



What is gene drive and how does it work?

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What is gene drive?

Gene drive is:

- A natural phenomenon that has evolved many times in different species
- A process of biased inheritance that scientists are trying to exploit to develop highly targeted, efficient, and sustainable tools to address long-standing challenges in the control of
 - disease vectors
 - invasive species
 - other pests

What is gene drive?

- A “buzz word” with no precise, widely accepted definition
 - Low threshold drives
 - High threshold drives
 - Integral drives
 - Tethered drives
 - Split drives
 - Daisy drives
 - Double drives
 - Under-dominant drives
 - Sex-limited drives
 - etc

Indicative of being a young, active field of research

What is gene drive?

What engineered gene drives have in common:

- They are LMOs (Living Modified Organisms)
 - no legal ambiguity as with some gene edited organisms
 - hence fall under current case-by-case assessment regulations

- The transmission of genes from one generation to the next is non-Mendelian

How does it work?

Different ways of getting non-Mendelian transmission: 4 examples

Cytoplasmic incompatibility

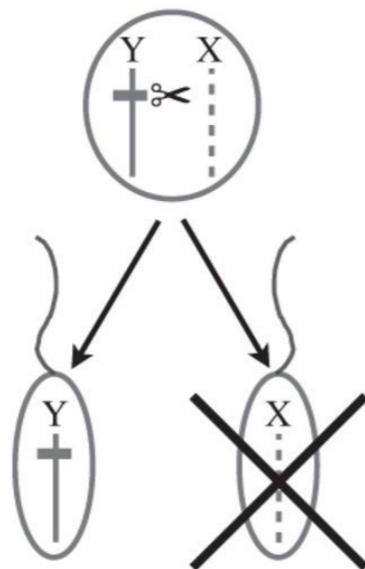
		male	
		W ⁻	W ⁺
female	W ⁻	✓	✗
	W ⁺	✓	✓

MEDEA

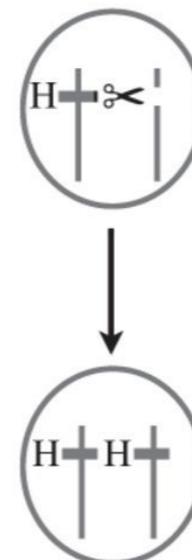
		sperm	
		M ⁻	M ⁺
egg*	M ⁻	✗	✓
	M ⁺	✓	✓

*from M⁺/M⁻ heterozygous females

Y drive



Homing



Diversity of gene drives

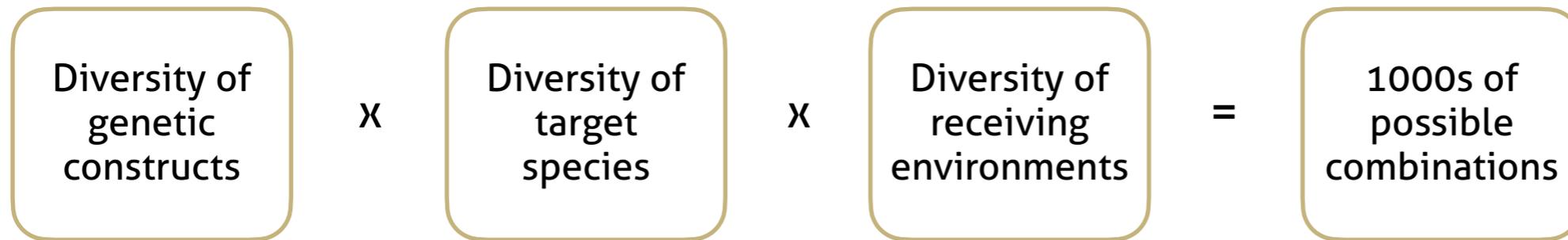
Gene drives under development differ in many dimensions

Molecular mechanisms	CRISPR-based Single locus etc	other Multi-locus
Intended effect	Suppression	Replacement
Required release rates (individuals)	10s - 100s	100,000s (or more)
Propensity to persist	Limited (requires repeated releases)	Decades (or more)
Propensity to spread geographically	Virtually none (like Sterile Insect Technique)	Throughout species range

Diversity of approaches fits the diversity of challenges

e.g., malaria across sub-Saharan Africa vs. mice on oceanic islands.

Diversity of scenarios



Diversity of scenarios argues in favour of:

- Case-by-case assessment of risks and benefits
- Narrowly focussed guidance on the nearest-term possibilities
 - James et al. (2018) developed guidance for a specific topic — low threshold gene drives for malaria-transmitting mosquitoes in sub-Saharan Africa. Took 45 experts, 3 meetings, > 1 year, ended up with something very useful. Much more appropriate level for detailed thinking and consensus building

Further reading

Review of naturally-occurring gene drive systems:

- Burt & Trivers 2006 *Genes in conflict: the biology of selfish genetic elements*. Belknap Press of Harvard University Press.

Reviews of engineered gene drive systems:

- Alphey (2014) *Annu. Rev. Entomol.* 59, 205–224
- Burt (2014) *Phil. Trans Roy Soc. Lond.* 369:20130432
- Champer et al. (2016) *Nat. Rev. Genet.* 17:146-159.

Guidance on low-threshold gene drive for malaria control in sub-Saharan Africa:

- James et al. (2018) *Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group*. *Am. J. Trop Med. Hyg.* 98(6 Suppl): 1–49