols have been submitted to MIT
• Dovetail Genomics has assembled the first white-footed mouse genome
• Awarded a Greenwall Foundation Grant for project ethics
Project Management

**Steering Committee**
7-9 members including Board of Health appointed representatives

**Data Safety Monitoring Board**
Independent of the Steering Committee, MIT, funding agencies or representative communities. Size and makeup TBD.

**Project Manager**
Reports to the Steering Committee
Proposed Decision Points

1st Evaluation Point: After immune mice have been created in our lab
- Project go/no go recommendation by DSMB
- If go, project must secure ...
  • Regulatory approval for next phase
  • Approval for the use of an uninhabited island from the land owner/local government involved
  • Continued interest by the Boards of Health

2nd Evaluation Point: After uninhabited island field trial
- Project go/no go recommendation by DSMB
- If go, project must secure ...
  • Regulatory approval for next phase
  • Warrants proposed by the Boards of Health at Town Meetings
  • Warrants approved at Town Meetings
Funding

- Initial MIT & Tufts support, Greenwall Foundation
- Possible government funding for lab work
- Philanthropic funding, possibly from multiple sources, for scale-up

Other projects of comparable scale require funding in the millions for operations and evaluation
Questions for the citizens of Nantucket

• Is this project still one you might wish to pursue?

• Should mice be immunized vs Lyme, vs ticks, or both?

• Where should the first field trial(s) be held?

• What criteria must be met for you to consider releasing mice on the Vineyard?

• Do you want to nominate anyone for the Steering Committee?
A Local Resident’s Questions...

Would this amount to wiping out the existing mice and replacing them with a new species?

No, the project would introduce mice bred from the same native population – State Fish & Wildlife requires this. The resulting population will be genetically identical except that they will all have protection that only a few scattered mice had before.

What would stop *Borrelia* from simply moving to birds, reptiles, dogs, cats, horses, etc?

They’re already in shrews, chipmunks, birds, reptiles, etc; but these are less likely to become infected or infect ticks. Fewer ticks infected by the mice means fewer infections of these other animals, then even fewer infected ticks in the next generation, and so on.

How are you going to test the effects without potentially causing irreversible damage?

If the independent monitors detect anything wrong on the uninhabited island, we can set traps and release wild-type mice to quickly replace the mice. All environmental changes have risks; the goal is to make the smallest possible change that can solve the problem.
Current Team

Key Collaborators

Dr. Sam Telford
Dr. Linden Hu

Research Team

Dr. Kevin Esvelt
Dr. Jeantine Lunshof

Ryan Kelly
Dr. Aurelie Kern
John Min
Devora Najjar
Joanna Buchthal
Questions?
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Relevant study #1

By-hand vaccination reduced *Borrelia* prevalence by

- **42%** in mice
- **25%** in ticks

This study did not control for unvaccinated mice migrating into the area.

Tsao JI, Wootton JT, Bunikis J, Luna MG, Fish D, Barbour AG (2004) *PNAS*
Relevant study #2

An oral bait-delivered vaccine reduced tick infection rates by

- **25%** when deployed for 2 years
- **76%** when deployed for 5 years

This study did not control for unvaccinated mice migrating into the area. Increase in mouse antibody levels was barely statistically significant. This study also had issues with proper controls, suggesting high site variability.

Management Plan: Project Operations

1. **Steering Committee (SC)**: 5-7 members incl. Board of Health appointed representatives
   - General supervision of the project
   - Develops study designs and “stopping rules” in collaboration with the Data and Safety Monitoring Board (DSMB)
   - Acts on recommendations of the DSMB

2. **Project Manager**: reports to the Steering Committee
   - Tracks project progress and budget
   - Liaison with regulatory authorities and funding organizations
   - Prepares regulatory documents, reports, grant requests and SC minutes

3. **Data Safety Monitoring Board (DSMB)**: independent of the SC, MIT, funding agencies or representative communities. Size and makeup TBD.
   - Ensures that there is no harm to the environment, animals or humans
   - Defines “stopping rules” in collaboration with the SC
   - Reviews and comments on all study designs
   - Reviews project compliance and progress at specified intervals and ad hoc if requested by the SC
   - Recommends discontinuing or altering the design of the project at pre-determined times or at any time in the interest of safety
Background

In December 2016, we held a workshop involving island citizens, scientists, ethicists, NGOs and regulators before starting experiments or seeking funding

Workshop Takeaways:
Island citizens must agree to the following...

• The points at which the project stops absent community approval to proceed
• Which approach should be chosen for trials
• Where the initial field trial should be held (e.g. uninhabited island(s) )
• Who will perform ecological monitoring and effectiveness tests
• Requirements for local release
• Any other decision deemed important by the community
No Gene Drive on the Vineyard!

There is no need for a drive system on the Vineyard due to the small size of the island.

A 'daisy drive' system could spread resistance faster with fewer mice, but again, it is not required.
Breaking the cycle

How might we identify the best antibodies and give them to the island mouse population?

How might we determine whether it works and identify possible ecological side-effects?
Timeline

- 2016: Make immune mice
- 2017: ~2.5 years to generate mice for a small island
- 2018: Uninhabited island(s)
- 2019: ~1 year to generate mice for a large island
- 2020: Larger, inhabited island?
Mice Immunity Options

Option 1:
Protect mice from the Lyme spirochete only
   *Should not affect other species, but would not prevent other tick-borne diseases.*

Option 2:
Immunize mice vs ticks
   *Should also prevent babesiosis, anaplasmosis, and ehrlichiosis.*
   *It would reduce the tick population, which may have side-effects.*

Option 3:
Do both
Leading By Example

A local and grassroots approach to guide science, technology development, and local ecological management – with decisions made using New England town hall democracy – could help other communities decide similar questions.
Genome Editing
CRISPR
Guide
Genome

CRISPR
Guide

Edited DNA (antibodies)
Gene Drive
Genome

CRISPR

Edited DNA (antibodies)

Guide
Gene Drive
This is worth considering. It could solve many problems, but could also do great harm. How are you sure of this? Are our tests thorough enough? It's far too risky. The precautionary principle says we mustn't risk it. Isn't that easy for us to say? Even so, the biotech box is probably too dangerous. If it could solve the problem, why not try it? The risks are almost certainly worth it, even if the side effects are comparatively bad. We need to be sure that it's our technology – developed and tested here.

WTF, mate?

Worth a shot, no? Not like we haven't got a lot of ecological problems! Or make worse!

Eh, it's more or less reversible.
CRISPR + Edited DNA + Guides

Daisy Drive

C ➔ B ➔ A
Open, Responsive, Community-Guided Science
Questions?

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