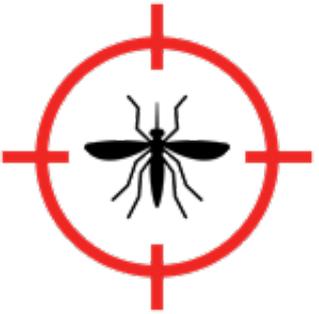


State of the art strategies for gene drive and biological risk mitigation

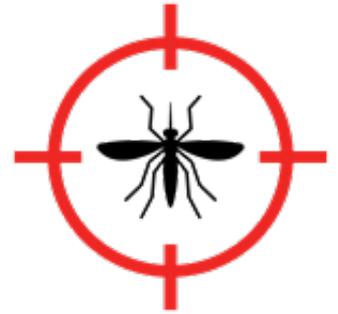
Omar S. Akbari



UC San Diego



Talk Overview



- current “state of the art” gene drive approaches
 - **Linked-Homing Drive**
 - **Split-Homing Drive**
- Population modification vs population suppression
- Current “state of the art” strategies for biological risk mitigation

CRISPR-CAS9: GENE DRIVE



Current “state of the art” Gene-Drive strategies

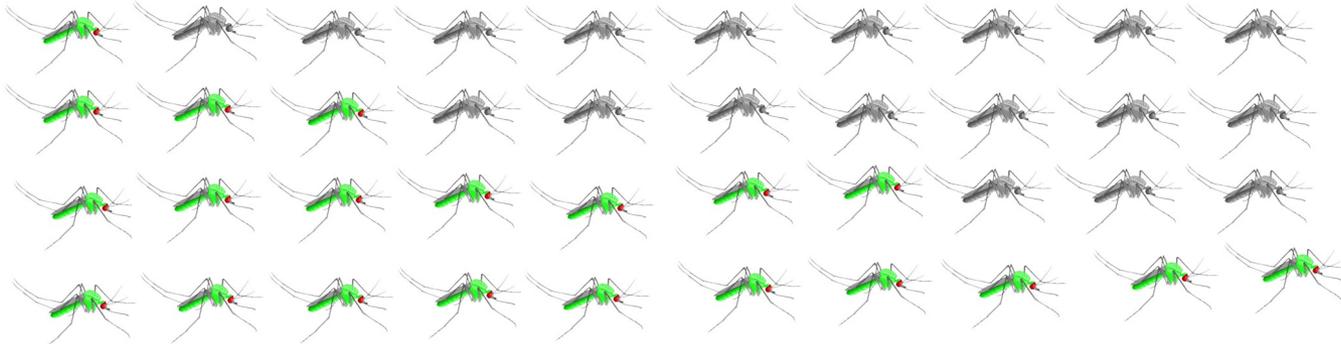
Approach	Examples	Temporal Dynamics	Geographic Reach
Gene Drives	Linked-homing#, Medea, CleaveR, TARE/TADE#	Self-propagating (low threshold)	Non-localized
	Translocations, Underdominance#, UD ^{MEL*} ,#	Majority wins* (high threshold)	Localized
	Daisy# split- homing# killer rescue	Self-limiting (temporally limited)	
Non-Drives	SIT#, RIDL#, fsRIDL#, pgSIT#		

- **Non-localized Drive systems**
 - **Low Threshold** – Self propagating - Non-localized – predicted to spread beyond release site.
- **Localized Drive Systems**
 - **High Threshold**– only spread if above a threshold – not predicted to spread beyond release site. Inherently confineable.
 - **Self-limiting** – temporally limited – do not persist indefinitely - not predicted to spread beyond release site.
- **Non-Drives** – will not spread or persist.

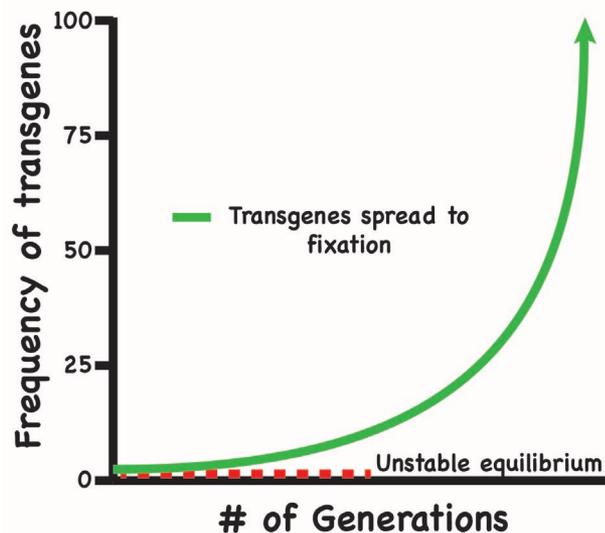
Talk will focus on: Linked-homing and Split-homing

Linked-Homing - Population Modification Gene Drives

Threshold independent Population Modification Gene Drives



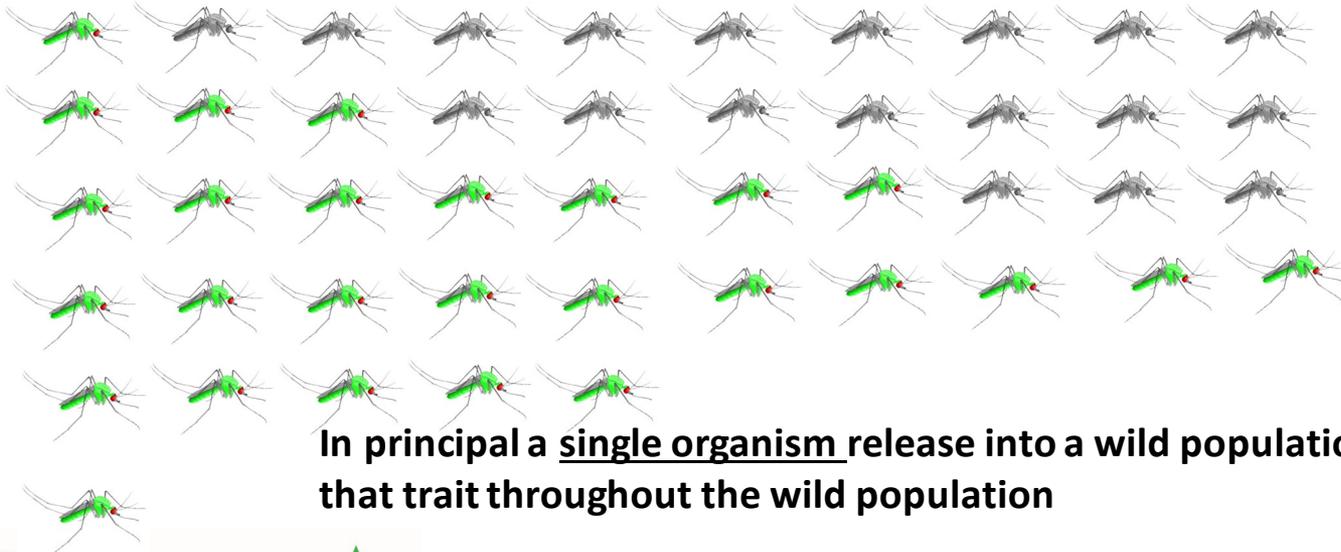
In principal a single organism release into a wild population could spread that trait throughout the wild population



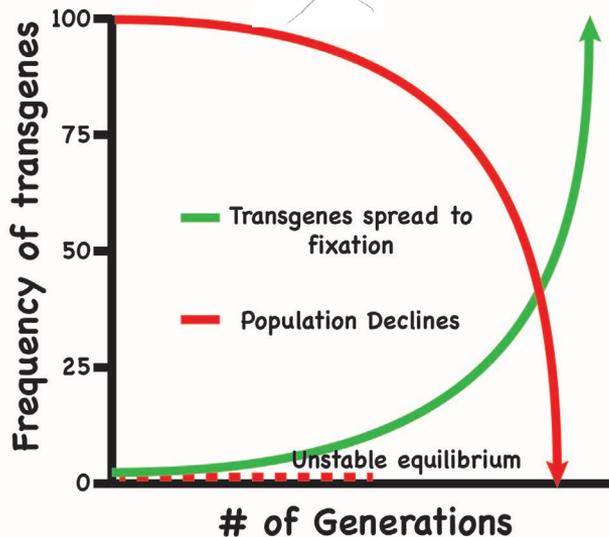
- Driving an engineered anti-pathogen gene into a **neutral site** to convert the entire population into a disease resistant population.
- **Ecologically For population modification** the engineered population would persist in the environment but they would no longer be able to transmit pathogens.

Linked-Homing - Population Suppression Gene Drives

Threshold independent **Suppression** Gene Drives



In principal a single organism release into a wild population could spread that trait throughout the wild population

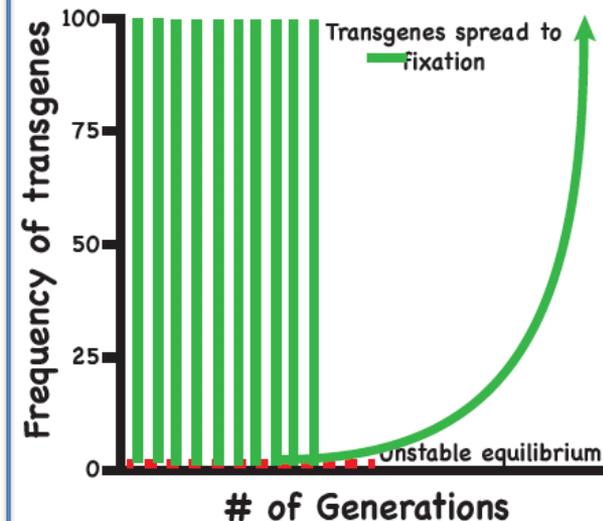
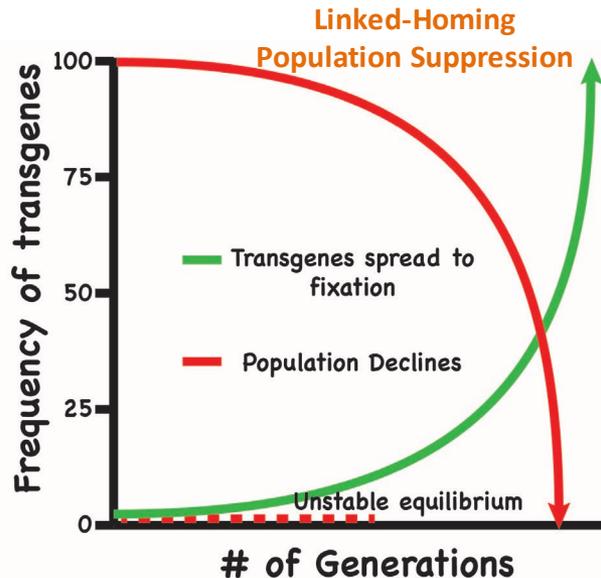
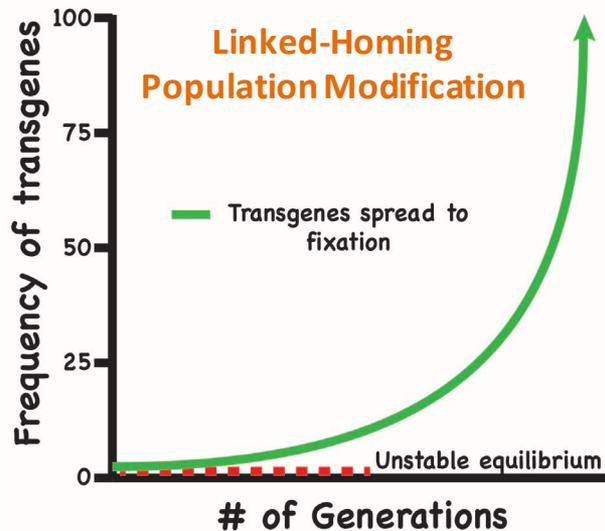


- Population Suppression** - Drive a population to extinction
- e.g. Drive into a recessive gene required for female fertility/viability
 - **Ecologically** For population suppression the engineered population would persist in the environment until fixation then the entire population would crash and be eradicated.

Categories of Gene Drives

Non-Localized

Localized



Potential Issues?

Desired Features

- **Non-Reversible** – need to release alternative system.
 - ERACR/eCHACRs (doi.org/10.1016/j.molcel.2020.09.003)
 - Reversal Gene Drives (doi.org/10.1038/nrg.2015.34)
 - **Acceptable to release another genetically engineered system for control?**
- **Non-localized** – Will spread beyond borders
 - Target a private allele – exclusive to an isolated population.
 - **Will these exist in intended target population? Do we have data to support this claim?**
 - Release on limited access ecologically isolated site/island.
 - **How isolated?**

- Controllable
- Inherently Confinable
- Reversible
- Safe
- Effective

- **Difficult to measure Risks / Unintended consequences?**
- **Regulatable?**
- **Public acceptance?**



Winning the Tug-of-War Between Effector Gene Design and Pathogen Evolution in Vector Population Replacement Strategies

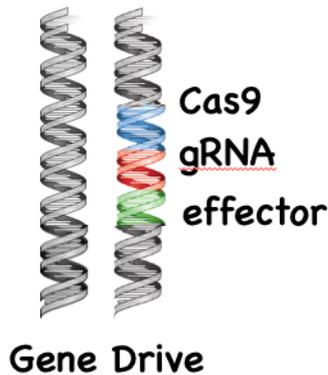
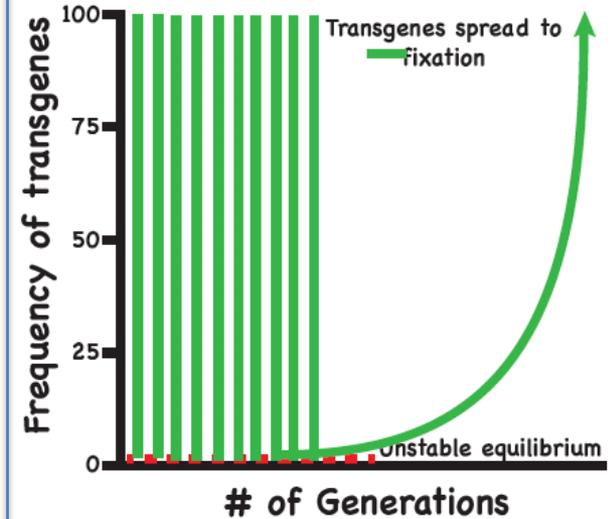
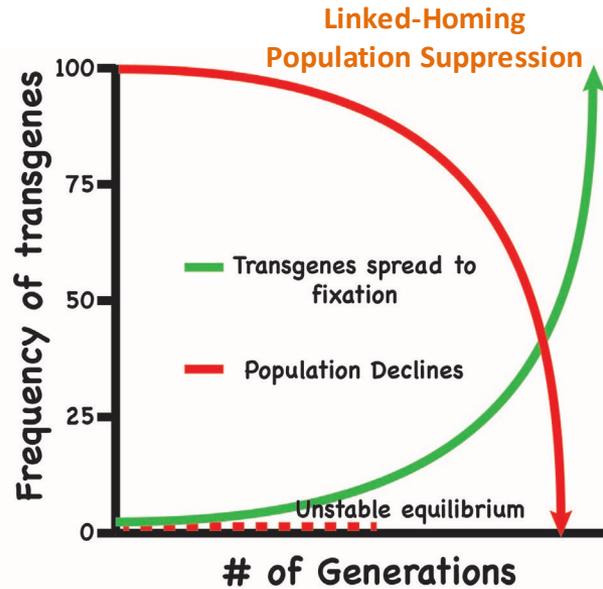
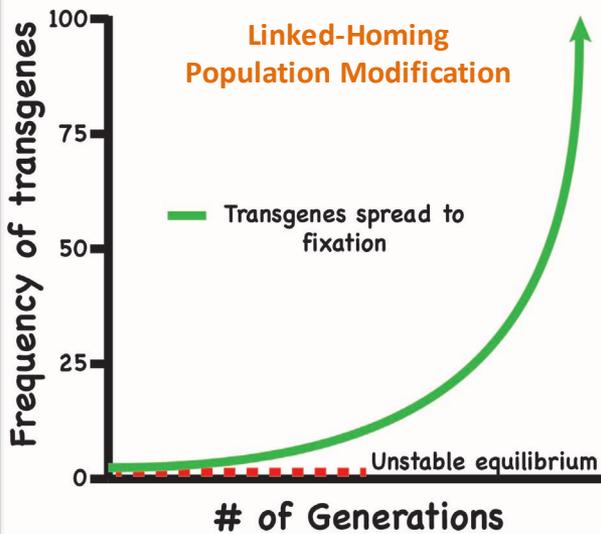


John M. Marshall^{1*}, Robyn R. Raban², Nikolay P. Kandu¹, Jyotheeswara R. Edula¹, Tomás M. León¹ and Omar S. Akbari^{1,4*}

Categories of Gene Drive

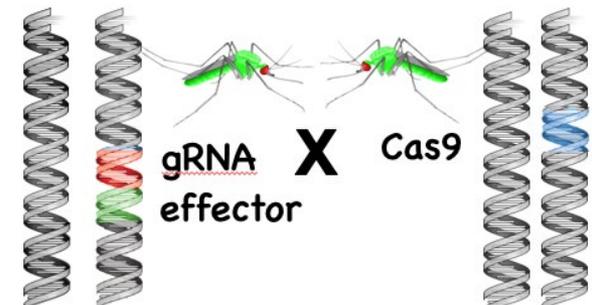
Non-Localized

Localized



Linked Gene Drive design

Split-Homing Drives



Split-Homing Drives have been engineered and proven to be effective in many species



Safeguarding CRISPR-Cas9 gene drives in yeast

James E DiCarlo^{1-3,7}, Alejandro Chavez^{1,2,4,5,7}, Sven L Dietz^{1,2,4,6}, Kevin M Esvelt^{2,4} & George M Church^{1,2,4}

**nature
biotechnology**

Split-Homing Drives have been engineered and proven to be effective in many species

Assessment of a Split Homing Based Gene Drive for Efficient Knockout of Multiple Genes



Nikolay P. Kandul,* Junru Liu,* Anna Buchman,* Valentino M. Gantz,* Ethan Bier,*¹ and Omar S. Akbari*^{1,1}

*Section of Cell and Developmental Biology and ¹Tata Institute for Genetics and Society, University of California, San Diego, La Jolla, CA 92093

ORCID ID: 0000-0002-6853-9884 (O.S.A.)



A transcomplementing gene drive provides a flexible platform for laboratory investigation and potential field deployment

nature communications

Víctor López Del Amo, Alena L. Bishop, Héctor M. Sánchez C., Jared B. Bennett, Xuechun Feng, John M. Marshall, Ethan Bier & Valentino M. Gantz

A home and rescue gene drive efficiently spreads and persists in populations



Nikolay P. Kandul, Junru Liu, Jared B. Bennett, John M. Marshall, Omar S. Akbari

doi: <https://doi.org/10.1101/2020.08.21.261610>

Report

Small-Molecule Control of Super-Mendelian Inheritance in Gene Drives

Cell Reports

Víctor López Del Amo¹, Brittany S. Leger^{2,8}, Kurt J. Cox^{3,4,5,8}, Shubhroz Gill³, Alena L. Bishop¹, Garrett D. Scanlon², James A. Walker^{2,6,7} , Valentino M. Gantz¹ , Amit Choudhary^{3,4,5,9}

Inherently confinable split-drive systems in *Drosophila*



Gerard Terradas^{1,2}, Anna B. Buchman¹, Jared B. Bennett³, Isaiah Shriner¹, John M. Marshall^{4,5}, Omar S. Akbari¹, and Ethan Bier^{1,2*}

A CRISPR homing gene drive targeting a haplolethal gene removes resistance alleles and successfully spreads through a cage population



Jackson Champer, Emily Yang, Esther Lee, Jingxian Liu, Andrew G. Clark, and Philipp W. Messer

Molecular safeguarding of CRISPR gene drive experiments



Jackson Champer^{1,2}, Joan Chung^{1,2}, Yoo Lim Lee^{1,2}, Chen Liu^{1,2}, Emily Yang^{1,2}, Zhaoxin Wen¹, Andrew G Clark¹, Philipp W Messer¹

Split-Homing Drives have been engineered and proven to be effective in many species



Letter | Published: 23 January 2019

Super-Mendelian inheritance mediated by CRISPR–Cas9 in the female mouse germline

Hannah A. Grunwald, Valentino M. Gantz, Gunnar Poplawski, Xiang-Ru S. Xu, Ethan Bier & Kimberly L. Cooper 

nature

Split-Homing Drives have been engineered and proven to be effective in many species



Development of a confinable gene drive system in the human disease vector *Aedes aegypti*

Ming Li¹, Ting Yang¹, Nikolay P Kandul¹, Michelle Bui¹, Stephanie Gamez¹, Robyn Raban¹, Jared Bennett², Héctor M Sánchez C³, Gregory C Lanzaro⁴, Hanno Schmidt⁴, Yoosook Lee⁴, John M Marshall^{3,5}, Omar S Akbari^{1,6*}



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Aedes aegypti Split-Homing drive is self-limiting and is confineable.

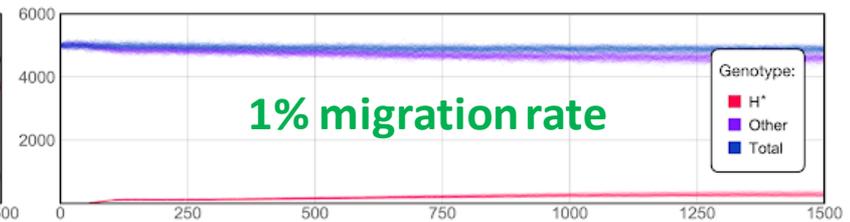
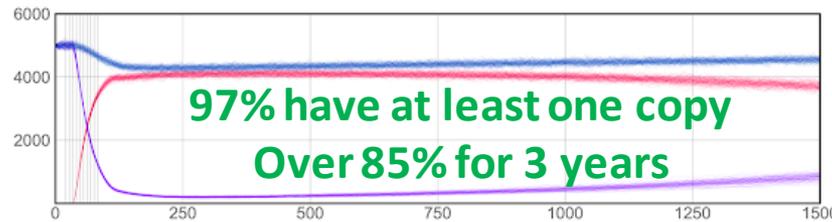
Stochastic simulations 10 releases of homozygous males at 1:1 total population

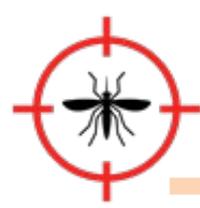
Release Population

Neighboring Population

Split Drive

A
No. Female Mosquitoes





Summary



- Multiple Kinds of Gene Drives Exist and their development has been accelerated by CRISPR
- **Linked-Homing Drives** Can be used for either population suppression / modification.
 - “State of the Art” Risk Mitigation Strategies
 - Drive Countermeasures
 - (e.g. Reversal Drives / ERACR’s / eCHACR’s)
 - Attempt to Localize the Drive
 - Design to target a Private allele.
 - Release on limited access ecologically isolated island.
- **Split-Homing Drives** Can also be used for either population suppression / modification.
 - Engineered and proven effective in many species
 - Inherently confinable,
 - Safe
 - effective.
 - **Inherently Self-limiting** : No need for the release of a second-generation countermeasures.



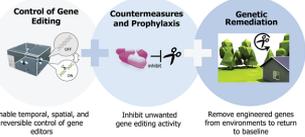
Are Confinable Split-Homing Drives the optimal choice for the first field trials of Gene Drives?



Thank You!!



Safe Genes



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