Why do we need a gene drive mosquito?

Chun-Hong Chen
National Health Research Institutes
There is no effective vaccine for Malaria, Dengue and Zika yet

Global number of reported smallpox cases

Dengue consists of four closely related but antigenically distinct viral serotypes (DEN1-4). All four serotypes can cause the full spectrum of disease.
There are limited drugs for Malaria, Dengue and Zika
The plasmodium parasite is spread by female Anopheles mosquitoes
Dengue is spread through the bite of the female mosquito (Aedes).

**Aedes aegypti**
- These mosquitoes live in tropical, subtropical, and some temperate climates.
- They are the main type of mosquito that spread Zika, Dengue, Chikungunya, and other viruses.
- Because *Ae. Aegypti* mosquitoes live near and prefer to feed on people, they are more likely to spread these viruses than other types of mosquitoes.

**Aedes albopictus**
- These mosquitoes live in tropical, subtropical, and temperate climates, but can live in a broader temperature range and at cooler temperatures than *Ae. Aegypti*.
- Because these mosquitoes feed on animals as well as people, they are less likely to spread viruses like Zika, dengue, chikungunya, and other viruses.
The traditional methods for mosquito control did not change too much in past decades
A typical mosquito treatment lasts about 30 days, but most less two weeks.
WHO: Failure of mosquito spraying to stop dengue raises questions for battle against Zika
Mosquito source reduction also cost huge labor and cost
The traditional mosquito control works pretty much like the work of Sisyphus. We need new tools for preventing vector borne diseases.
Two Major strategies for mosquito control: population suppression and population replacement.

- Chemical Frogging
- Source reduction
- SIT
- Transgenic Oxitec

Wild Type

SIT, or Oxitec male
Two Major strategies for mosquito control: population suppression and population replacement.
Two Major Goals:

**Effector genes** for Malaria or Dengue Virus resistance

**A driver gene** for spreading the effector gene into population

The solution: Link genes for pathogen resistance with a selfish genetic element
The Idea of Gene drive for disease control

After Some generations

Disease Non-transmitted strain + Disease transmitted strain = Disease Non-transmitted strain

100% WT
50% WT, 50% NTS
100% NTS
Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite

Figure 1. Mechanism for Blocking Malaria Transmission in the Mosquito
The life cycle of the dengue virus

http://www.oxitec.com/
Anti-DENV/CHIKV phenotype of transgenic AeP Ub>10miR and AeCP A>10miR mosquitoes suppress Dengue and CHIKV replication

Refectory design for Zika and four types of DENV

A. Diagram showing the refection design process for Zika and four types of DENV.

B. Table showing the structural and non-structural proteins of Zika virus.

C. Images showing the comparison between WT and anti-ZIKV samples.

2018 PLOS Pathogen
2019 PNAS
Gene Drive

A

Standard altered gene
1 copy inherited from 1 parent
50% chance of passing it on

B

Altered gene + gene drive
1 copy → 2 copies
100% chance of passing it on

C

Cut
Repair

Medea drives population replacement in Drosophila

Science. 2007 Apr 27;316(5824):597-600.
Transgenic gfp111A-2 males that contained a modified intron-encoded endonuclease_I-PpoI suppress wild-type mosquito caged populations
A CRISPR–Cas9 gene drive targeting _doublesex_ causes complete population suppression in caged _Anopheles gambiae_ mosquitoes

Kyros Kyrour1,2, Andrew M Hammond1,2, Roberto Galizi1, Nace Kranjc1, Austin Burt1, Andrea K Beaghton1, Tony Nolan1 & Andrea Crisanti1
Three take home messages

1. We need new tools for preventing vector borne diseases.

2. Gene drive once developed, there is less need for repeating re-release. It might mean less cost.

3. Gene drive is more specific than other control methods. It only aims for specific species.