Results of the Workshop: "Problem Formulation for the Use of Gene Drive in Mosquito"

Andrew F Roberts, PhD
Director
Center for Environmental Risk Assessment (CERA)

September 20, 2016

ILSI Research Foundation

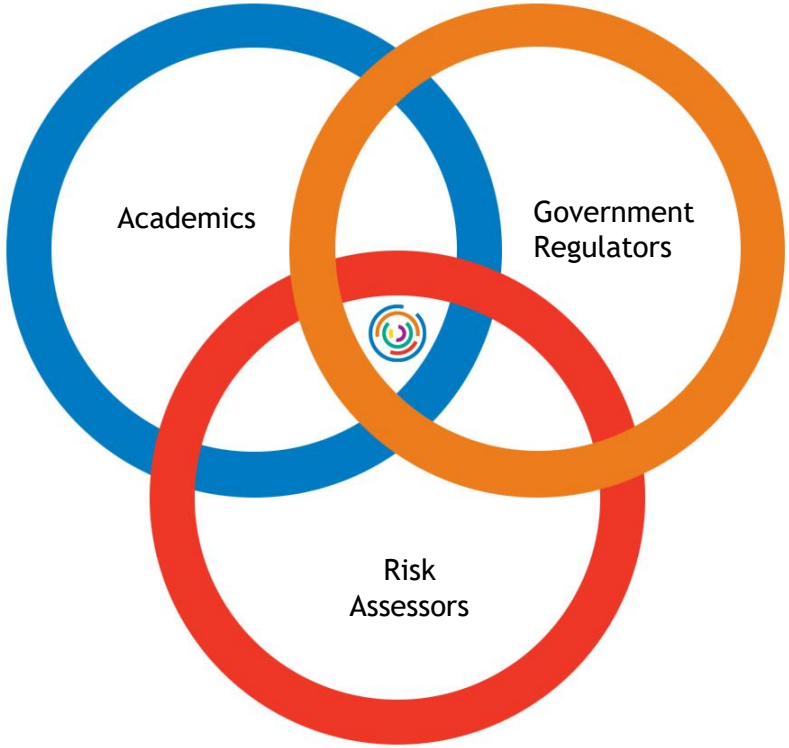
Contents of My Presentation

- Brief introduction to the workshop
- How did we conduct the problem formulation exercise?
- Summary of conclusions
- Next steps

ILSI Research Foundation

Workshop: Problem Formulation for the use of Gene Drive in Mosqutio

- Took place in Reston, Virginia, May 25-27, 2016
- 47 participants
  - Wide geographic representation
- Funding provided by the Foundation for the National Institutes of Health (FNIH)



FNIH
Foundation for the National Institutes of Health

ILSI Research Foundation

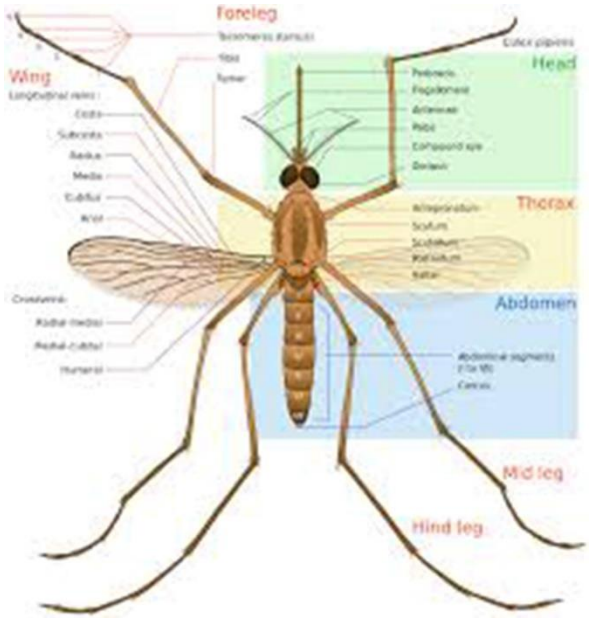
Purpose of the Workshop

- **To begin conversations** about Environmental Risks associated with the use of gene drive for malaria control
- **To identify areas** where researchers and development programs should be thinking about collected data in support of risk assessment
- **Provide a rational starting point** for regulators to think about the use of this technology

ILSI Research Foundation

Day 1: Scientific and Technical Background

- Biology of *Anopheles* mosquitoes
- What is Gene Drive?
- Applications of Gene Drive in Malaria Control
  - Population suppression
  - Population alteration
- Modeling the potential benefits of malaria control



Scientific & Technical Background → Breakout Groups → Building Consensus

ILSI Research Foundation

Day 1: Scientific and Technical Background

- What is Risk Assessment, and why do we do it?
- Introduction to Problem Formulation
- Problem Formulation Case Example: *Aedes aegypti* OX513A
- Environmental Protection Goals and Priorities in a Sub Saharan Country
- Introduction to the case study

ILSI Research Foundation

Day 2: Breakout Groups

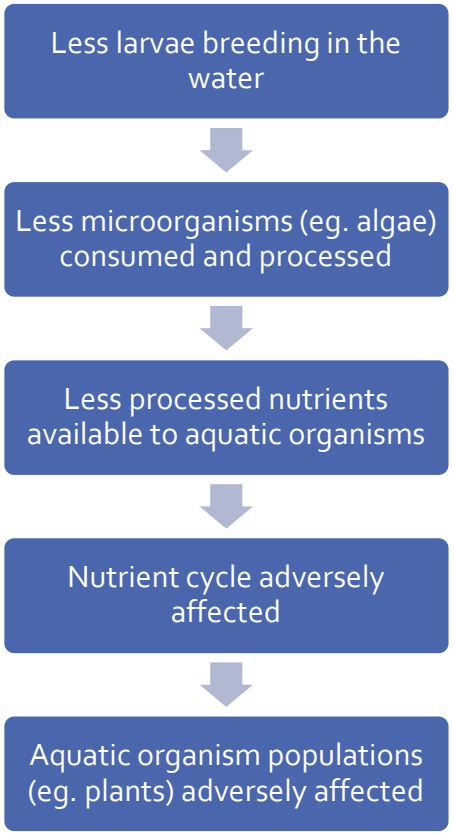
- Case Study Document
  - 10 pages of background material (similar to Day 1 presentations)
  - Four hypothetical examples of the use of gene drive in *Anopheles gambiae*
- Workbook – walking through Problem Formulation
  - Identification of pertinent protection goals
  - Refining protection goals and identifying plausible pathways to harm
  - Identifying information (data) that would be useful to determine likelihood of risk

ILSI Research Foundation

Protection Goal: Water Quality

Harm: Aquatic organism population adversely affected (eg. less larvae breeding in the water impacts nutrient cycle)

Pathway to Harm



Plausibility: Low

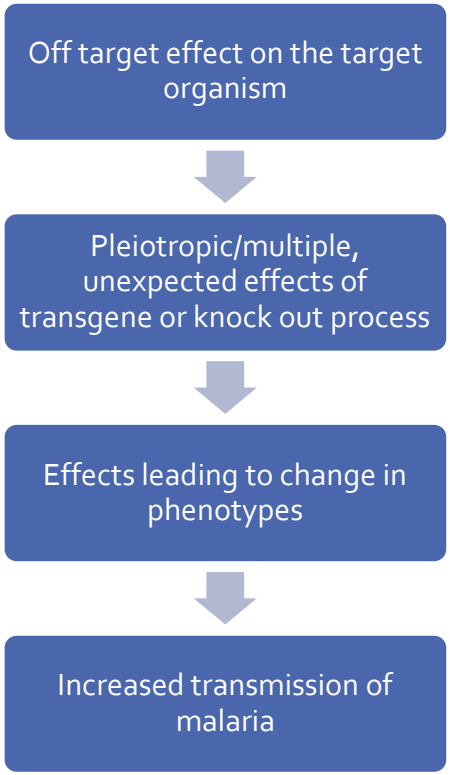
A large fraction of habitats are temporary and do not support complex communities.

Knock-in Suppression: Same

Protection Goal: Human Health

Harm: Human health is adversely affected by a change in the phenotype of the mosquito, thereby increasing the ability to transmit malaria

Pathway to Harm



Examples:

- *Response to chemicals*
- *Longevity*
- *Aestivation and desiccation*
- *Ability to transmit other pathogens – broaden vector competence*
- *Lack of females leads to increased male competition*
- *Timing of feeding*

Plausibility: Yes

Further research on the consequences of mutation of target and off-target effects is necessary.

Knock-in Suppression: Same

Day 3: Building Consensus

- Morning session spent with each group presenting their results
- Afternoon session was a discussion of consensus points, based on the morning's presentations.

ILSI Research Foundation

Consensus Points

Human Health

Animal Health (i.e. livestock)

Biodiversity

Water Quality

Pertinent Broad Protection Goals

Non-Pertinent Broad Protection Goals:

- Soil Quality
- Air Quality
- Natural Resources (other than biodiversity)
- Agricultural Production (excluding animal health)

ILSI Research Foundation

General Statement on Exposure Related to Species Specific Population Suppression And Population Alteration Strategies

- **Population Suppression**
  - Gene Drive Mosquitos for population suppression are designed to eventually reduce in numbers in the environment over a relevant time.
- **Population Alteration**
  - Gene Drive Mosquitos for population alteration are designed to persist in the environment over a relevant time.

ILSI Research Foundation

Human Health

Human Health

- **The relevant interaction for human health is biting**
  - **Incidental exposure through inhalation, ingestion, etc. is not likely to result in any significant levels of exposure leading to harm to human health**
- Proteins introduced into *Anopheles gambiae*, including components of the gene drive and markers, should be considered with respect to toxicity and allergenicity potential.
- Horizontal gene flow to humans is extremely unlikely to occur.

ILSI Research Foundation

Human Health

Human Health

- Because *Anopheles gambiae* is an important disease vector, consideration should be given to potential alterations in disease transmission
  - This includes altered P. falciparum transmission or virulence, other human malarial transmission as well as altered transmission of other diseases.

ILSI Research Foundation

Biodiversity (General Consensus Statements 1 of 2)

Biodiversity

- *Anopheles gambiae* is not a "keystone" species in the environment and is not known to provide any non-redundant ecosystem services
  - Changes in population size or even elimination of *Anopheles gambiae* from a particular environment are unlikely to harm biodiversity or ecosystem services. This is based on existing knowledge and experience with vector control programs.

ILSI Research Foundation

Biodiversity (General Consensus Statements 2 of 2)

Biodiversity

- *Anopheles gambiae* interacts with other species by feeding on them, being consumed as prey, or competing with them.
  - These interactions may require consideration for species of relevance to the assessment such as threatened, endangered, or valued species
  - Incidental contact between organisms and *Anopheles gambiae* carrying gene drives is not likely to lead to harms to those organisms, compared to interactions with other *Anopheles gambiae*.

ILSI Research Foundation

Biodiversity (Refined harms and priorities for consideration)

Biodiversity

- *Anopheles gambiae* is not known to be the sole or primary food source for any organism, with the possible exception of a few species of spider known to prefer Anophelines.
- Removing *Anopheles gambiae* from the environment is unlikely to harm species that feed on it, due to the availability of other prey, including Anophelines.
  - Birds, bats, fish etc.
  - This is primarily relevant for suppression strategies
- Consideration should be given to any proteins introduced into *Anopheles gambiae* (including gene drive components or markers) for toxicity to other species

ILSI Research Foundation

Biodiversity (Gene Flow)

Biodiversity

- Gene flow to other species within the *Anopheles gambiae* s.l. complex through hybridization is likely, and does not create additional pathways to harm.
- Horizontal gene transfer is not likely to occur to other organisms on any relevant time scale and is not a pertinent pathway to harm

ILSI Research Foundation

Animal Health (livestock)

Animal Health

- Potential harm could result from altered pathogen transmission dynamics to livestock.
- Harm resulting from other mechanisms, including toxicity from introduced proteins, was considered unlikely.

ILSI Research Foundation

Other Considerations (1 of 2)

- The use of gene drives in *Anopheles gambiae* should be considered as a complementary strategy to other vector control methods and malaria mitigation strategies.
- The potential harms identified for the use of gene drive in *Anopheles gambiae* should be considered in the context of other vector control methods and malaria mitigation strategies

Other Considerations (2 of 2)

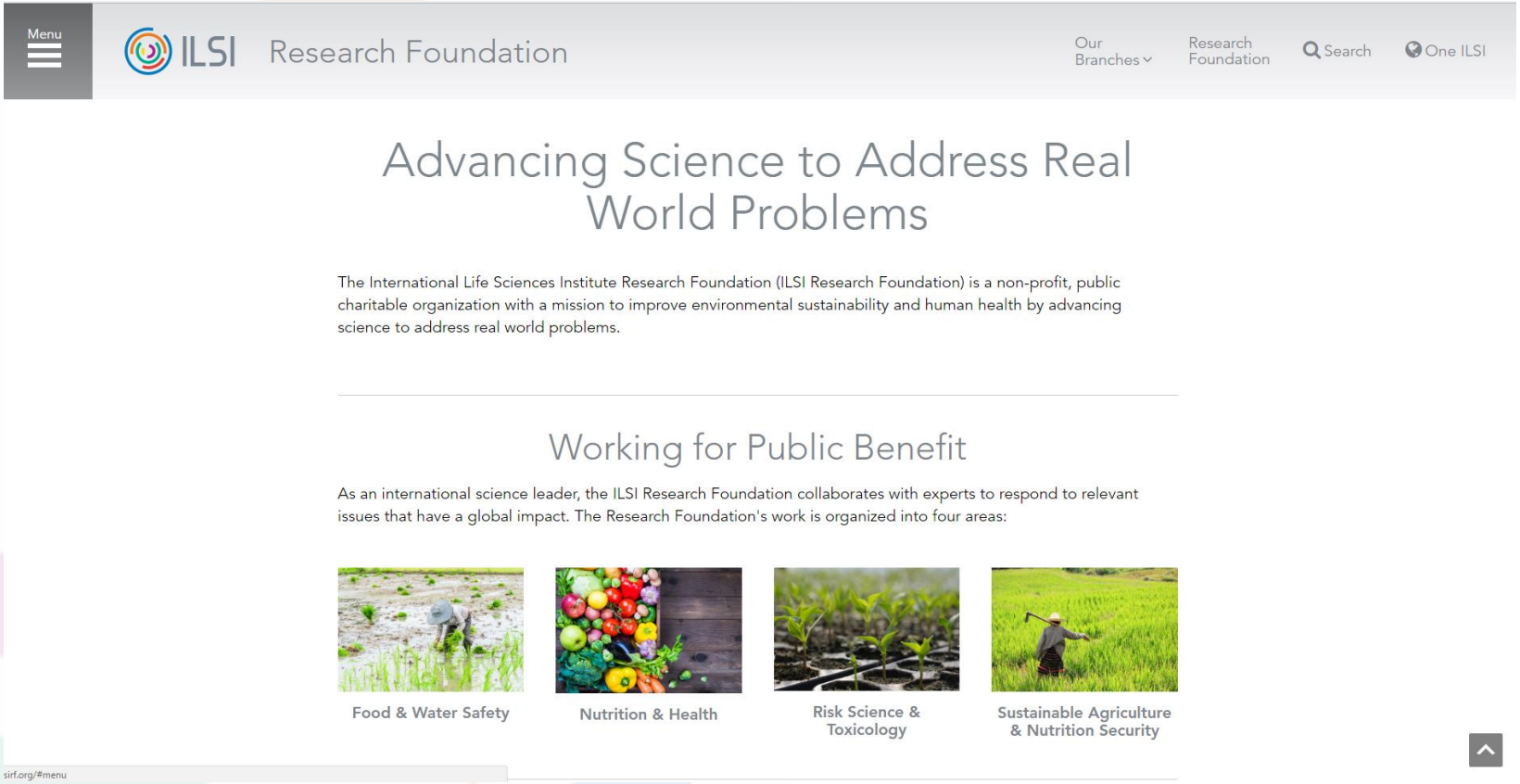
- Failure to sustain a successful malaria vector control strategy can have harmful effects on malaria incidence.
  - This is not unique to gene drive, and would be the same for other malaria control or eradication techniques
  - The ability to control resurgence needs be sustained and effective additional control methods need to be available

Conclusion

- The consensus points from the workshop provide a good starting point for a case specific risk assessment
- They are not intended to be immutable
  - Rather to allow developers and risk assessors to focus their efforts on the areas that are likely to be important for risk assessment
- These results have been submitted for peer review to the American Journal of Tropical Medicine and Hygiene (AJTMH)
  - Currently under peer review
- Additional workshops are planned for West, Southern and East Africa

ILSI Research Foundation

Thank you!
www.ilsirf.org



ILSI Research Foundation