Engineering Gene Drives: Rewriting the Evolution of Wild Insect Populations

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ABSTRACT

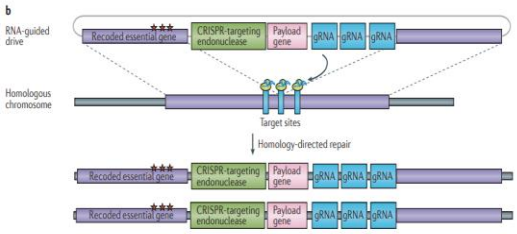
Gene drives are emerging as a powerful tool in the field of genetic engineering, offering the potential to rapidly alter the genetic makeup of wild insect populations. This technology leverages the principles of CRISPR-Cas9 and other gene-editing techniques to propagate specific genetic traits throughout a population at a rate far exceeding traditional inheritance. The ability to engineer gene drives holds promise for addressing critical challenges such as controlling vector-borne diseases, managing agricultural pests, and conserving endangered species. This paper explores the scientific principles behind gene drives, their potential applications, and the complex balance between their benefits and risks.

INTRODUCTION

Gene drive systems have the potential to offer ground breaking solutions to significant public health and environmental challenges. Many proposed engineered gene drives are built upon naturally occurring genetic elements that behave in a "selfish" manner, meaning they increase in prevalence with each generation regardless of whether they confer any fitness advantages to their host. This mechanism leads to inheritance patterns that deviate from Mendelian principles (Curtis *et al*., 1968). Gene drives could potentially allow us to overcome the evolutionary hurdles associated with desirable traits, spreading them throughout wild populations. Additionally, they could be

employed to suppress populations of specific target species entirely (Bier, 2022). Different types of gene drives that can be used for the manipulation of wild population of insects are as under:

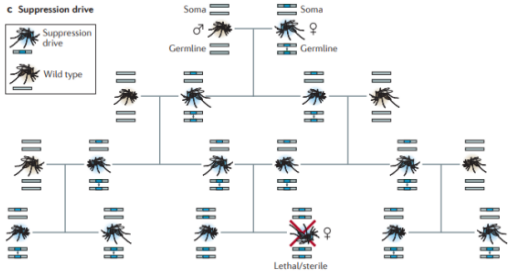
1. **Homing endonuclease genes (HEGs):** First proposed for use in manipulating populations by Burt in 2003. An Endonuclease encoded either as a freestanding gene within introns, as a fusion with host protein or as a self-splicing intein, with the ability to home into the opposite chromosome, resulting in more than half of offspring inheriting the HEG. Exhibit significant drive rates and can be utilized for both population suppression and modification purposes. In a study by Yadav *et al.* (2023), split homing drives were developed and assessed targeting the doublesex (*dsx*) gene in *Drosophila suzukii* (Matzumura). The drive component comprised *dsx* single guide RNA and DsRed genes, which were inserted into the female-specific exon of *dsx.* In most strains, females with one copy of the gene were sterile and produced the male *dsx* transcript. Expressing Cas9 with two nuclear localization sequences from the *D. suzukii nanos* promoter showed high transmission rates of the DsRed gene (ranging from 94 to 99%). Finally, mathematical modeling demonstrated that the strains could effectively suppress laboratory cage populations of *D. suzukii* through repeated releases at relatively low ratios (1:4).



A homing element generated using an RNA-guided CRISPR (clustered regularly interspaced short palindromic repeats) endonuclease together with one or more small guide RNAs (gRNAs)

2. **The X chromosome shredder**: Operates by altering gender ratios, specifically favoring the increase of male individuals within the population. This method involves disrupting the transmission of the X chromosome by causing multiple DNA double-strand breaks during male meiosis. Endonucleases are employed to target the X chromosome, with their activity restricted to male gamete formation. Meccariello *et al.* (2021) enabled the endogenous CRISPR/Cas9 and CRISPR/Cas12a activity during spermatogenesis in the Mediterranean fruit fly *Ceratitis capitata* (Wiedemann). Analysis of genome sequencing data from both males and females resulted in identification of two clusters of abundant sequence repeats specific to the X chromosome. When these repeats were targeted by guide RNAs in combination with Cas9, cleavage resulted in a significant and consistent shift in sex ratio toward males across various transgenic strains. Furthermore, employing different combinations of these genetic distorters led to a strong bias, with approximately 80% of the offspring being male.

3. **Maternal effect dominant embryonic arrest (*Medea*)**: Represents a type of gene drive mechanism. It involves a clever combination of maternally expressed toxin and a zygotically expressed antidote,

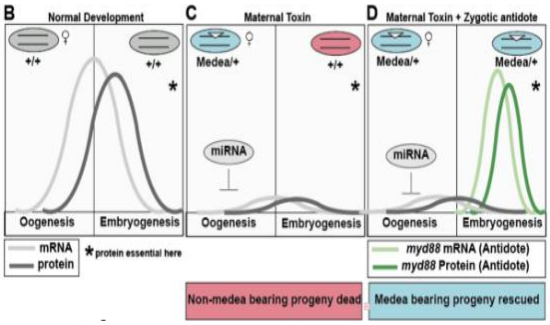


A suppression drive targeting a recessive gene required for viability or fertility

ensuring the survival of 50% of embryos from a *Medea*-carrying heterozygous female. Those embryos failing to inherit the

Medea element do not survive. Two new synthetic *Medea* elements were synthesized and their population genetic behavior studied, aiming to drive population replacement by manipulating signaling pathways related to cellular blastoderm formation or Notch signalling in *Drosophila*. The study revealed changes in mRNA and small RNA profiles in the ovaries and early embryos of *Medea*-carrying females. Lastly, modeling was utilized to demonstrate how *Medea* elements containing genes leading to diapause-dependent female lethality could be employed for population suppression purposes (Akbari *et al.*, 2014).

4. **Underdominance gene drives:** Underdominance, also known as heterozygote inferiority, occurs when heterozygotes (or their progeny) have a lower fitness than parental homozygotes. Underdominant systems function as a bistable switch: A phenomenon in which a certain threshold frequency for a gene drive system defines its eventual fate in a population. If the frequency of individuals



with the gene drive in a population is above that threshold, it will spread and eventually reach fixation

Other types of gene drive system include:

- **Supernumerary B-chromosomes**: have also been suggested as vehicles to carry payload genes, as these small chromosomes are inherited at rates that are greater than Mendelian rates and can express transcripts
- **The Killer–Rescue system**: uses a toxin and an antidote gene at separate.
- The inverse Medea system relies on a toxin that takes effect in the zygote unless it receives a maternally delivered antidote. **The Merea system** functions similarly to Medea, but the antidote to the maternal toxin is recessive
- The **Semele system**, conversely, uses a paternal semen-based toxin and a maternally delivered antidote
- **Medusa system**, which induces a population crash by utilizing a pair of sex-linked toxins and antidote

Gene drives can also be used for reversing the apparent resistance found in many insect pests; one such example would be House fly. A recurring mutation found in various pests and disease vectors affects the voltage-gated sodium channel (*vgsc*) gene, commonly known as knockdown resistance (*kdr*), leading to resistance against commonly used insecticides like pyrethroids and DDT. Kaduskar *et al.* (2022) introduced common kdr mutations into isogenic laboratory *Drosophila* strains through CRISPR/Cas9 editing. Sensitivity was observed to permethrin and DDT among these mutants. Notably, authors employed a CRISPR-based allelic-drive to replace a resistant *kdr* mutation with a susceptible wild-type version in population cages highlighted the successful demonstration of targeted reversal of insecticide-resistant populations to a susceptible state or replacement of malaria-transmitting mosquitoes with those carrying naturally occurring parasite-resistant alleles. This study highlights the utilization of gene drives in potential resistance management in mosquitoes.

CONCLUSION:

Since their inception, gene drives have made significant progress. New and improved

vehicles now hold great potential for deploying anti-malarial agents or reducing mosquito populations. Flexible add-on features like CRISPR/Cas9 could enhance or broaden the capabilities of existing drives. Additionally, strategies are now in place to halt or remove drives if they veer off course. These technologies could potentially be adapted for use in other insect species and, with continued advancement, may even be applicable to other organisms such as vertebrates, plants, and bacteria.

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