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Could this zoo of mutant mosquitoes lead the way to eradicating Zika?

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Researchers in California have used the gene-editing system CRISPR-Cas9 to make all kinds of new mosquitoes. Why? *Dom Smith/STAT*

RIVERSIDE, Calif. — In a warm and very humid room, behind a series of sealed doors, Omar Akbari keeps a zoo of mosquito mutants. He's got mosquitoes with three eyes, mosquitoes with malformed mouthparts, mosquitoes with forked wings, mosquitoes with eerie white eyes, and mosquitoes that are bright yellow instead of black.

Akbari loves them unabashedly; he feeds them fish flakes, mouse blood, and sugar water and calls some of them "beautiful." But they're not pets: Akbari's lab here at the University of California, Riverside, is at the leading edge of a revolutionary technology — gene drive[11] — that could one day deploy mosquito mutants to rid the world of scourges like malaria, dengue, and Zika.

The technology[22] is moving faster than anyone dreamed. Just three years ago, the idea of disabling or destroying entire populations of disease-causing mosquitoes using gene drives seemed a distant theoretical possibility. But advances in gene-editing have shoved the field into overdrive. And that vision is now very much in reach.

Gene drives are genetic systems that break the natural Mendelian rules of inheritance. Normally, offspring have a a 50 percent chance of inheriting any given gene from a parent. Using genetic engineering, scientists can greatly increase the odds a specific gene will be passed on. That lets them rapidly push a particular gene — say one that makes mosquitoes sterile[33] or unable to carry the malaria parasite — through a population. And that, in turn, could — at least in theory — halt the spread of certain diseases, like malaria.

"I really think it's solvable," said Akbari, a molecular biologist who is in the process of moving his lab to the University of California, San Diego. "It's not cancer. It's not Alzheimer's. It's literally a mosquito biting you. We can stop that."

Related Story: [11]
Gene drive gives scientists power to hijack evolution [11]

But with that promise comes great risk. Full gene drives can spread unchecked through a population — potentially altering entire species and vast ecosystems.

That's why the military's Defense Advanced Research Projects Agency is spending $65 million to understand[44] not only how gene editing technologies and gene drives work — but also how to control, counter, or reverse them. "These are very new technologies and they have a lot of unknowns associated with them," said Safe Genes[55] program manager Renee Wegrzyn. "The idea of having safety features built in from the start seems like a good approach."

Here are some of the ways scientists are trying to make safer, more efficient gene drives:

Make a ton of mutants

A gene drive will only work against disease if it targets the right gene. One way to find those genes: make a lot of mutants.

Akbari recently created a new transgenic line[66] of dengue and Zika-carrying Aedes aegypti mosquitoes that express the Cas9 enzyme in all of their offspring. While it may seem obscure to non-scientists, the achievement has mosquito researchers buzzing because it means they no longer need to laboriously inject the gene-editing enzyme into each mosquito egg they want to edit.

Related Story: [77]
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[77]

Those injections are physically tricky to do under the microscope; fragile eggs often explode when injected with too much fluid. And the injections don't always succeed.

The new transgenic line means scientists can edit genes in mosquitoes far more efficiently — perhaps injecting just 10 eggs with guide RNA instead of 500 to generate a mutation. It works so well, Akbari found he could create double and triple mutations with a single injection. Now, he's freely sharing the mosquitoes, shipping them to other researchers in hopes of speeding up work on gene drives and mosquito genetics.

"Everyone wants them," he said.

Ensure it takes two to tango

Akbari doesn't want to create a full-on gene drive that could push new genes through a mosquito population with unstoppable momentum. Like many in this emerging field, he thinks it's too risky[88].

Instead, he's developing a "split gene drive" that requires two parts — a gene editor like the CRISPR-Cas9 system partnered with specific guide RNA that tells the editor where to cut.

Akbari's gene drive will only work when mosquitoes encoded with the Cas9 enzyme are bred with mosquitoes encoded with guide RNA. To keep the engineered gene moving through a population, new waves of Cas9 mosquitoes must be released and start breeding. If new critters aren't released, "it just kind of self-eliminates," Akbari said.

Fight the resistance

One of the biggest barriers to gene drives is natural resistance. Animals that aren't susceptible to the gene drive — perhaps because of natural variations in their own genomes — might thrive and take over an ecosystem after a gene drive is introduced.

"It's a race. Evolution is going to be a problem," Akbari said. "With what we see, it seems that's going to happen quickly."

One way to predict these problems is to use math — to model populations and genetic changes. Akbari and John Marshall, a modeler from the University of California, Berkeley who is part of Akbari's DARPA-funded team, recently proposed "multiplexing"[99] or creating a gene drive that edits the same gene in multiple places. That makes it harder for any given mosquito to resist the changes the scientists are trying to impose. Think multiple drug cocktail, but with CRISPR[1010].

Scientists are also trying to create gene drives in multiple species beyond mosquitoes — including fruit flies, nematodes, and baker's yeast — to get a better grasp on how the engineered genes move through large populations.

Get inside a mosquito's brain

Gene drives might not work as well for all varieties of mosquitoes. For example, what happens among species that mate only in swarms?

In general, little is known about the behavior of wild mosquitoes, which tend to be feistier than their laboratory brethren. To fill this gap, Craig Montell, a a fly neuroscientist at the UC Santa Barbara, plans to study sex drive, circadian rhythms, and feeding strategies in mosquitoes.

"We can't yet even imagine the questions to ask," Montell said. "We really are just scratching the surface of trying to understand the behavior of these animals."

Create sex-crazed (but sterile) mosquitoes

A number of labs are working to create reverse gene drives to deploy if the gene drives they release go awry. But what if those reverse gene drives fail? Montell is working on other backups.

One idea: create sterile males with high sex drives that will rush to breed with the genetically altered mosquitoes, slowing the spread of the gene drive.

Another: engineer mosquitoes that can be programmed to self-destruct when some external factor, say temperature, hits a certain threshold. This mechanism would ensure that the gene drive mosquitoes die out come summer — and then scientists could release another batch later, if needed.

Related Story: [1212]
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Test, test, and test some more

Excited as they are about gene drives, the scientists don't plan to release any into the wild — at least not yet. (That's why Akbari's lab is secured behind multiple sealed doors. His team boils all water before discarding it, to kill off any stray eggs. They even autoclave their trash.) His DARPA contract specifically forbids the release of gene drives.

Instead, Akbari's team plans to test gene drives in the lab in progressively larger and more ecologically realistic enclosures.

Win over the humans

Even if the safety issues surrounding gene drives are resolved, there's still one big hurdle: humans.

Team member Cinnamon Bloss, an associate professor at the UC San Diego School of Medicine, studies the ethical implications of emerging technologies. And she recognizes that the public is frightened and wary[1313].

"Scientists tend to think if people just understood the technology, they'd accept it," she said. "I don't think that's the case."

Related Story: [33]

Malaria kills a half-million Africans a year. Gene-edited mosquitoes might stop it [33]

The issue is complicated, said Bloss, because it's not feasible to get informed consent from all human residents when a technology affects large regions or even entire continents. Bloss, who has conducted much of her work on human genetics technologies, said she's struggling to find any precedent that brings up the many ethical issues raised by gene drives.

Other teams are grappling with similar issues: In West Africa, a group called Target Malaria[77] — funded with $70 million from the Gates Foundation — is educating residents and building support for a possible future release, years down the road, of gene drive mosquitoes.

The careful thought going into the team's work is praised by Massachusetts Institute of Technology's Kevin Esvelt, a leading gene drive researcher and watchdog who also receives funding from DARPA's Safe Genes project. Esvelt urges researchers to conduct work on gene drives openly and safely — and to involve the public in every step of the process.

The work, he said, is too important to let a slip up in a lab — something he calls "bioerror" — derail the entire field.

"There is an overwhelming moral imperative to do something about malaria," Esvelt said in a recent phone interview. "In the time we have been talking, probably six to eight children have died."

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