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Scientists zero in on mosquito DNA to repel malaria transmission

Clive Cookson

Big buzz: Anthony James of the University of California regards developments so far as 'significant'

Researchers are waging war against malaria on two broad fronts. One is development of drugs and vaccines against *Plasmodium*, the protozoan parasite that directly causes the disease. The other uses new technology to attack the mosquitoes that transmit the parasite between people.

Long before the 19th century discovery of the role mosquitoes play in transmitting malaria, people recognised that the disease was most prevalent in marshland. They blamed the bad air (*mal'aria* in old Italian) associated with swamps and, as they drained the land, health improved because mosquitoes no longer had stagnant water in which to breed.

This ancient and inadvertent method of mosquito control was extended during the 20th century with chemical warfare, which was waged with insecticides and insect repellents.

The 21st century promises to bring biology to the forefront of the battle. This is through releasing genetically modified (GM) mosquitoes that either suppress the wild population of disease-transmitting insects or replace it with a GM strain that does not carry the parasite.

GM insect technology is not yet in commercial use anywhere in the world and some environmental campaigners oppose its introduction, saying it poses an unacceptable ecological risk. Nonetheless, research is increasing rapidly.

There are two main reasons for the current urgency in the battle against mosquitoes. The most immediate is a new epidemic of Zika, a mosquito-borne disease, in Latin America.

Although the *Aedes* mosquitoes that transmit Zika — and other diseases including dengue, chikungunya and yellow fever — are a different genus to the *Anopheles* carriers of malaria, much of the research is likely to be applicable to both types.

The second accelerator of GM insect research is the emergence over the past three years or so of new "gene editing" technology. In particular, this involves a technique called Crispr — pronounced "crisper" — and which is short for "clustered regularly interspaced short palindromic repeats". The method enables researchers to manipulate specific genes — adding, subtracting or changing DNA — far quicker and more precisely than previous techniques of genetic engineering.

Crispr has a guidance molecule that can be targeted to any stretch of DNA. Then a companion enzyme cuts the DNA in exactly the right place, allowing scientists to snip out unwanted DNA, add new DNA or regulate genetic activity, before joining up the cut ends.

Several labs have reported successful mosquito-modifying experiments using Crispr, which include the "gene drive" technique. This process overrides the normal constraints of evolution and ensures that when a GM mosquito mates with an unmodified wild mosquito almost all of the offspring receive the edited gene, rather than half, as would otherwise be the case. As a result it can spread very fast through an insect population.

Last November, for example, scientists at the University of California inserted a gene for anti-malaria antibodies with a gene drive system into *Anopheles* mosquitoes. The research is at an early stage and further lab tests are needed to show how effectively the antibodies prevent malaria infection.

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>
> - Professor Austin Burt

"This is a significant first step," says Anthony James of the University of California, Irvine, the project leader. "We know the gene works. The mosquitoes we created are not the final brand but we know this technology allows us efficiently to create large populations."

Scientists at Imperial College London have created a different type of gene drive, which disrupts egg production in female *Anopheles gambiae*, the most important carrier of malaria in Africa. This infertility would quickly reduce wild mosquito populations — and therefore the malaria transmission to humans — to very low levels.

African ecosystems should not be affected significantly by suppressing just one of the continent's 800 mosquito species, researchers say, while the benefits to human health could be enormous.

"As with any new technology, there are many more steps we will go through to test and ensure the safety of the approach we are pursuing," says Professor Austin Burt of Imperial College. "It will be at least 10 more years before gene drive malaria mosquitoes could be a working intervention."

One approach, based on older GM technology, however, is much closer to commercialisation. The "sterile insect technology" produced by Oxitec, a UK company spun out of Oxford university in 2002, inserts a "dominant lethal gene" that enables males to mate with females but kills their offspring while young. A sufficient number of these GM males are bred in the laboratory to be released and swamp their wild counterparts. They mate with all available females, which then fail to reproduce. The effect is to suppress the pest population greatly.

The strategy, tested over the past five years in field trials in several tropical countries, means releasing many millions of insects — 10 times more at least than the wild population.

Oxitec is focusing its research and development efforts on *Aedes* mosquitoes but Hadyn Parry, chief executive, says the company's scientists have shown that the same technology can be applied to the *Anopheles* mosquitoes that transmit malaria.

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