Verily project releases millions of factory-reared mosquitoes

Fresno County in California has given the green light to the environmental release of millions of mosquitoes infected with a common bacterium, aimed at shrinking populations of the yellow fever mosquito *Aedes aegypti*. This type of mosquito, which first appeared in the state's Central Valley in 2013, is a disease vector for viruses such as dengue, West Nile, Zika and chikungunya (although currently none of these pathogens is circulating in the Fresno area). The 'Debug Fresno' program's *Wolbachia pipientis*-infected mosquitoes are grown in the laboratory by MosquitoMate in partnership with Alphabet-backed Verily Life Sciences. This year the project has ramped up, with thousands of bacteria-carrying mosquitoes released each day in more Fresno neighborhoods, including the city of Sanger. The aim is to surpass the 68% drop in female *A. aegypti* achieved last year, and so far, mid-season, the project has recorded a greater than 90% reduction in mosquito release areas relative to control sites, according to a Verily spokesperson. In Australia, the not-for-profit World Mosquito Program (WMP) has been running pilot trials in the city of Townsville that also use *Wolbachia*-infected mosquitoes to interrupt disease transmission (*Gates Open Res.* **2**, 36, 2018). At the World Health Organization's instigation, the program is now running larger studies in Brazil and Colombia, as well as randomized trials in Indonesia and Vietnam (*Adv. Exp. Med. Biol.* **1062**, 355–360, 2018).

A parallel endeavor pioneered by UK company Oxitec complements these efforts. Oxitec, a subsidiary of Intrexon, aims to reduce mosquito populations using lab-reared, genetically modified (GM) mosquitoes. The latter approach, termed RIDL (release of insects carrying a dominant lethal), involves the release of transgenic OX513A male mosquitoes, which are sterile as a result of a *piggyBac*-based transposon containing the tetracycline-repressible transcriptional activator, which is lethal when expressed at high levels in the absence of the antibiotic (*Nat. Biotechnol.* **26**, 725, 2008). OX513A mosquitoes have been used to successfully reduce by >80% wild mosquito populations in Grand Cayman, Brazil and Panama.

Which of these two biocontrol approaches will ultimately prevail is likely to depend on several factors. These include practical issues, such as the feasibility of rearing sufficient numbers of sterile insects in the lab and the number of cycles of sterile insect release needed to suppress wild-type populations. But other issues, such as public perception and regulatory concerns—which have traditionally dogged GM organisms—are also likely to influence adoption

Ray Wilson / Alamy Stock Photo

A. aegypti larva

Fresno County's efforts to use bacteria-carrying mosquitoes as a biopesticide began in 2017. The bacteria *Wolbachia* has been studied extensively by microbiologists and entomologists for decades and lives symbiotically within more than half of all insect species. While it is common among insects, including bees and butterflies, it cannot be transmitted to humans

Last November, the US Environmental Protection Agency (EPA) gave the biotech startup MosquitoMate, founded by medical entomologist Stephen Dobson of University of Kentucky, the go-ahead to use its *Wolbachia*-infected male mosquitoes (ZAP Males) to fight the Asian tiger mosquito (*Aedes albopictus)* in the District of Columbia and 20 US states

Wolbachia-carrying male mosquitoes are rendered sterile by the bacteria. When released into the environment, they mate with females in the wild and the eggs don't hatch, thus reducing the local mosquito population. The company sells its product to homeowners, golf courses, hotels and other customers.

In China, researchers from Sun Yat-sen University in Guangzhou, in collaboration with Michigan State University in East Lansing, are also using factory-reared *Wolbachia*-infected mosquitoes to reduce *A. albopictus* populations. Pilot studies with

Smallpox antiviral ends decades-long search

A 17-year-long saga ended in July with the first approval of a drug for treating smallpox infections. Long sought after, but particularly so after the anthrax attacks in 2011, a small-molecule inhibitor of virus extrusion from cells, Tpoxx (tecovirimat), was approved by the FDA in July, after the agency's Antimicrobial Drugs Advisory Committee voted unanimously for approval in May. SIGA Technologies of New York took the molecule through clinical trials, after they showed in 2005 that it protected mice from lethal infections with a related poxvirus. (*J. Virol.* **79,** 13139–13148). The FDA based its decision on results from mice, enabled by the 'animal rule', which kicks in when human studies are unethical. In a pivotal trial, 380 healthy people were dosed for 14 days with no severe adverse events, as reported in June (*N. Engl. J. Med.* **379,** 44–53, 2018). The government had been seeking a treatment for smallpox for decades. Vaccination programs for smallpox ended around 1979, when the virus was deemed eradicated. Hence, people below a certain age are susceptible to infection by smallpox, considered a category A bioterror agent. Although there are millions of doses of a vaccine stockpiled in the event of an infection, it cannot be given to immune-compromised people and sufferers of some skin disorders. Although all known stocks of the virus were believed to be accounted for, in 2014 researchers at the NIH discovered vials of smallpox in the institute's basement. Finally, the recent synthesis of a poxvirus from scratch has people worried that smallpox, natural or synthetic, might someday find its way into the public sphere. Tpoxx development began at the now defunct ViroPharma in collaboration with the US Army Medical Research Institute of Infectious Diseases, SIGA, and others. After the preclinical work and early safety trials, the US government ordered 1.2 million doses for the Strategic National Stockpile, garnering SIGA $500 million. Now, with the approval, SIGA will get the first Material Threat Medical Countermeasure Priority Review voucher, which could be worth many millions more.

> **"There's 1,600 trials right now with PD-1 plus something and most of them are just empirical. There's no rational basis for picking the combinations other than maybe 'this kills T cells',"** Jim Allison, from the University of Texas MD Anderson Cancer Center, explains why, with colleagues, he has created a platform using patient data and mechanistic insights to pick combinations of checkpoint inhibitors. (*BioCentury*, 19 July 2018)