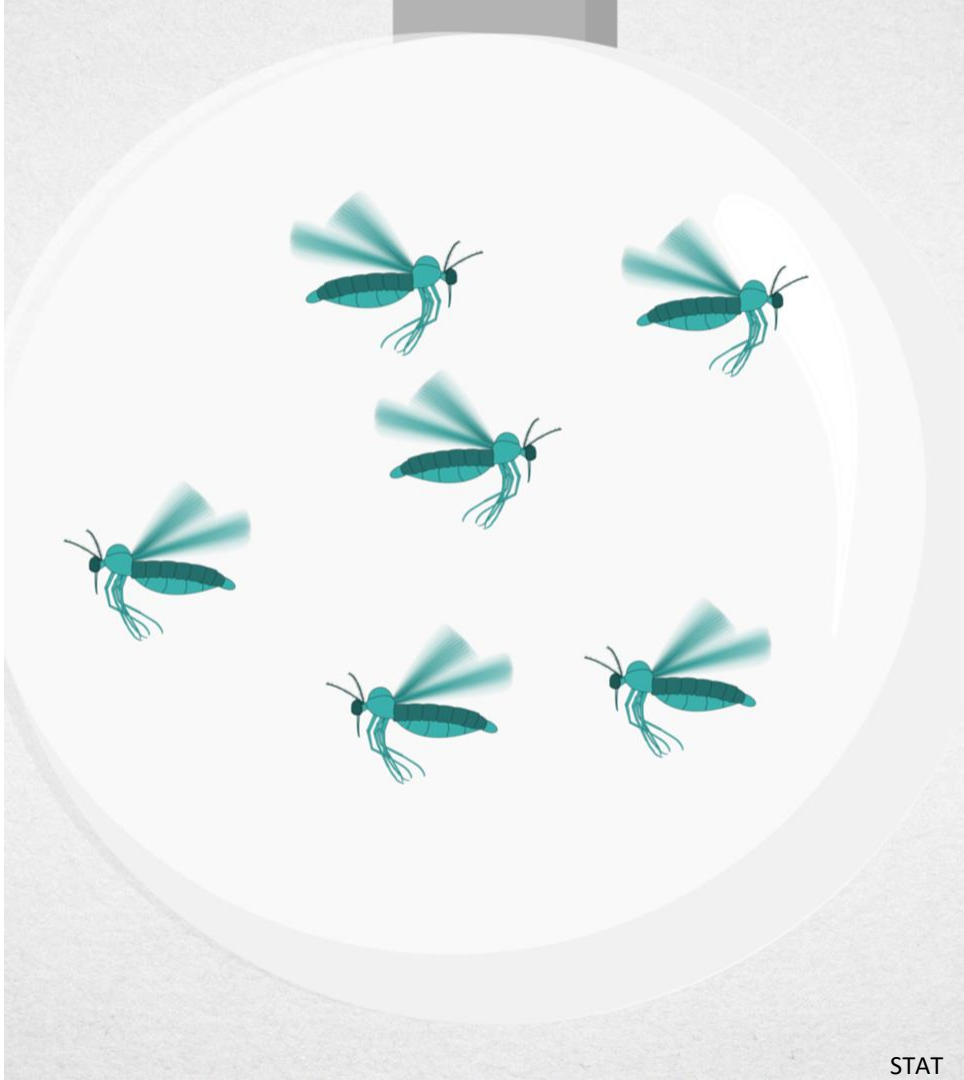
Putting Gene Drive in Context

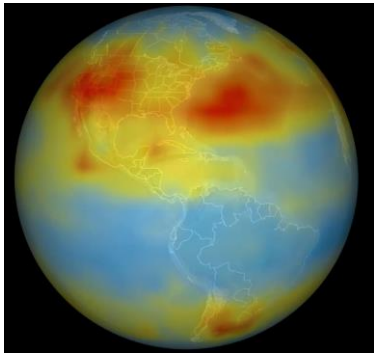
History, Precedents and Experiences

Prasad Paradkar| 10th June 2021



Vector-borne Diseases

- Increase in vector-borne diseases
  - Global climate change
  - Urbanisation
  - Travel and trade







- No specific therapeutics and limited effective vaccines
- High disease burden –tropical and subtropical region

- Focus on vector control



History of Vector Control

- Sir Ronald Ross: Malaria
- Sir Patrick Manson: Filaria
- Dr. Walter Reed: Yellow fever













- Environmental control
  - Removing stagnant water
- Non-persistent insecticides
  - Pyrethrum spraying
- DDT- persistent insecticide (1940s-50s)
  - Global Malaria Eradication Program
  - Silent Spring (1962)- R. Carson
  - Resistance development

"Sometimes, technological progress is fundamentally at odds with the natural processes and it must be curtailed"

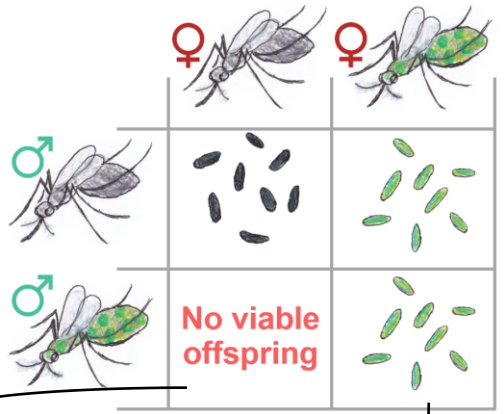
Novel methods

- Genetic technology
  - Sterile Insect Technology (SIT)
    - Insect X-ray sterilization: screwworm sterilization program (North America, 1968)
    - Tsetse fly population suppression
  - Population suppression: cytoplasmic incompatibility (IIT)
    - Sex ratio distorters (males), detrimental genes
  - Population replacement
    - Vector competence determinants

Wolbachia as a strategy

- Maternally inherited
- Natural drive (Biocontrol agent)

- Driver for a synthetic gene construct?



Uni of Melbourne

Population suppression
Ae. Albopictus (wPip)

Pathogen blocking

Population replacement
Ae. Aegypti (wMel)

Implementations

- Socio-political context and community engagement
- Mosquito rearing and releases
  - Suppression: large scale facility and repeated deployment
  - Replacement: relative self-sustaining
- Mosquito population, gene-flow and dispersal modelling
- Risk analysis- other infections, horizontal transfer, escape
- Continuous monitoring for *Wolbachia* establishment

- Effect on disease reduction: monitor (RCTs)

Biotech in vector biology

- Identification of insect transposons: *piggyBac*
- Naturally occurring selfish genetic elements
- Tissue-specific and developmental promoters
- Genome sequencing technologies
- Fluorescent markers

- Targeted approaches for gene modification:
  - Homing Endonuclease Genes (HEGs)
  - Zinc Finger Nucleases (ZFNs)
  - Transcription activator-like effector nucleases (TALENs)



LETTER

doi:10.1038/nature09937

A synthetic homing endonuclease-based gene drive system in the human malaria mosquito

Nikolai Windbichler[1], Miriam Menichelli[1], Philippos Aris Papathanos[1], Summer B. Thyme[2,3], Hui Li[4], Umut Y. Ulge[4,5], Blake T. Hovde[6], David Baker[2,3,7], Raymond J. Monnat Jr[4,5,6], Austin Burt[1,8]* & Andrea Crisanti[1,9]*

RIDL technology

- **R**elease of **I**nsects carrying a **D**ominant **L**ethal
  - OX513A *Ae. aegypti*
  - Specific gene target
  - Self-limiting (use of tetracyclin)
  - Releases
    - Cayman islands trial (80% reduction over 23 weeks)
    - Brazil: field test sites
      - Considered as a response to Zika outbreak
  - First US field test in Florida beginning now (May 2021)
    - Friendly™ mosquitoes (female death)



Flores *et al* 2018

CRISPR-Cas9 in gene drive

- Population replacement

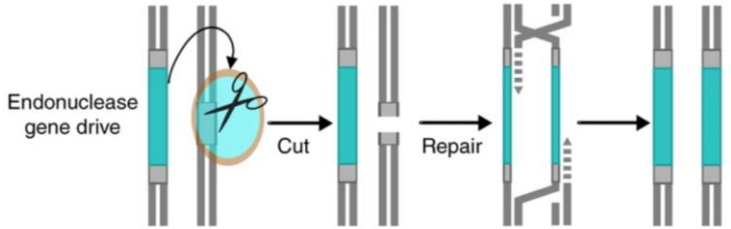
PNAS

Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*

Valentino M. Gantz[a,1], Nijole Jasinskiene[b,1], Olga Tatarenkova[b], Aniko Fazekas[b], Vanessa M. Macias[b], Ethan Bier[a,2], and Anthony A. James[b,c,2]

[a]Section of Cell and Developmental Biology, University of California, San Diego, La Jolla, CA 92093-0349; [b]Department of Molecular Biology and Biochemistry, University of California, Irvine, CA 92697-3900; and [c]Department of Microbiology and Molecular Genetics, School of Medicine, University of California, Irvine, CA 92697-4500

Contributed by Anthony A. James, October 26, 2015 (sent for review October 11, 2015; reviewed by Malcolm Fraser and Marcelo Jacobs-Lorena)



- Population suppression

LETTERS

nature biotechnology

A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*

Andrew Hammond[1], Roberto Galizi[1], Kyros Kyrou[1], Alekos Simoni[1], Carla Siniscalchi[2], Dimitris Katsanos[1], Matthew Gribble[1], Dean Baker[3], Eric Marois[4], Steven Russell[3], Austin Burt[1], Nikolai Windbichler[1], Andrea Crisanti[1] & Tony Nolan[1]

SCIENTIFIC REPORTS

OPEN

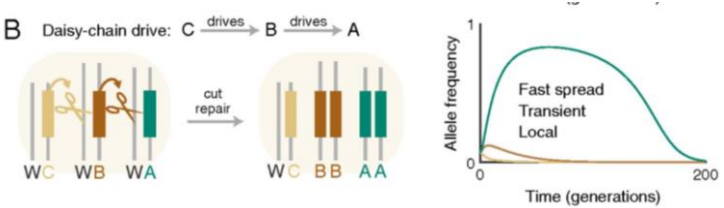
A CRISPR-Cas9 sex-ratio distortion system for genetic control

Roberto Galizi[1,*], Andrew Hammond[1,*], Kyros Kyrou[1], Chrysanthi Taxiarchi[1,2], Federica Bernardini[1], Samantha M. O'Loughlin[1], Philippos-Aris Papathanos[2], Tony Nolan[1], Nikolai Windbichler[1] & Andrea Crisanti[1]

Received: 30 April 2016

Technical concerns

- Containment of gene drive
  - ‘Split’ gene drive
- Resistance to gene drive





Considerations

- Public engagement
- Mosquito fitness compared with wild
- Costs
  - Initial costs
  - Long-term costs
- Local capability
- Long-term sustainability









Gene drive in other animals

- Reduce invasive population
  - Rodents
  - Cane toads
- Conservation
- De-extinction





Thank you

Dr. Prasad Paradkar

Group Leader, Health & Biosecurity

+61 3 5227 5462
Prasad.Paradkar@csiro.au