A conversation with the Foundation for the National Institutes of Health, February 14, 2018

Participants

- Dr. Stephanie James – Director of Science, Foundation for the National Institutes of Health (FNIH)
- Dr. Karen Tountas – Scientific Program Manager, FNIH
- Nicole Ross – Research Analyst, Open Philanthropy Project
- Alexander Berger – Managing Director, Open Philanthropy Project

Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Dr. James and Dr. Tountas.

Summary

The Open Philanthropy Project spoke with Dr. James and Dr. Tountas of the FNIH as part of a follow-up on our 2016 grant to support an FNIH-facilitated working group to develop recommendations specific to testing mosquitoes modified with gene drive technology for the purpose of reducing the burden of malaria in Africa. The conversation covered the topics that the working group's meetings focused on, several key issues raised by the FNIH's report, and the FNIH's plans for translating its recommendations into policy.

Working group meetings

The FNIH engaged a core working group of twelve scientists from various relevant fields and organizations, and convened three in-person working group meetings, each about three days long. These meetings focused on testing phases described in the WHO Guidance Framework for testing genetically modified mosquitoes (http://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/):

1) *First meeting*: research in contained laboratory and semi-field testing (outdoor insectary) environments.
2) *Second meeting*: initial releases in ecologically-confined environments, larger scale staged open field releases, and measuring disease impact.
3) *Third meeting*: implementation of gene drive mosquitoes as a malaria control tool, and post-implementation surveillance to monitor efficacy and safety over time.

Participants in the meetings included:

1) The twelve core working group members, who remained with the project for the entire year-and-a-half project period.
2) A number of "ad hoc" working group participants, who attended about one or two meetings each depending on their areas of expertise.
3) Experts that the FNIH approached to provide background information or give presentations about particular issues raised during a given meeting; these

contributors either gave a live presentation to working group members or provided white papers for consideration. These experts did not participate in working group discussions.

4) Observers from various agencies, e.g. the World Health Organization (WHO), DARPA, the Bill & Melinda Gates Foundation, and the U.S. National Institutes of Health.

The FNIH started working on recommendations and drafting its report in between working group sessions. Once the sessions were complete, the FNIH spent the rest of the year a) finishing the report draft, b) receiving and incorporating comments from workshop participants, and c) sending the draft to external reviewers with expertise in relevant fields and incorporating their comments.

Consensus that safe testing is possible

One outcome of the working group meetings was receiving consensus among participants that gene drive mosquitoes can be safely tested provided recommended precautions are followed and required approvals are obtained. The working group process was an opportunity to a) carefully consider potential testing pathways in detail, b) identify areas where new ideas and policies, or more information or resources, are still needed, and c) make recommendations about how to handle issues related to the characteristics of low threshold gene drives. This process has increased consensus that safe testing is possible and has provided a much more solid basis for developing and deploying the technology.

Difficulty of guaranteeing containment

A key general consensus outcome among working group members is that it will not be possible to guarantee containment of gene drive modified mosquitoes, which will be important to understand for studies conducted in malaria endemic regions of Africa. Modeling exercises to date suggest that even a few modified mosquitoes in the environment, which could accidently escape during laboratory or semi-field studies conducted in malaria endemic areas, could lead to the modification becoming established in the local wild-type population. Therefore, the working group stressed that it is especially important to thoroughly test for safety in a contained, laboratory setting before taking mosquitoes to the field (even in a semi-field caged environment). There was consensus that the transition from laboratory-based research to field testing needs to be treated as a major decision point, and the report covers the need for conducting risk assessments and rigorous safety testing before that point, as is already common practice for exotic biocontrol agents.

Although biocontrol regulatory pathways may exist, the recommendations in the report address regulatory needs that are specific to gene drive technology. For example, because of the intended spread of the modification in the wild mosquito population, it is recommended that regulators coordinate across country borders.

Ideal characteristics for the site of first release

There was some remaining disagreement among working group members about the ideal characteristics for the site of first release (for instance, whether first release ought to be on an island to keep the mosquitoes geographically isolated, or whether an island location would adequately prevent further spread of the modification). It seems very unlikely that any site will have every ideal characteristic for initial release testing – e.g. adequate local scientific infrastructure (scientists, insectaries, communications, etc.), established regulatory infrastructure, appropriate isolation, and so on. To get a broader sense of which characteristics people consider most important for the site of first, small scale release of any given investigational gene drive mosquito product, the FNIH plans to send a follow-up survey to working group participants and other experts, asking them to prioritize and weight various site-selection criteria that can be roughly categorized as regulatory, scientific, and engagement. Data from the survey will be analyzed for trends of agreement and disagreement.

Self-limiting release recommendation

The report does not make the release of mosquitoes modified with a self-limiting gene drive construct – a form of biological or molecular confinement as opposed to physical or ecological confinement – a strict pathway requirement, although it does recommend a self-limiting intermediate step for:

1. Providing information about ecological interactions for a first-in-class product.
2. Giving research teams in malaria-endemic countries, which may not have experience working with genetically modified organisms or with containment practices, the opportunity to develop necessary skills and build system capacity.
3. Testing the efficacy of a population modification approach on the particular parasites circulating at the test site.

Some disadvantages of utilizing mosquitoes modified with self-limiting constructs include:

1. The potential inability to be effective over a sufficient area or timeframe to provide a sustainable reduction of malaria transmission in Africa.
2. The expectation that such products may not have exactly the same environmental interactions and implications as the self-sustaining version.
3. The increased cost (development time and resources).

The report does make a firm recommendation that external hazards risk assessments should be completed before advancing an individual investigational mosquito product to the next testing phase, and the kind of information that a self-limiting intermediate version would provide could inform such a risk assessment.

Field cage testing

The working group's recommendations did not include field cage testing as a critical-path requirement prior to the first small-scale release. The working group did produce suggestions of experiments involving field cage testing that could potentially provide useful information.

Process for translating recommendations into policy

The FNIH has submitted its report for publication so that it will be available to all interested parties, including policy-makers. Both WHO and the New Partnership for Africa's Development (NEPAD) had representatives attending the working group meetings, and so are familiar with the recommendations. The FNIH hopes the report will contribute to upcoming discussions about gene drive research in venues such as the Convention on Biological Diversity.

The FNIH gave a presentation about the recommendations at a meeting of the WHO Vector Control Advisory Group (VCAG), which evaluates new vector control technologies (both for malaria and for neglected tropical diseases). VCAG works with the developers of new control methods to help plan field trials, evaluate the results of field trials, and decide whether to recommend that the WHO should approve the tool for its described purpose. In this case, if VCAG decided to recommend the tool, it would first make a recommendation to the WHO's Global Malaria Program, which in turn would decide whether to make a recommendation to the WHO in general, which would then decide whether to endorse the use of gene drive mosquitoes for malaria control.

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