Scientists prove new technology to control malaria-carrying mosquitoes

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Scientists at Imperial College London and the University of Washington, Seattle, have taken an important step towards developing control measures for mosquitoes that transmit malaria. In today's study, published in *Nature*, researchers have demonstrated how some genetic changes can be introduced into large laboratory mosquito populations over the span of a few generations by just a small number of modified mosquitoes. In the future this technological breakthrough could help to introduce a genetic change into a mosquito population and prevent it from transmitting the deadly malaria parasite, Plasmodium, to humans.

Malaria is a debilitating disease that affects more than 300 million people every year, and kills nearly 800,000 annually. In Africa, a child dies of malaria about every 45 seconds. Public health experts have called for malaria eradication, but there is a recognised need for better and lower cost tools to achieve the eradication goal. Scientists around the world are keenly seeking novel strategies to tackle malaria.

The researchers bred mosquitoes with a green fluorescent gene, as a marker that can easily be observed in experiments. They allowed these insects to mingle and mate with a small number of mosquitoes that carried a segment of DNA coding for an enzyme capable of permanently inactivating the fluorescent gene. After each generation, they counted how many mosquitoes still retained an active fluorescent gene.

They found that in experiments which began with close to 99% of green fluorescent mosquitoes, more than half had lost their green marker genes

in just 12 generations. The study is the first successful proof-of-principle experiment of its kind, and suggests that this technique could similarly be used to propagate a genetic change within a wild mosquito population.

Professor Andrea Crisanti, from the Department of Life Sciences at Imperial College London, a senior author of the study and head of the research group, said: "This is an exciting technological development, one which I hope will pave the way for solutions to many global health problems. It demonstrates significant potential to control these disease-carrying mosquitoes. We expect to conduct many more experiments to determine its safety and reliability."

Scientists at Imperial were the first to genetically modify a mosquito species, in early 2000. Research by other scientists has since shown that such modifications could be used to generate mosquitoes that are less able to transmit the malaria parasite. However, even if such mosquitoes were to be released in large numbers, the modification would quickly disappear since it gives the insect no advantage over the unmodified mosquitoes. Thus, this new research addresses what has been a long-standing obstacle to the success of this promising malaria control strategy.

In the new experiments, the researchers inserted a unique segment of DNA producing a homing endonuclease enzyme into the mosquito Anopheles gambiae, one of the main carriers of malaria. Homing endonucleases are found widely in nature, in organisms such as fungi. The particular DNA element used in the study not only produces the enzyme that inactivates the green fluorescent gene but at the same time inserts a copy of itself in the place of the inactivated gene. This occurs in the mosquitoes' sperm cells, so that when the insects mate almost all the offspring receive the DNA that produces the enzyme. In this way the DNA element can spread through the population over successive generations.

Professor Austin Burt, from the Department of Life Sciences at Imperial College London, who is also a senior author on the study, said: "Malaria is still a terrible disease. There are around 3,500 species of mosquito in the world, but only a few of them transmit the deadly malaria parasite, Plasmodium falciparum. This technology allows us to focus exclusively on controlling these most dangerous species."

The lead author on the paper, Dr Nikolai Windbichler, also from Imperial's Department of Life Sciences, said: "In our mosquitoes the homing endonuclease gene is only passed on, through reproduction, directly to the carrier's offspring. This makes for a uniquely safe biological control measure that will not affect even very closely related mosquito species."

The scientists are now working to move from the synthetic fluorescent target used in this study to target genes that are required by the mosquito for its reproduction or for malaria transmission. With this technology, the release of a small number of modified mosquitoes could eventually result in dramatic reduction of numbers of malaria-carrying mosquitoes over wide areas in countries where the deadly disease is currently endemic. This could provide a low cost, safe, and highly effective public health tool for malaria eradication. The scientists expect this additional research will take 5-6 years.

The research group expects to continue their experiments at the new EU INFRAVEC Mosquito Confined Release Facility once it is built later in 2011. The study is supported by the Foundation for the National Institutes of Health (FNIH) through the Grand Challenges in Global Health Initiative.

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