JOE RAEDLE/GETTY

Biotech firm Oxitec placed boxes of its mosquito eggs in selected spots in the Florida Keys.

FIRST RESULTS FROM US TRIAL OF GENETICALLY MODIFIED MOSQUITOES

Biotechnology company says its insects behaved as planned – but a larger study is still needed.

By Emily Waltz

Researchers have completed the first open-air study of genetically engineered mosquitoes in the United States. The results, according to the biotechnology firm running the experiment, are positive. But larger tests are still needed to determine whether the insects can achieve the ultimate goal of suppressing a wild population of potentially virus-carrying mosquitoes.

The experiment has been under way since April 2021 in the Florida Keys, a chain of tropical islands near the southern tip of Florida. Oxitec, which developed the insects, released nearly five million engineered *Aedes aegypti* mosquitoes over the course of seven months, and has now almost completed monitoring of the release sites.

Based in Abingdon, UK, the firm reported the first results from the experiment during a webinar on 6 April, although it has not yet published the data.

Wild *A. aegypti* mosquitoes can carry viruses including chikungunya, dengue, Zika and yellow fever, so scientists have sought ways to reduce their populations. Oxitec's engineered males carry a gene that is lethal to female offspring. If all goes to plan, when released into the environment, the engineered males will mate with wild females, and their female offspring will die before they can reproduce. Male offspring will carry the gene and pass it on to half of their progeny. As each generation mates, more females will die, and the *A. aegypti* population will dwindle.

"We've dealt with multiple disease outbreaks. We're looking at any tool that could be helpful."

To make sure the mosquitoes follow this scheme, researchers placed boxes of Oxitec mosquito eggs on private properties in the Keys and surrounded them with traps, covering a radius of more than 400 metres. Some traps served as egg-laying sites, and others caught adult mosquitoes.

The researchers found that the males that hatched from the eggs typically travelled within a one-hectare area around the release box – the same range over which wild *A. aegypti* fly. The engineered mosquitoes, which don't bite, mated with the wild population, and wild females laid eggs in Oxitec traps, as well as in sites such as flower pots, rubbish-bin lids and soft-drink cans.

Oxitec researchers collected more than 22,000 eggs from the traps and took them back to their laboratory to hatch under observation. The firm reported that all females that inherited the lethal gene died before reaching adulthood. (Researchers can determine this because mosquitoes carrying the lethal gene fluoresce under certain light.)

Furthermore, the team found that the lethal gene persisted in the wild population for two to three months, or about three generations of mosquito offspring, and then disappeared. No mosquitoes carrying the lethal gene were found beyond 400 metres of the release points, even after several generations. Oxitec monitors the sites for ten weeks after the last lethal gene-carrying mosquito is found.

"I like the way they're going about it," says Thomas Scott, an entomologist at the University of California, Davis. "They're doing it in a systematic, thoughtful way. So I'm encouraged, but they have a lot of work ahead of them," he says.

The pilot study was not intended to determine how well the method suppresses the wild population. Oxitec plans to gather those data in an extension of the Florida Keys study. It needs approval from state regulators, but hopes to begin soon. The company plans to release mosquitoes at a second study site in Visalia, California, where it is building a research and development facility.

Quashing outbreaks

But these expanded studies will not assess whether Oxitec's method reduces transmission of dengue or other viruses carried by *A. aegypti*. "They're not going to be able to do a trial to show that it actually has a public-health impact," Scott says. "There's not enough *Aedes*-transmitted viral infection in the Florida Keys," or anywhere in the continental United States to do that kind of study, he says. To run such an experiment, the company would have to invest in a controlled trial elsewhere, and run the study like a clinical trial, which would be enormously expensive.

Disease outbreaks can occur even when *A. aegypti* populations are low, so reducing the mosquito population won't necessarily translate into disease suppression anyway, Scott adds. "It's just not that simple."

Neither will suppressing *A. aegypti* reduce the need for pesticides. *Aedes aegypti* makes up only about 4% of the mosquito population in the Keys. The black salt marsh mosquito (*Aedes taeniorhynchus*) – more of a nuisance than a disease vector – probably represents

about 80% of the mosquito population on the islands.

Still, the Florida Keys Mosquito Control District (FKMCD), the local abatement group, supports Oxitec's trials. "We've dealt with multiple disease outbreaks, so we've got to do everything we can to protect our people down here and the economy," says Andrea Leal, executive director of the FKMCD. That means trying new things, she says. "We're looking at any tool that could be helpful."

The Keys experienced an outbreak of dengue fever in 2010, with 68 locally transmitted cases, and again in 2020, with 72 locally transmitted cases, according to the FKMCD. In 2017, the group worked with MosquitoMate, a biotech firm in Lexington, Kentucky, to release *A. aegypti* males that were infected with the bacterium *Wolbachia pipientis*. The laboratory-grown males mate with members of the wild population to produce eggs that do not hatch.

In 2020, the FKMCD approved Oxitec's trial after seeking community input. In a 2016 referendum, 31 out of 33 precincts in Monroe County, where the Keys are located, voted in favour of the project, although some local residents and environmental groups protested against the plan. It's particularly important, Scott says, that the FKMCD and Oxitec have made an effort to interact with the community,especially "for something as controversial as genetically modified mosquitoes".

The US Environmental Protection Agency (EPA) and the state of Florida also gave Oxitec permission to run the 2021 project. The firm's 2022 projects in Florida and California were approved by the EPA in March, and the company awaits permission from both states.

TROVE OF TUMOUR GENOMES OFFERS CLUES TO CANCER ORIGINS

Largest-ever study uncovers patterns of mutations that might pinpoint cancer's causes.

By Heidi Ledford

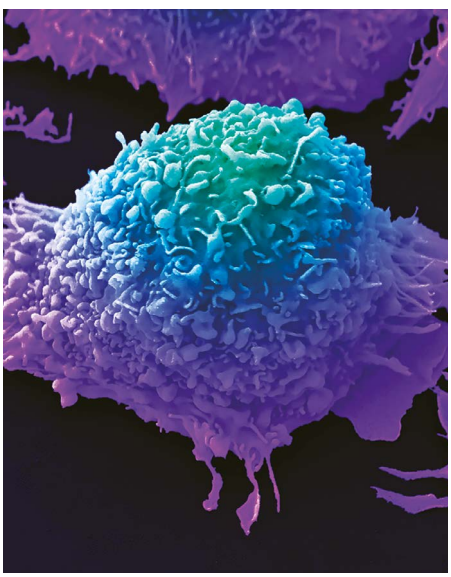
By sifting through hundreds of millions of mutations lurking in the genomes of more than 12,000 tumours, researchers have identified patterns of DNA changes that could offer clues to the genetic and environmental causes of cancer.

The study, published online in *Science* on 21 April, is the largest of its kind (A. Degasperi *et al. Science* **376**, eable9283; 2022). It adds dozens of entries to the growing catalogue of 'mutational signatures' that accompany cancer, and could, in some cases, help clinicians to select the best treatments for individuals.

Size matters for these analyses, says Núria López-Bigas, a computational cancer biologist at the Institute for Research in Biomedicine in Barcelona, Spain. The new work has revealed rare mutational patterns that could not have been picked out from smaller data sets. "When you have this number of whole genomes, you have more power and can make a more complete set of mutational signatures," she says. "It is still early days, but it has a lot of potential in diagnosis and to understand how these tumours have been created."

An individual cancer cell can contain hundreds of thousands of mutations, sometimes more than one million, but only a handful of these will contribute directly to the development of a tumour. For years, researchers have been trawling through genomic data in search of these cancer drivers, in the hope that they could point to new therapies.

The many remaining 'bystander' mutations can also be informative. Some cancer-causing agents create characteristic patterns of DNA changes. Ultraviolet light, for example, can cause a DNA base, or 'letter', called cytosine to be replaced by another called thymine at certain sites in the genome. Such changes are often found in melanomas.



ANNE WESTON, EM STP, FRANCIS CRICK INST./SPL

A lung cancer cell. Identifying mutational 'signatures' could lead to tailored treatments.

These patterns of mutations can be likened to footprints on a sandy beach, says Serena Nik-Zainal, a computational biologist at the University of Cambridge, UK, and a co-author of the *Science* study. "The footprints may look random, but they are not – they are occurring for a very particular reason," she says. "You would be able to distinguish a human from an animal, a dog from a bird, even an adult from a child and whether they were walking or running."

The largest previously reported study of mutational signatures was published in 2020 and analysed about 5,000 whole-genome sequences from tumour samples collected in an international effort (L. B. Alexandrov *et al. Nature* **578**, 94–101; 2020).

In the new study, the team analysed more than 12,000 cancer genomes collected by the UK National Health Service as part of the Genomics England 100,000 Genomes Project. The researchers then used previously published data sets to verify their findings. This involved developing new analytical tools and an algorithm capable of handling hundreds of thousands of mutations, says Andrea Degasperi, a computational biologist at the University of Cambridge and a co- author of the study.

The work – which included samples from 19 tumour types – yielded dozens of previously unknown mutational footprints, some of which could be traced back to defects in specific cellular methods for repairing DNA.

Researchers have probably now found all of the most common mutational signatures, says Dávid Szüts, a cancer biologist at the Research Centre for Natural Sciences in Budapest. "It seems unlikely that the major processes are missed at this point," he says. But the hunt for rare signatures that occur in less than 1% of tumours in a given organ will probably continue as cancer-genome projects flourish worldwide.

In addition to searching for further mutational signatures, Degasperi hopes to be able to track down the origins of the more mysterious ones that have not yet been linked to a cancer-causing event. He also wants to investigate other kinds of genetic change: the current study focuses on changes to between one and three DNA letters, but DNA sequences can also be deleted, inserted or rearranged in larger chunks.

The hope is that these studies will eventually lead to cancer treatments that are tailored to individual people, Degasperi says. "When you understand the mechanism, you might understand a possible correlation with a drug."