Gene drive technology might limit the ability of *Anopheles gambiae* mosquito to transmit malaria to humans.

CDC/James Gathany

How will we keep controversial gene drive technology in check?

By **Kelly Servick** | Jul. 19, 2017 , 4:00 PM

We don't yet know whether the gene-spreading approach known as gene drive, intended to wipe out invasive pests or reduce the spread of insect-borne disease, will work in the wild. But groups of genetic experts are already talking about how to make it stop working if needed.

And at a symposium today in Washington, D.C., organized by the International Life Sciences Institute and the National Academies of Sciences, Engineering, and Medicine, researchers and policy experts discussed how to measure and limit a gene drive strategy's environmental risks. And the U.S. military's research arm announced it will fund efforts by several high-profile genetics labs to develop ways to reverse or limit the spread of an introduced gene if it should have unintended consequences on animals or an ecosystem.

"We're in the business of preventing technological surprise, but also being prepared for the surprises that come from the use of these technologies," said Renee Wegrzyn, a program manager at the Defense Advanced Research Projects Agency (DARPA) in Arlington, Virginia, which today announced seven research teams that will share a $65 million pot of funding under the agency's Safe Genes program over the next 4 years.

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Gene drive works by tinkering with the rules of inheritance, increasing the likelihood a gene will be passed to the next generation. The phenomenon occurs in nature by a variety of mechanisms, but all increase a gene's ability to permeate a population quickly and thoroughly, even if it doesn't carry any survival advantage. Inspired by natural gene drives, researchers have spent decades trying to perfect a system that might endow a population of mosquitoes with a malaria resistance gene, for example, or spread a lethal gene that cuts down a local population of invasive insects or rodents.

Progress surged with the discovery of CRISPR/Cas9 gene editing. By inserting the gene for a new trait alongside genes for a DNA-cutting enzyme and an RNA guide, scientists can prompt a cell to slice out copies of the original, wild-type gene from its chromosomes and use the inserted gene as a template for repair. Its sperm and egg cells will thus bear two copies of the new gene, which radically increases the odds that its offspring will inherit it.

Breeding controversy

But the notion of wiping out an entire species or unleashing a gene that could spread like wildfire through a population has also bred controversy. Evidence that CRISPR gene drives **could be extremely efficient** in lab-reared insects led prominent researchers to urge caution.

Today's meeting included some practical discussion of how gene drive might be contained. Molecular biologist Bruce Hay of the California Institute of Technology in Pasadena presented his lab's research into "high-threshold" gene drives, designed to spread effectively only if individuals with the new gene make up a large fraction of the total population. Wayward migrants thus wouldn't manage to spread the gene widely outside the intended area. And if an

introduced gene had unexpected consequences, researchers might reverse a gene drive by introducing more wild, unmodified individuals to outnumber the new ones. "I think we really can do safe, local, and reversible gene drive," Hay told the audience. "This is not just a fantasy."

But CRISPR brings a whole new set of unknowns. It **might have unpredictable, off-target effects** on the genome, and scientists don't know how to shut it down. Among the seven teams selected for the Safe Genes program are some CRISPR pioneers. Harvard University geneticist George Church will lead efforts to develop more precise gene-editing systems that distinguish between similar sequences. Molecular biologist Jennifer Doudna of the University of California (UC), Berkeley, will, according to DARPA's news release, look for "anti-CRISPR proteins" that could prevent unwanted editing.

Several more projects explicitly focus on gene drive applications: A group at UC Riverside led by molecular biologist Omar Akbari will try to document the genetic diversity of the *Aedes aegypti* mosquito and test ways to limit or reverse gene drives in contained test environments. Biologist John Godwin's team at North Carolina State University in Raleigh will test ways to cut down rodent populations by targeting gene variants present only in invasive communities.

Experts still predict that testing of gene drive in the field **is still years away**. "This is such early days in the field," Wegrzyn told the audience today. "Why don't we build those [control] tools in now, rather than trying to retrofit them into these systems?"

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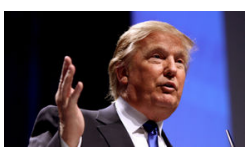

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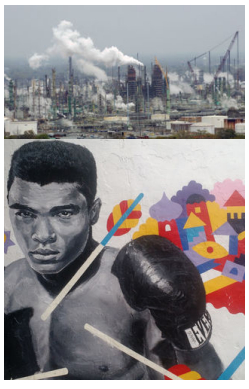

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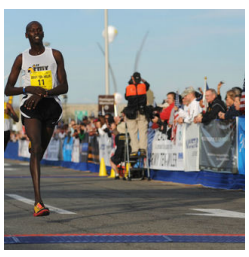

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