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Mosquito Maladies: Genetic Manipulation of Mosquitoes Leads to Potential Solution to the Spread of Malaria

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Genetic Manipulation of Mosquitoes Leads to Potential Solution to the Spread of Malaria

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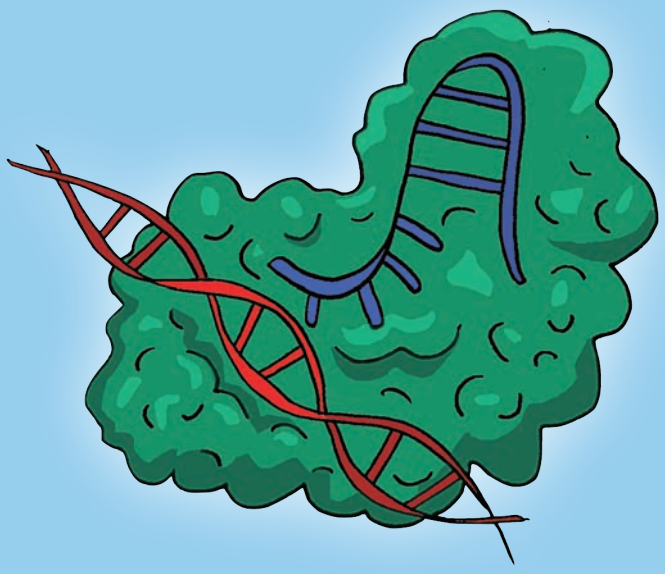
Twenty years ago, Anthony James, a molecular biologist and professor at the University of California Irvine, aimed to engineer a mosquito that could not transmit malaria. After years of failure, he succeeded in 2015 by inserting two anti-malaria genes in the mosquito genome that make it impossible for the malaria parasite Plasmodium falciparum to survive inside the insect. However, this discovery was only half of the battle; the other half was to discover a method that could get these anti-malaria genes added to the wild mosquito population.

Plan A was to breed 100,000 mosquitoes homozygous for the malaria-resistant allele and release them into a village that had 10,000 mosquitoes; this would cause the gene to be largely transmitted to future generations of the population via sexual reproduction. Introducing 100,000 extra mosquitoes was not a particularly popular idea among the village's inhabitants, so James opted for a Plan B instead. He contacted Ethan Bier, Professor of Cell and Developmental Biology at the University of California San Diego, who had previously developed a technique called mutagenic chain reaction (MCR), a procedure that utilizes and builds upon CRISPR/Cas9 gene editing, which James felt could be modified to become the crux of his Plan B.

Together, Bier and James used MCR to engineer two mosquitoes to be homozygous for the anti-malaria genes. It is important to note that the anti-malaria phenotype is only expressed when the recessive anti-malaria gene is homozygous, or present on both of two homologous chromosomes. When the anti-malaria genes are heterozygous, or present on only one homologous chromosome, the mosquitoes are still able to transmit malaria, just as if they were homozygous for not possessing the anti-malaria genes.

To test their MCR-based genetic manipulation, the researchers put two mutant (anti-malaria) mosquitoes in a box with thirty wild-type (non-mutated) mosquitoes, and allowed them to reproduce via random mating. Here is where the special effects of MCR really came to play. Usually when a mutant mosquito (homozygous recessive for the anti-malaria genes) mates with a wild-type mosquito (homozygous dominant for not having the anti-malaria genes) their offspring will be heterozygous and thus will still be able to transmit malaria. However, MCR works such that when this mating happens and a heterozygote baby mosquito is conceived, anti-malaria genes present in one of its homologous chromosomes will get duplicated onto its other homologous chromosome, making the offspring homozygous for the anti-malaria genes instead of heterozygous. Experimentally, this technique caused almost all of the 3,800 offspring to be homozygous for the malaria-resistant genes within two generations.

Thus, with this discovery Bier and James unlocked a potential



method to stopping malaria transmission forever. By inserting an anti-malarial gene in just 1% of a mosquito population, malaria could be eradicated in about a year. In a single year, dengue fever, chikungunya, yellow fever—diseases all carried by mosquitoes—could all also be eliminated if genes preventing these diseases were found and targeted by MCR.

Furthermore, the same gene manipulation techniques used in mosquitoes could get rid of invasive species, and hundreds of endangered or vulnerable native species that have been pushed to the brink of extinction could potentially be restored. For example, one of the most well known case studies of invasive species in North America is the Asian carp. Highly detrimental to the environment in the U.S., the invasive Asian carp could be removed by creating a gene drive that insured that all its offsprings would be male; therefore within a couple of generations, there would be no mating within the species, and it would become extinct in the U.S.

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However, using these gene drive techniques also poses some risks. Gene drives are when the inheritance of a specific gene is increased to promote the presence of that gene within a population. In theory, gene drives are so efficient that accidents, such as an experimental organism with MCR-modified genes escaping from a laboratory, could change an entire species. James bred his mosquitoes in a biocontainment lab, using a species that was not native to the U.S.; thus, in the case that some escaped, they and their modified genes would presumably die off for lack of mates. However, less careful experiments could pose a much larger ecological risk.

To understand why it is important to prepare for the possibility of a rampant gene drive, take an example where interbreeding between mutant escapees and wild-type individuals is possible: if a dozen Asian carp in the Great Lakes are given an all-male gene drive and then are accidentally carried back to Asia, they could potentially wipe out the native Asian carp population by making all of the native carps' offspring male. This scenario is not as unlikely as it may seem given how interconnected our world has become. In fact, this is exactly why there are invasive species problems around the globe. With organisms like mosquitoes and fruit flies that can travel undetectably, there is no way to contain them—and their genes—to specific environments.

Scientists up to this point have been allowed to play the mad genius; they could generally mess around with an organism's genes as much as they cared to do so. It was assumed that if any of their specimens were to escape, natural selection would take care of them. However, if an added trait is neutral or beneficial, the mutant could potentially spread the modified gene until, after many generations, every individual in the population possesses it. Gene drives don't work this effectively yet, but James and Bier think that they will soon. Because of gene flow, in which neighboring species occasionally interbreed and exchange genetic information, a gene drive can affect many populations, and thus the mutated gene could expand beyond the target species. This is not necessarily a bad situation if it promotes a trait beneficial to a vulnerable population (or to humans), but some gene drives could unintentionally harm populations or the ecosystems in which those populations live.

Gene drives do have limitations; they only work with sexually reproducing species, so they cannot be used to genetically engineer populations of viruses or bacteria. Additionally, the manipulated gene can only spread between generations; it is therefore only practical to work with species that have a fast reproductive cycle. With organisms such as humans, it would take centuries for a trait to spread widely. Additionally, the introduction of a mutant gene does not necessarily mean that the targeted trait will spread; how much it spreads will depend on how it affects fitness, the rate of gene flow, and on the strength of of genetic drift, which causes random fluctuations in allele and genotype frequencies and could lead to the disappearance of the introduced allele.

Where do gene drives leave us? It might be a bit of an exaggeration, but gene drives, if perfected, allow us to alter an entire species permanently. But is this something we should do? Some scientists are creating safeguards, where gene drives could self-regulate by replicating until a certain percentage of the population has the gene or where the gene drive stops completely after a few generations. Other scientists are debating who is allowed to use gene drives and for what purposes. Soon, if gene drives are perfected, governments will likely attempt to integrate them into health regulation programs, as countries that suffer greatly from malaria and other tropical diseases carried by mosquitoes would benefit significantly.

Altering DNA and using gene drives are not inherently evil. Currently, our solution to combat malaria is by spraying pesticides that hurt other species and pollute water supplies, yet this still leaves 1,000 people dying of malaria every day. It might be frightening to play with DNA, but the fallout of inaction could be worse.