ScienceWatch -The End of Malaria?

"This breakthrough shows that gene drive can work, providing hope in the fight against a disease that has plagued mankind for centuries."–A. Crisanti

Each year malaria causes about a half million deaths worldwide. In Africa it kills a child every two minutes. The disease is caused by a microscopic parasite, *Plasmodium* that infects red blood cells, producing symptoms like fever, chills and anemia that can lead to coma and death. While several species of mosquitoes in the genus *Anopheles* can spread malaria, one, *A. gambiae* is the prime disease vector. Now a report in the November 2018 issue of *Nature Biotechnology* has employed a *gene drive* to eradicate this disease-carrying mosquito. Gene drives disobey normal inheritance rules, forcing themselves onto all an organism's progeny and spreading rapidly through a population.

A research team, led by Andrea Crisanti, Imperial College London, UK, used a powerful new gene editing tool called *CRISPR** to mutate a gene to make lab female mosquitoes sterile. CRISPR contains two molecular components: (1) The G*uide RNA* has an RNA sequence that can be custom designed to seek out and bind to a specific DNA sequence; (2) *Cas9** is an enzyme that cuts out the targeted DNA sequence and allows a different one to replace it.

Crisanti *et al*. selectively altered the *doublesex* (*dsx*) gene that determines sex in insects by injecting *A. gambiae* embryos with a CRISPR that targeted the normal *dsx* gene and replaced it with a mutated version ($dsxF^-$). Females with two copies of the mutant gene have altered mouth parts that prevent them from biting to get a blood meal. Thus, they are unable to produce eggs and are sterile.

A mutation causing sterility would normally be hugely disadvantageous in the wild and quickly wiped out. So the team changed the odds to favor inheriting $dsxF^-$ by attaching CRISPR to the mutated gene to create a gene drive that could spread the mutation and cause extinction.

When *dsx* and $dsxF^-$ mosquitoes mate, the $dsxF^-$ gene would normally be inherited by only 50% of each new generation. This is because each progeny receives a chromosome from each parent, each with a different gene copy. But the new gene drive composed of CRISPR and $dsxF^-$ changed the inheritance pattern. The progeny still inherit one chromosome with *dsx* and the other with $dsxF^-$, but the $dsxF^-$-containing chromosome also contains CRISPR. Now CRISPR can excise *dsx* on the adjacent chromosome inducing the cell to repair the damage by copying CRISPR and $dsxF^-$ onto the chromosome that previously lacked them. This effectively converts the normal gene into the mutant (see Figure).

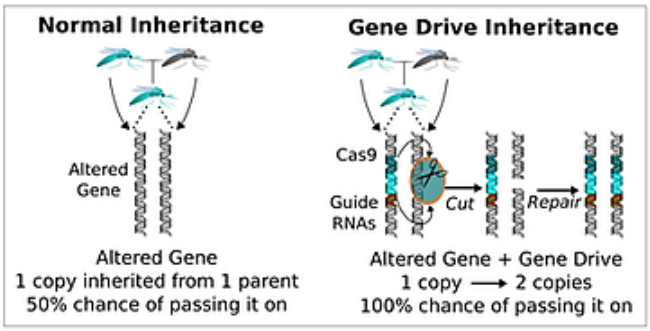

Image credit: Kevin Esvelt

The scientists expected the new gene drive to spread *dsxF*$^{-}$ throughout each new generation until all the females were sterile and that is exactly what happened. They set up two laboratory cages containing hundreds of normal and modified mosquitoes and let them mate. They randomly picked 650 eggs laid by these mosquitoes to start the next generation, and repeated the process for each new generation. One cage yielded no progeny by the 8th generation and other by the 12th.

By making a laboratory population of *Anopheles* mosquitoes go extinct, the scientists have caused some to worry about releasing such genetically modified mosquitoes in the wild. Suppose the gene drive somehow transfers itself to honeybees? Others are concerned that the mosquitoes in the wild may develop resistance to the gene drive, blocking its spread. But while lab mosquitoes developed resistance to other gene drives, that didn't happen here. "We have a solution to the functional resistance that arises in gene drives," says team member Kyros Kyrou.

Crisanti is also part of the "Target Malaria" project, an international consortium funded by the Bill and Melinda Gates Foundation, which has received permission to release gene drive mosquitoes in three African countries. In January 2019 they released 10,000 mosquitoes genetically modified to cause male sterility but lacking a gene drive in a Burkina Faso village to study the impact on the wild mosquito population.

The group plans to release mosquitoes with the *dsxF*$^{-}$ gene drive in 2024. Stay tuned.

Saul Scheinbach

*CRISPR = Clusters of Regularly Interspersed Short Palindromic Repeats
*Cas9 = CRISPR associated protein 9