

Gene knockout using new CRISPR tool makes mosquitoes highly resistant to malaria parasite

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Mosquito that causes malaria, *Anopheles gambiae*. Credit: NIAID, CC BY

Deleting a single gene from mosquitoes can make them highly resistant to the malaria parasite and thus much less likely to transmit the parasite to humans, according to a new paper from scientists at Johns Hopkins

Bloomberg School of Public Health's Malaria Research Institute.

The scientists used the new CRISPR/Cas9 system, which permits precise DNA editing, to delete a gene called FREP1 from the genome of *Anopheles gambiae* [mosquitoes](#), the chief transmitters of [malaria](#) to humans. Within the modified mosquitoes, malaria parasites were much less likely to survive and multiply. The CRISPR/Cas9 system used in this study was developed by Eric Marois, research scientist at the University of Strasbourg,

The study, published March 8 in *PLoS Pathogens*, is the first to show that deleting a gene from mosquitoes can make them resistant to malaria parasites. It also underscores the potential of this strategy to modify wild mosquito populations and thereby reduce malaria transmission to humans.

The CRISPR/Cas9 system is a set of DNA-editing molecules implicated in bacterial defense mechanism against viruses. In recent years, biologists have adapted it as a precise tool for genetic engineering—in scientific experiments, and in prospective genetic-modification strategies against diseases such as malaria.

"Our study shows that we can use this new CRISPR/Cas9 gene-editing technology to render mosquitoes malaria-resistant by removing a so-called host factor gene," says study senior author George Dimopoulos, PhD, professor in the Bloomberg School's Department of Molecular Microbiology and Immunology. "This gives us a good technological platform for developing advanced malaria-control strategies, based on [genetically modified mosquitoes](#) unable to transmit the disease, and for studying the biology of malaria parasites in their mosquito hosts."

The World Health Organization estimates there were more than 200 million cases of the disease in 2016 and more than 400,000 deaths, the

majority occurring among children under age five in sub-Saharan Africa. A malaria vaccine is available, but its protection is only partial and temporary, and like antimalarial medicines, the vaccine has a limited supply. Researchers are turning to potentially cost-effective strategies that target malaria-carrying mosquitoes to prevent the spread of malaria in the first place.

For the research, conducted in the insectary at the Johns Hopkins Malaria Research Institute in Baltimore, Dimopoulos and colleagues modified *Anopheles gambiae* mosquitoes by deleting the gene FREP1, which encodes an immune protein, fibrinogen-related protein 1. For reasons that aren't fully clear, the protein helps malaria parasites survive within the mosquito gut and progress to the developmental stages needed for their transmission to people. FREP1 is thus considered a malarial "host factor."

The elimination of this host factor via the deletion of the FREP1 gene had other effects besides reducing the number of mosquitoes infected with malaria. After the FREP1 deletion, most of the modified mosquitoes had no evidence in their salivary glands of the sporozoite-stage parasites that enter the human bloodstream through a mosquito bite.

"The resistance to malaria parasites that's achieved by deleting FREP1 is remarkably potent," Dimopoulos says. "If you could successfully replace ordinary, wild-type mosquitoes with these modified mosquitoes, it's likely that there would be a significant impact on [malaria transmission](#)."

Replacing ordinary mosquitoes in the wild with genetically modified mosquitoes hasn't yet been attempted, though scientists have been working on "[gene drive](#)" techniques that cause DNA modifications to spread quickly into a wild population via ordinary breeding. Gene drives use CRISPR/Cas9's DNA-editing ability to essentially hack the

conception process, pushing a gene modification into all or nearly all the offspring of a modified animal. In 2016, for example, researchers reported that they had created a CRISPR/Cas9 gene drive that forces a fertility-reducing gene modification into female *Anopheles gambiae* mosquitoes—which could quickly reduce local *Anopheles* populations if unleashed in the wild.

In principle, the deletion or inactivation of FREP1 also could be incorporated in a gene drive system. Because it doesn't aim at reducing mosquitoes' health or ability to reproduce—reducing "fitness" in the Darwinian sense—a FREP1 inactivation would create less of an opportunity for mosquito mutations that resist its effects.

Dimopoulos and his research team found that deleting FREP1 entirely from *Anopheles* did however come with some fitness costs to the modified mosquitoes. Compared to their wild-type cousins, the FREP1-less mosquitoes developed into adults more slowly, were less likely to take blood meals when given the opportunity and laid fewer and less viable eggs.

"We're now making mosquitoes in which FREP1 will be inactivated only in the adult gut," Dimopoulos says. "We predict that when we do that, the mosquito won't suffer the same fitness costs."

In addition, he and his team are using their CRISPR/Cas9 DNA-editing platform to study the effects of deleting other potential malaria host-factor [genes](#) and to learn more about the roles of these host factors in mosquitoes. "We're focused not just on developing a malaria control strategy, but also learning more about the biology of malaria-carrying mosquitoes," Dimopoulos says.

More information: "CRISPR/Cas9-mediated gene knockout of *Anopheles gambiae* FREP1 suppresses malaria parasite infection" *PLoS*

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