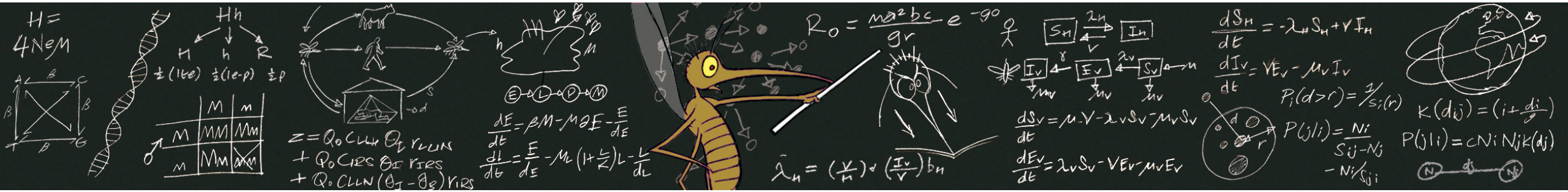
Modeling novel genetic control strategies for *Aedes aegypti* disease vectors

John M. Marshall, Héctor M. Sánchez C., Jared B. Bennett, Sean L. Wu, Tomás M. León, Gordana Rašić, Omar S. Akbari

John Marshall
Divisions of Epidemiology & Biostatistics
School of Public Health
University of California, Berkeley
john.marshall@berkeley.edu

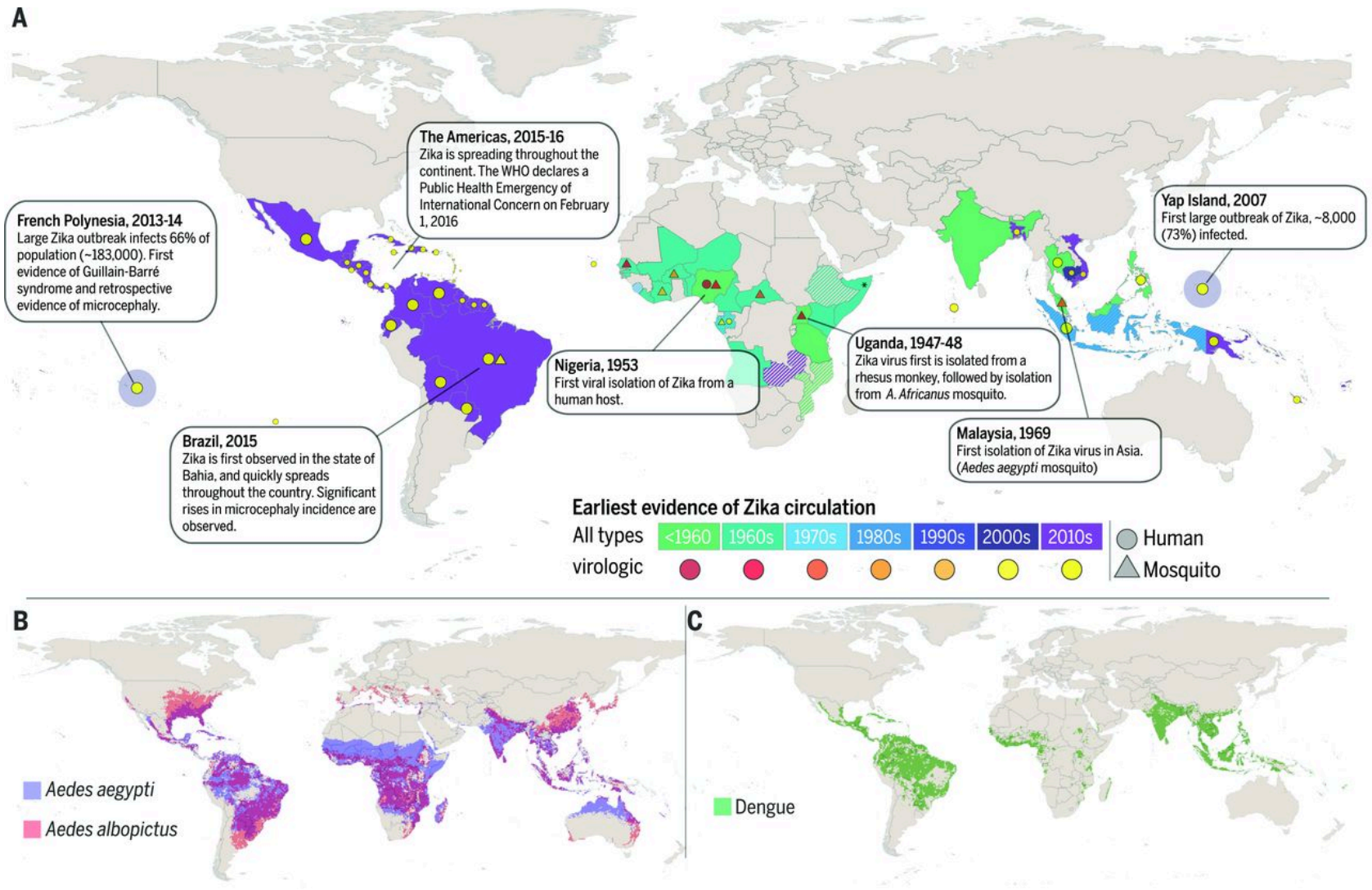
Berkeley Public Health

Talk outline



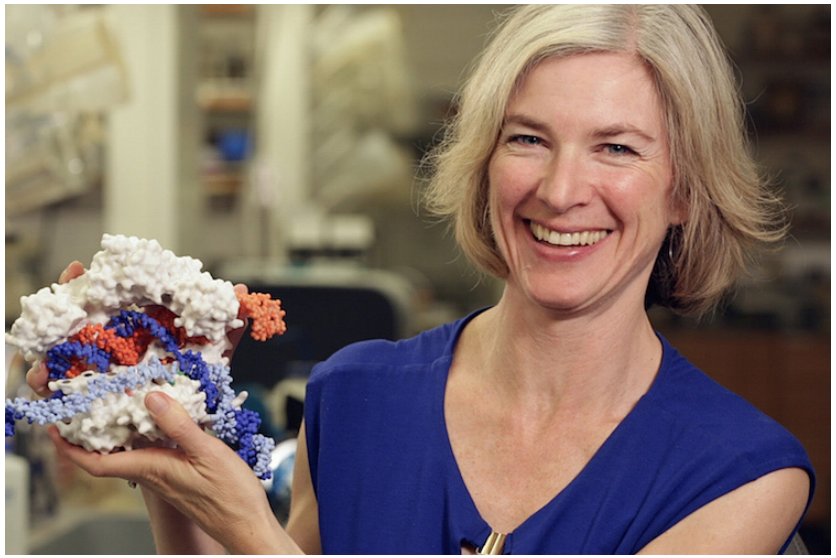
1. Why genetic control?
2. Modeling framework (Mosquito Gene Drive Explorer)
3. Novel genetic control technologies:
    i. Chromosomal translocations as threshold-dependent systems
    ii. CRISPR-based split drive as a self-limiting system
    iii. Precision-guided sterile insect technique (pgSIT)
4. Role of these technologies in *Ae. aegypti* control

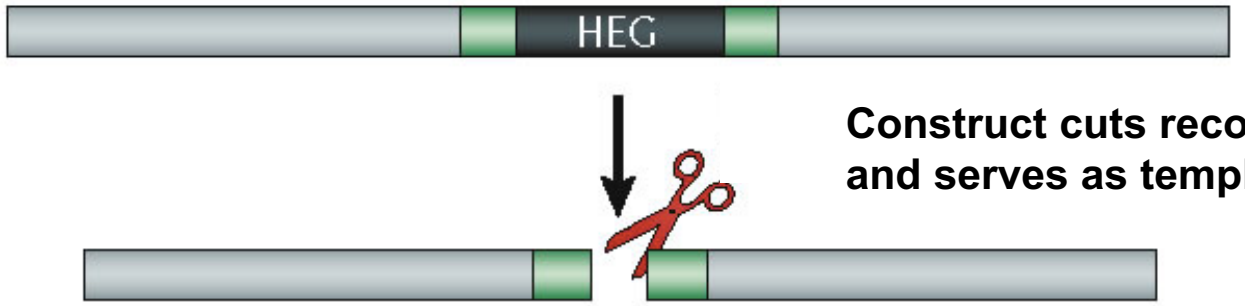
Arboviruses on the rise worldwide



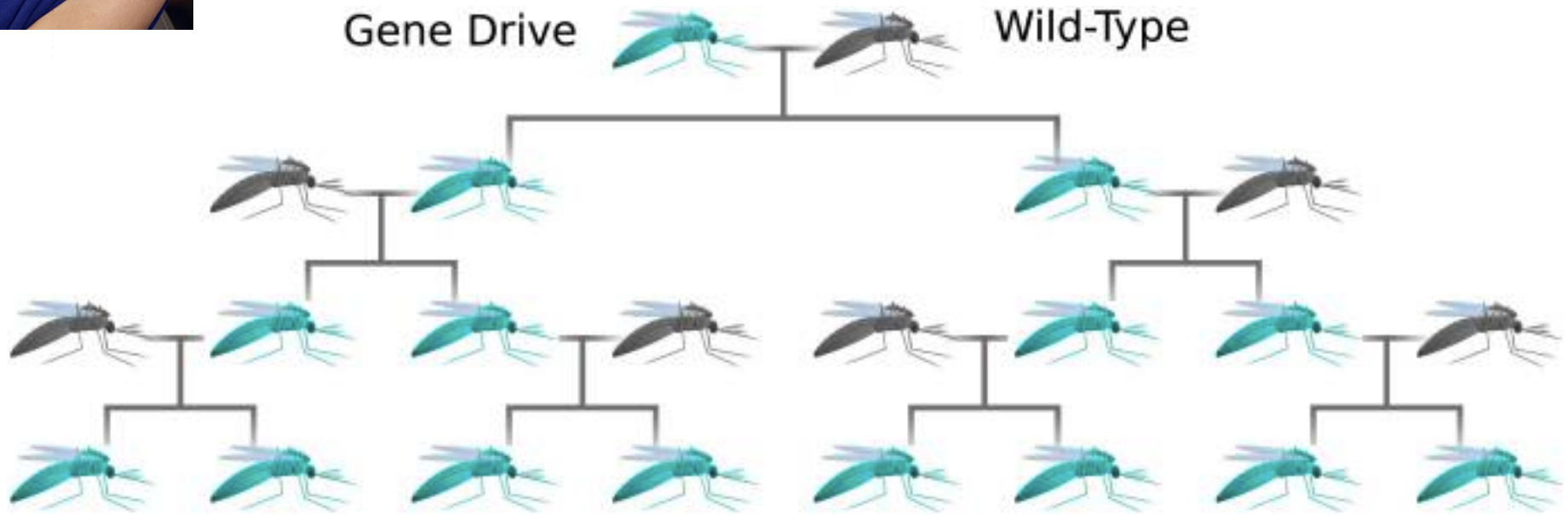
- Lessler J, Chaisson LH, Kucirka LM, Bi Q, Grantz K *et al.* (2016) Science 353: aaf8160

Discovery of CRISPR, applied to gene drive

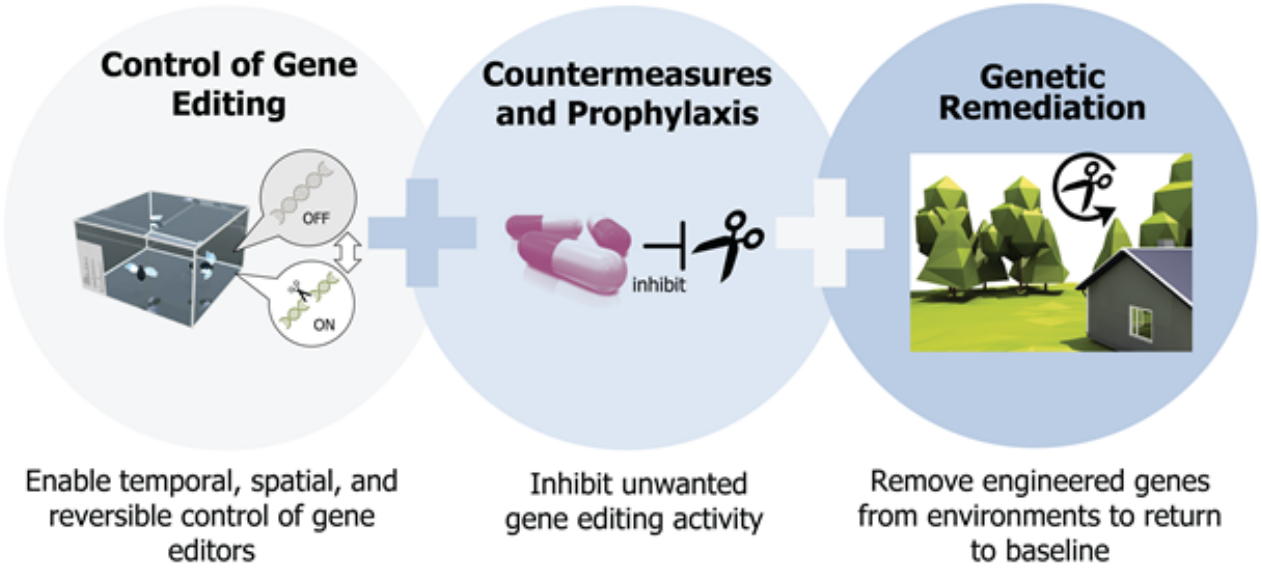




Construct cuts recognition site and serves as template for repair



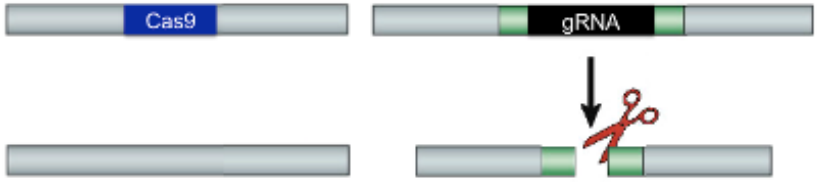
DARPA Safe Genes Program & Team CA



Enable temporal, spatial, and reversible control of gene editors

Inhibit unwanted gene editing activity

Remove engineered genes from environments to return to baseline



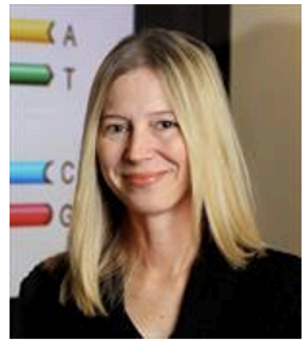
Omar Akbari

Ethan Bier

Anthony James

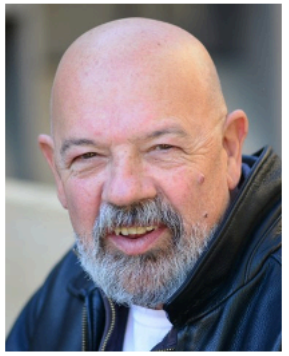
John Marshall

Craig Montell



Cinnamon Bloss

Valentino Gantz

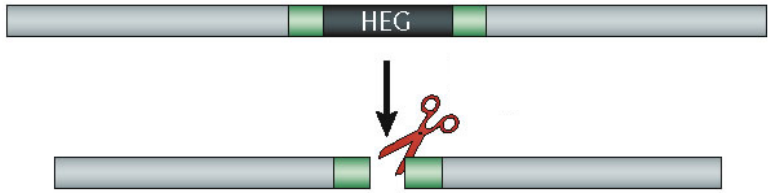


Greg Lanzaro

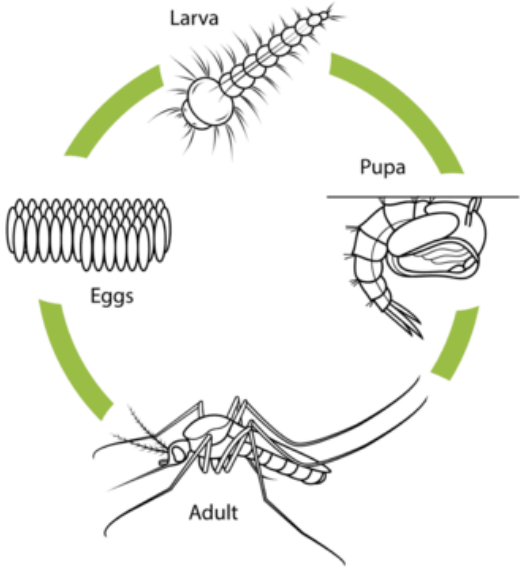
Sergey Kryazhimskiy

Mosquito Gene Drive Explorer (MGDrivE)

Inheritance pattern:

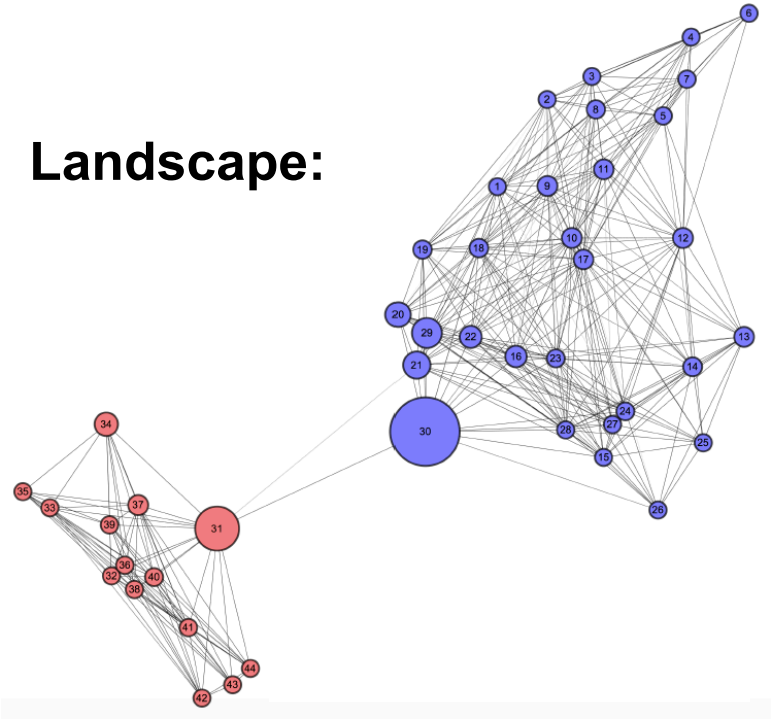


Mosquito life cycle:



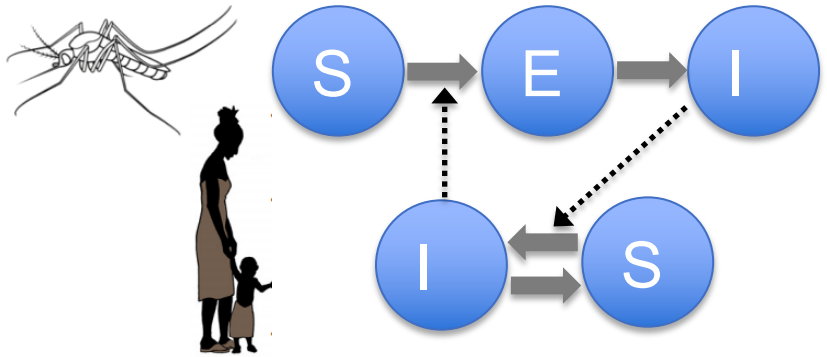
Temperature & rainfall

Landscape:



Temperature & rainfall

Disease epidemiology:



Temperature & rainfall

Mosquito Gene Drive Explorer (MGDrivE)

MGDrivE

Mosquitos + Tensors + Genetics + CS + Networks + Math + Coffee

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Developed in John Marshall's Lab by:

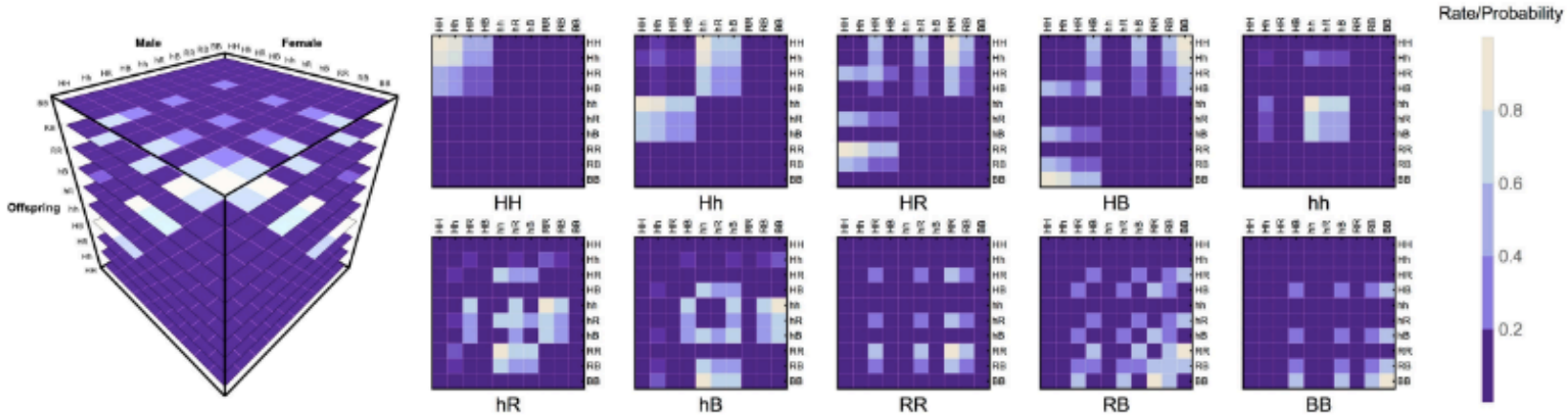
-Lead: Héctor M. Sánchez C.
-Core Dev: Sean L. Wu,Jared Bennett
-Spatial Analysis: Biyonka Liang, Sarafina Smith, Sabrina Wong
-Movement Kernels: Partow Imani

...and, of course, our PI: John M. Marshall!

Mosquito Gene Drive Explorer

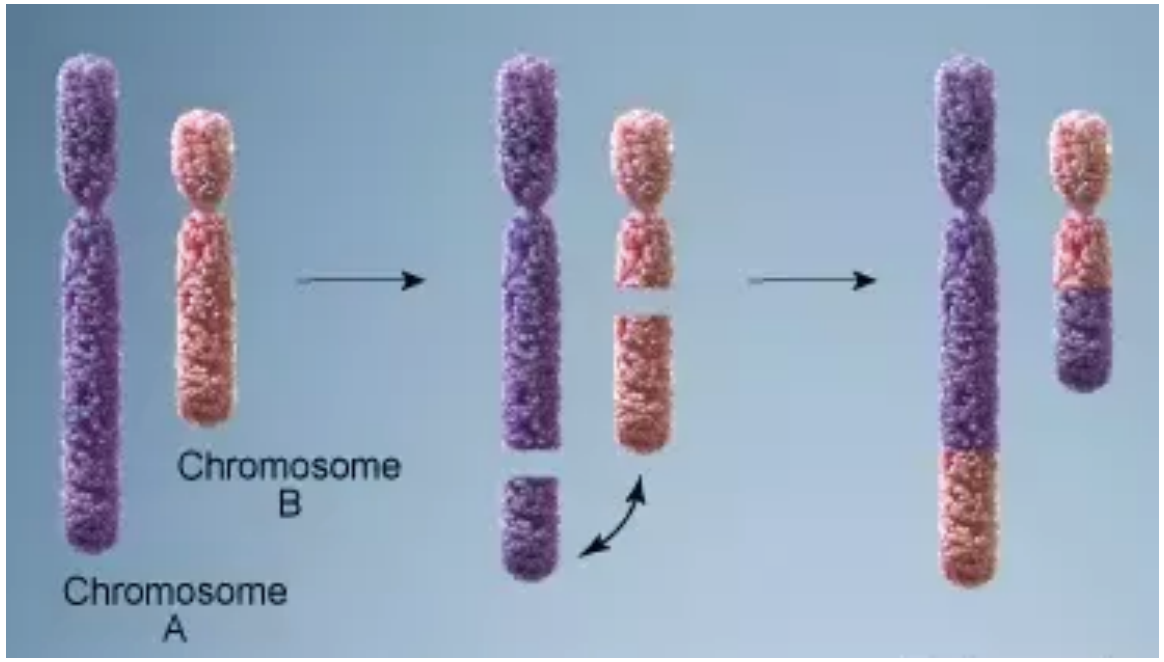
Brief Description

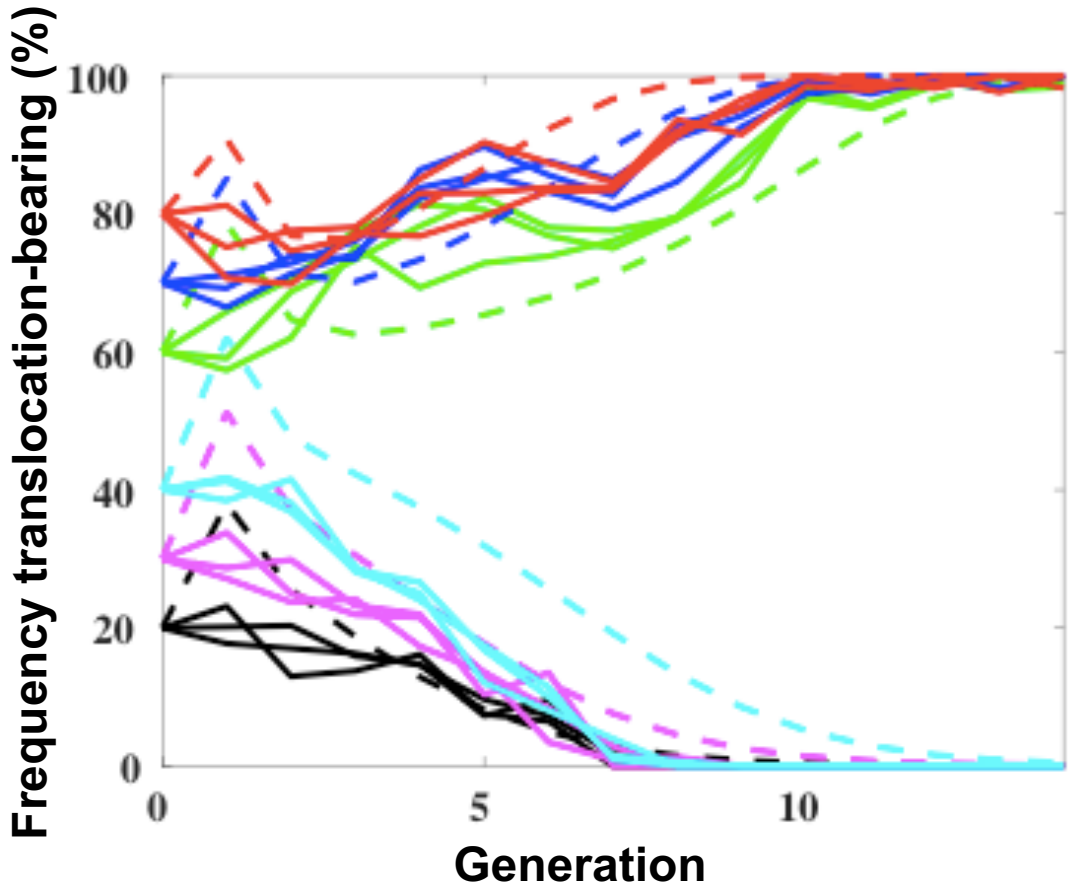
MGDrivE is a framework designed to serve as a testbed in which gene-drive releases for mosquito-borne diseases control can be tested. It is being developed to accommodate various mosquito-specific gene drive systems within a population dynamics model that allows migration of individuals between nodes in a spatial landscape.



- Sánchez HM, Wu SL, Bennett JB, Marshall JM (2019) Methods in Ecology and Evolution

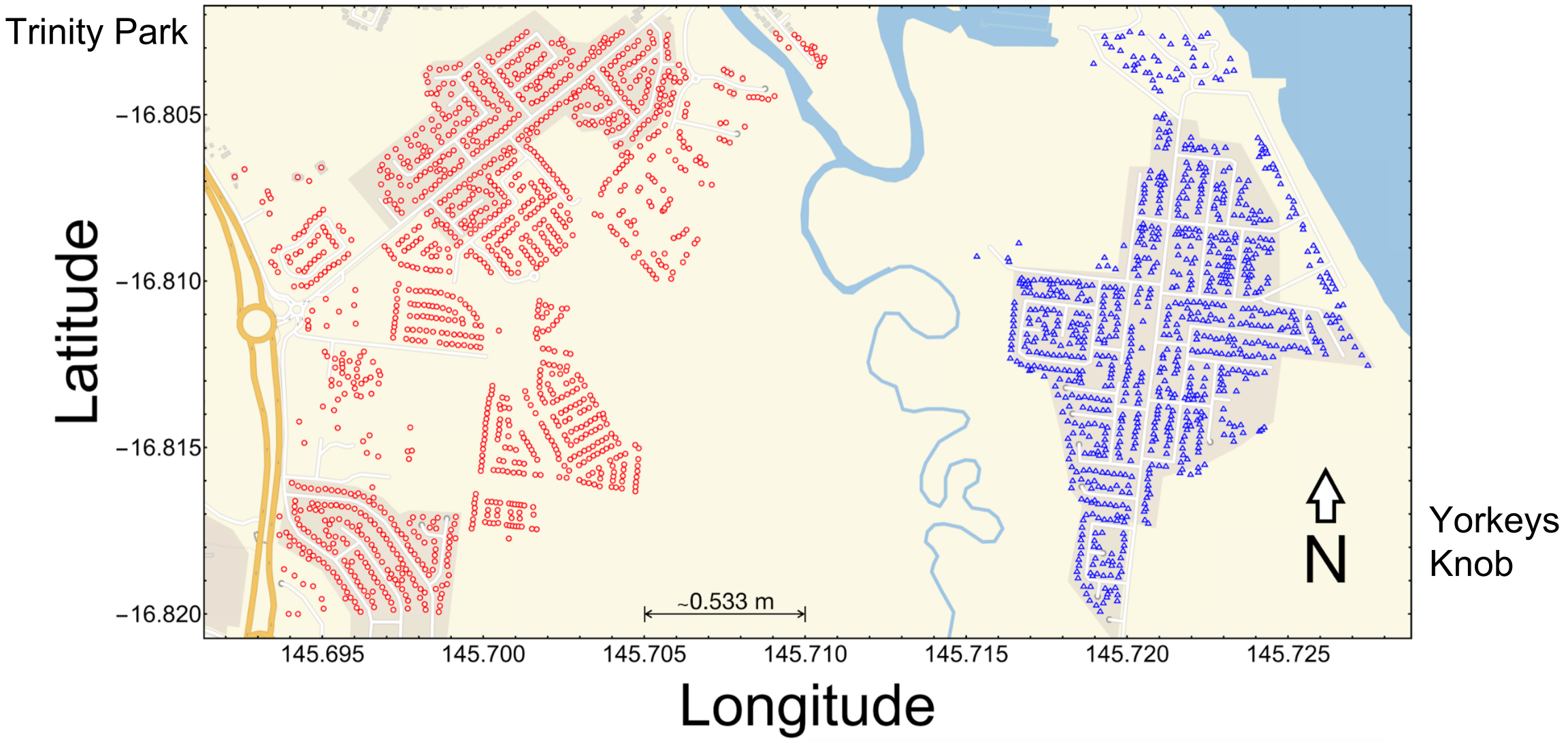
Reciprocal chromosomal translocations





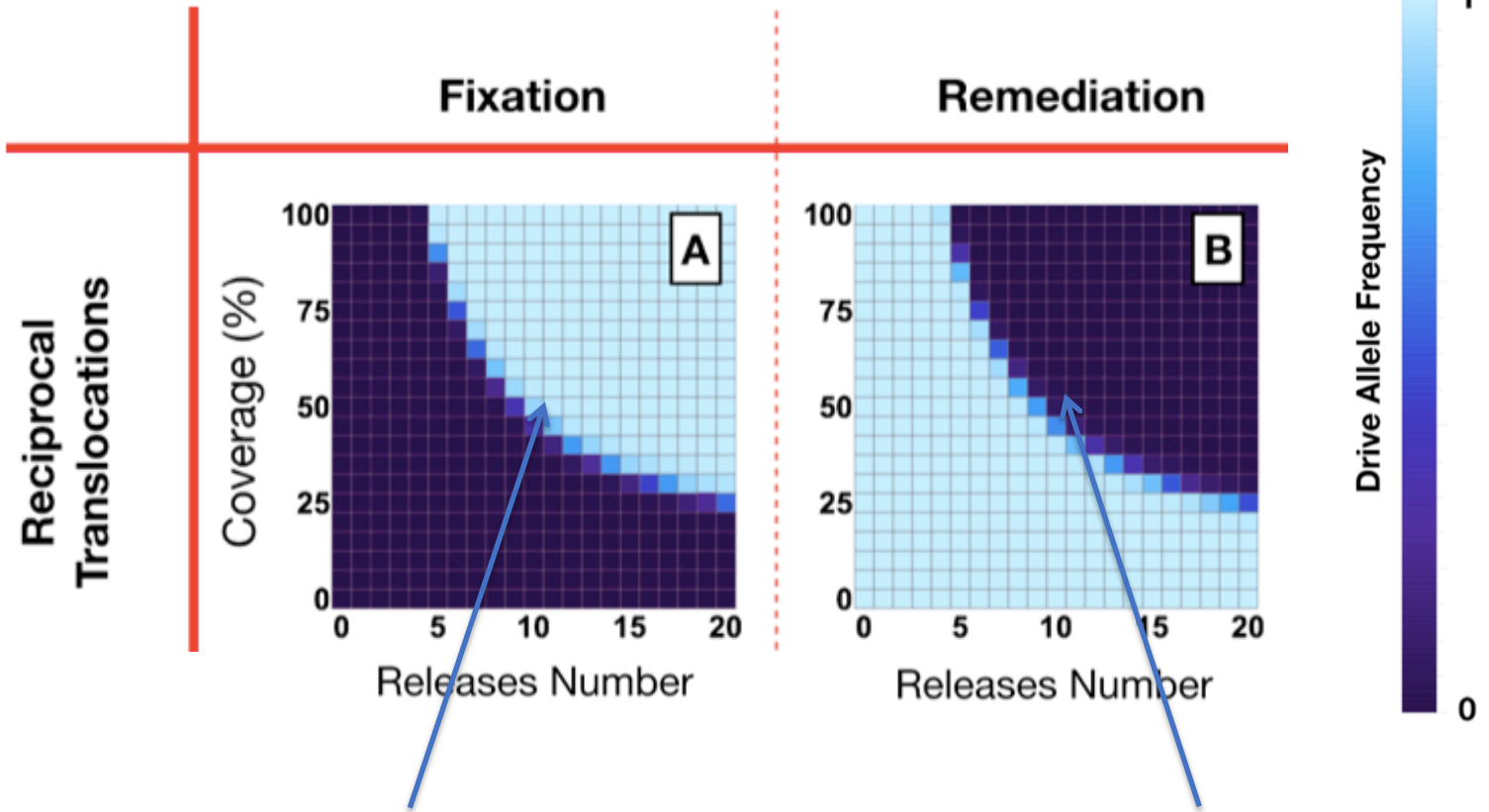
- Buchman A, Ivy T, Marshall JM, Akbari OS, Hay BA (2018) ACS Synthetic Biology

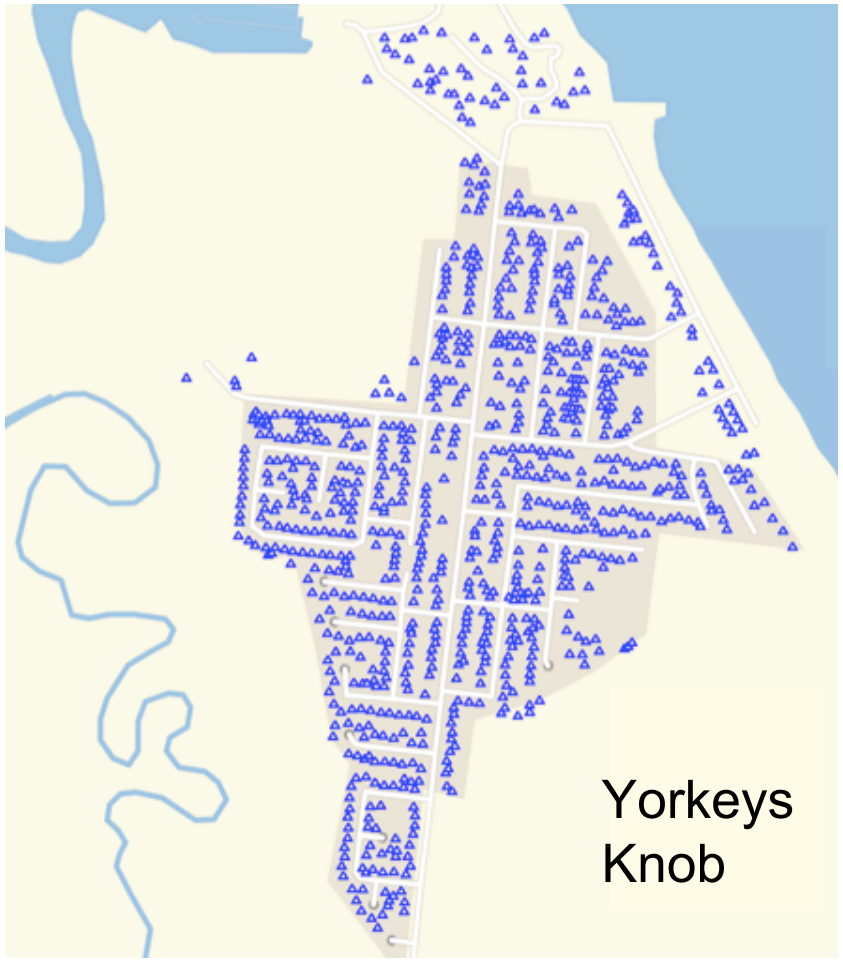
Simulations at Yorkeys Knob, Queensland



Fixation & remediation of translocations

- Data suggests there are ~15 adult *Ae. aegypti* per household
- Weekly releases of 20 adult males having the translocation
- Vary household coverage & number of releases



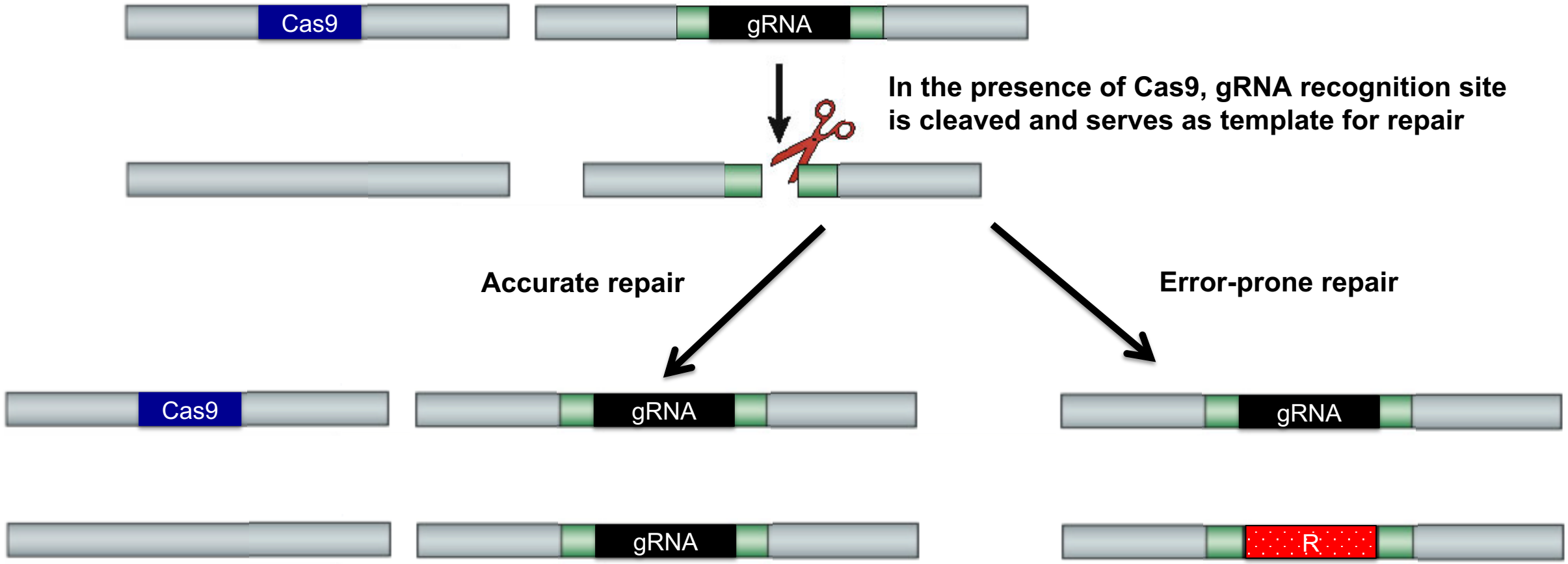


At a coverage level of 50%, ≥10 releases result in fixation

At a coverage level of 50%, ≥10 releases result in remediation

- Sánchez HM, Bennett JB, Wu SL, Rasic GL, Akbari OS, Marshall JM (2020) BMC Biology

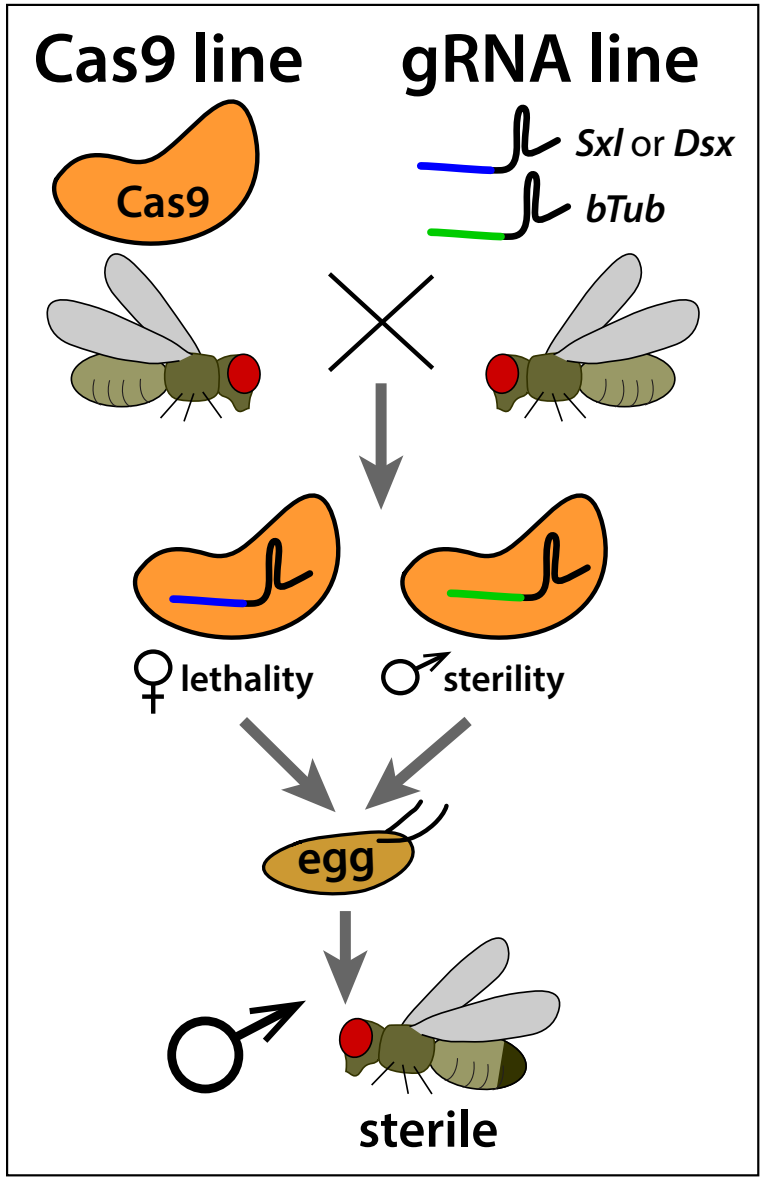
CRISPR-based split drive

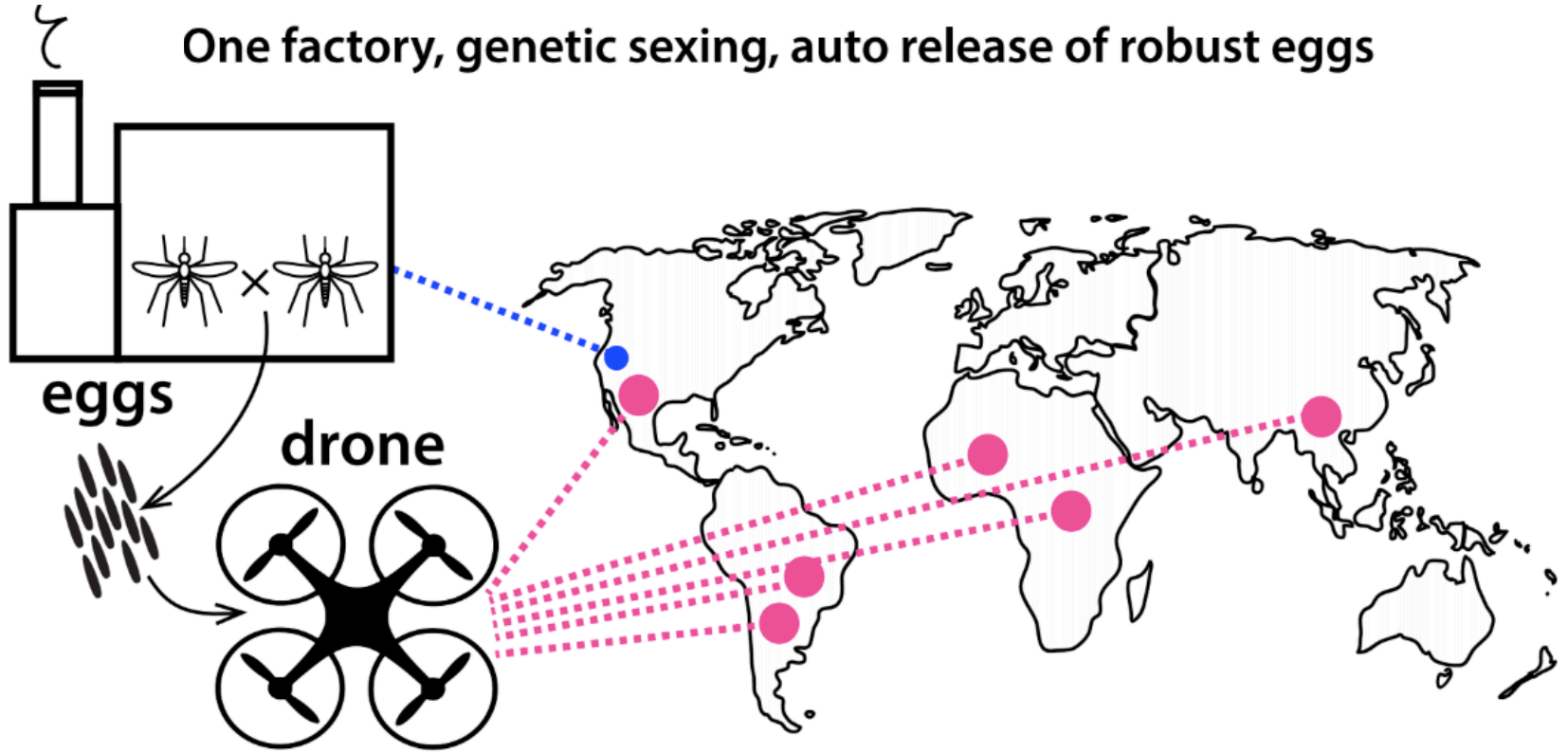


- Li M, Yang T, Kandul N, Biu M, Gamez S, Bennett JB, Sánchez HM, …, Marshall JM, Akbari OS (2020) eLife

Simulations at Yorkeys Knob, Queensland

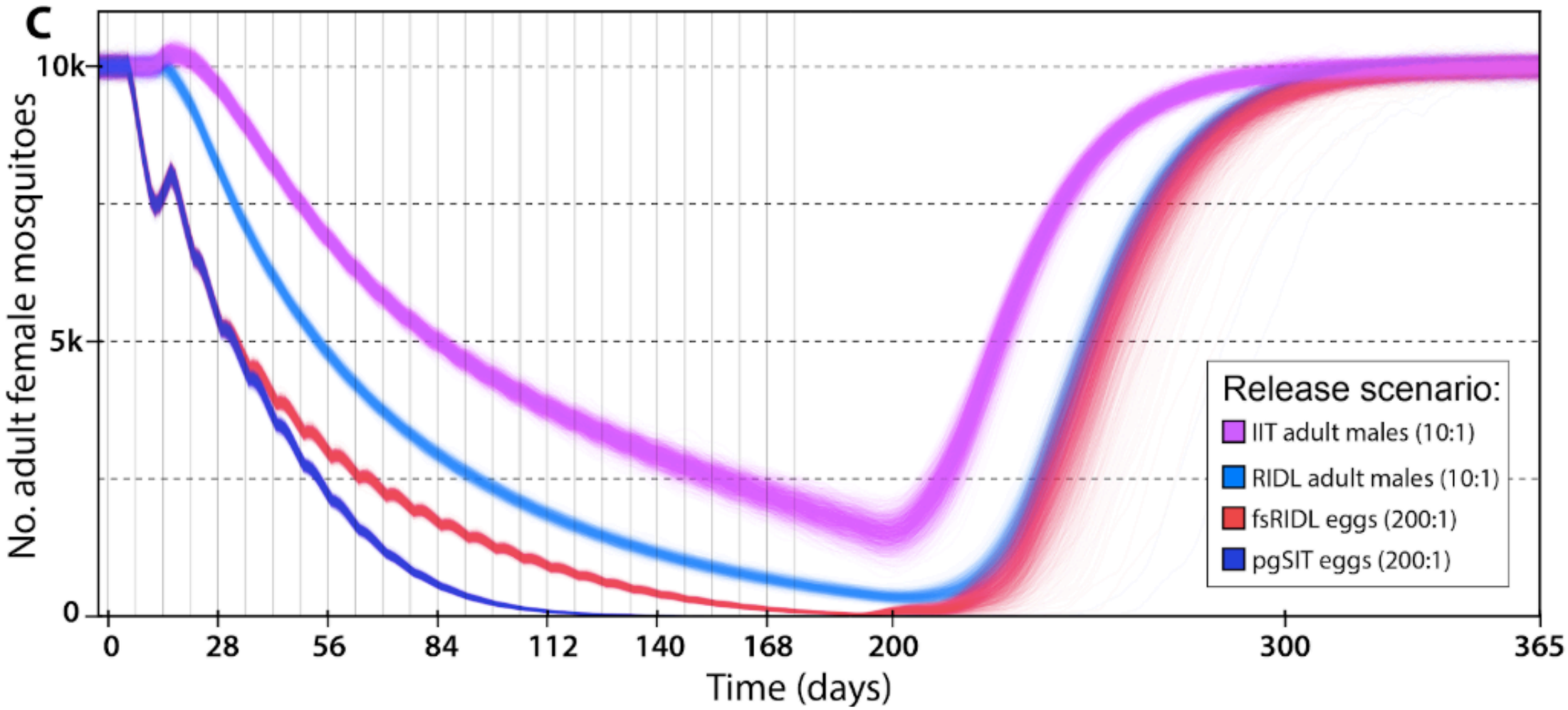
Precision-guided SIT (pgSIT)





- Kandul NP, Liu J, Sánchez HM, Wu SL, Marshall JM, Akbari OS (2019) Nature Communications

Modeling pgSIT in *Ae. aegypti*



- Kandul NP, Liu J, Sánchez HM, Wu SL, Marshall JM, Akbari OS (2019) Nature Communications

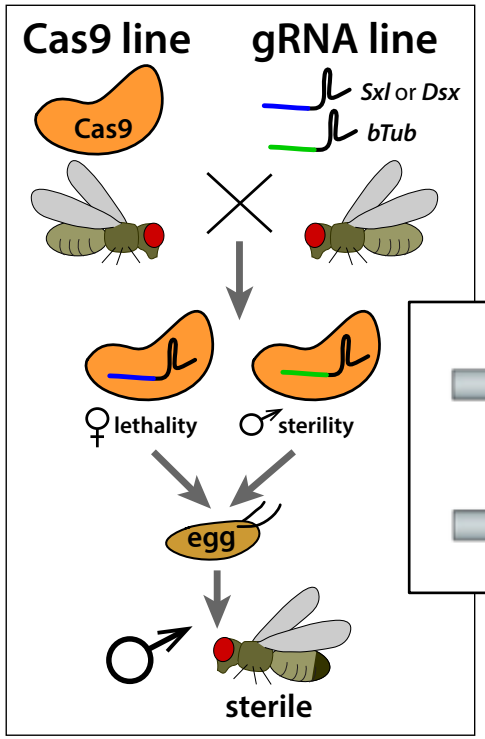
Conclusion

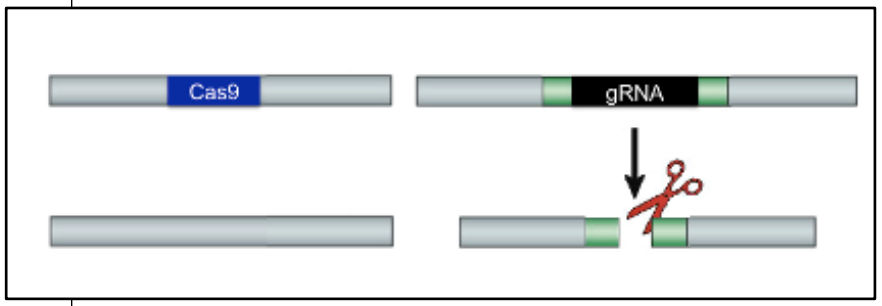
- CRISPR-based strategies offers for more tools for the tool kit.
- *Ae. aegypti* control has been marked by technological innovations through *Wolbachia* transfection & transgenesis.
- Translocations may offer an opportunity to introduce a disease-refractory into an *Ae. aegypti* population gene locally.
- Split drive may be an effective precursor to linked drive.
- pgSIT may be an effective suppression system in some locations.

OXITEC

World Mosquito Program™

Debug by verily





Acknowledgements

LAB MEMBERS:

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- Sean L. Wu
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- Agastya Mondal
- Francois Rerolle
- Hao Wang
- Ameek Bindra
- Chris De Leon

COLLABORATORS:

- **Akbari Lab** @ UC Riverside
- **Lanzaro Lab** @ UC Davis
- **James Lab** @ UC Irvine
- **Bier Lab** @ UCSD
- **Hay Lab** @ Caltech
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- **School of Public Health** @ UC Berkeley

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