A path forward for gene drive technologies

Report from UCSD, J. Craig Venter Institute outlines environmental safety precautions

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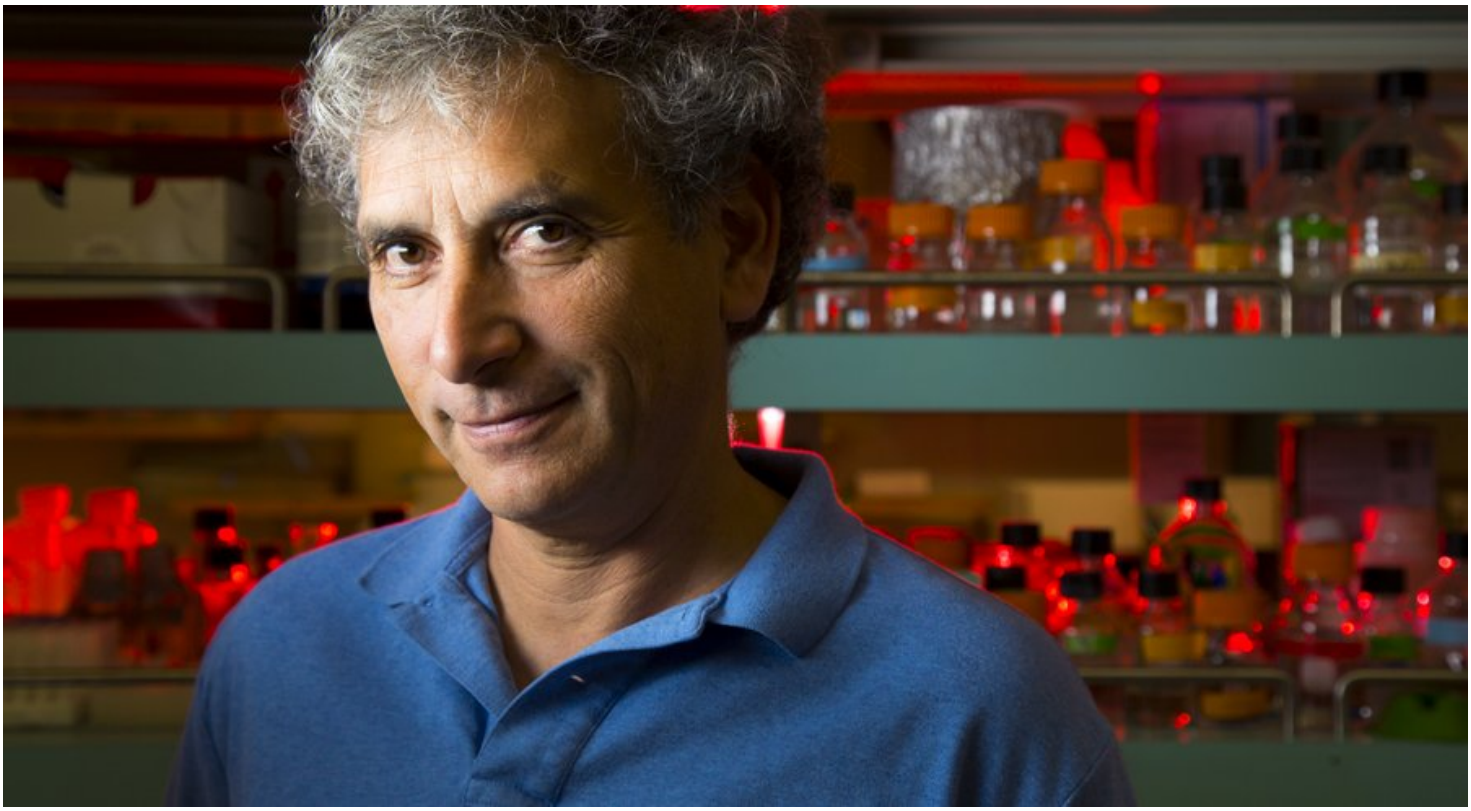

Ethan Bier, scientist and professor of cell and developmental biology at University of California, San Diego, and his team of researchers are using the approach called "gene drive" to make engineered mosquitoes that no longer can infect people with malari — *Howard Lipin / San Diego Union-Tribune*

A new report from UC San Diego and the J. Craig Venter Institute (http://j.mp/genedrivejcvi) outlines a possible path forward to getting the benefit of recent powerful advances in genetic engineering, while minimizing potential harms.

Scientists traditionally relied on the slow and inefficient process of breeding to introduce modified genes into a population. But in recent years, scientists have designed genes that drive themselves into breeding populations in the lab, and potentially in nature. It's called gene drive or more broadly, active genetics (http://www.ncbi.nlm.nih.gov/pubmed/26660392).

A version of this gene drive technology developed at UC San Diego employs a modified gene that copies itself to replace any unmodified counterparts in insects (http://www.sandiegouniontribune.com/news/2015/mar/19/crispr-ucsd-gantz-bier/), the first time this has been demonstrated in animals.

That power could be used for good purposes such as to fight insect-borne diseases, control agricultural pests and improve the yield of crops. Some worry it could also be used for bioterrorism and other evil purposes. But the spread of frightening diseases such as Zika underscores there is a price to pay for not using gene drives.

In January, the J. Craig Venter Institute in La Jolla hosted a workshop to discuss how these challenges can be addressed. Not only researchers, but representatives of government agencies such as the U.S. Food and Drug Administration, the National Institutes of Health and the U.S. Department of State participated.

Earlier this week week, the institute and UC San Diego released a report on the workshop's findings. The report, written for an audience of non-scientists and accessible at j.mp/genedrivejcvi (http://j.mp/genedrivejcvi).

“The task we gave those 30 or so (workshop) participants was how could you move this technology forward,” said Bob Friedman, a workshop organizer and vice president for policy and university relations at JCVI. “It was done with the realization that perhaps you can’t figure out a way to do this safely.”

Indeed, a report released in June (http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=23405) by the National Academies of Sciences, Engineering, and Medicine said gene drive organisms shouldn’t be released into the environment just yet. More research and controlled field trials are needed first.

The UCSD/JCVI report provides one path to getting there.

Among the recommendations:

Researchers should reach out to the public to explain their work, listen to questions and respond to concerns. They should also develop a variety of gene drive technologies with differing characteristics.
Regulators should establish a “single door” for researchers to get regulatory guidance. They should also clarify the roles of each agency so there is no turf conflict. Stages of testing should be created, from basic research to field testing and deployment.
International agencies such as the World Health Organization should review and update guidance and training documents. WHO should also develop risk assessment guidelines for genetically engineered mosquitoes. Other organizations should help in developing regulatory processes. And where release of these modified organisms poses a significant chance of spreading across borders, bilateral or multilateral agreements should be reached first among the concerned parties.

Taking care

This cautious approach dates back to the beginning of biotechnology, with the discovery of recombinant DNA technology in the early 1970s. For the first time, scientists could create DNA in forms that didn’t exist in nature, by merging DNA of different species. DNA sequences from animals can be attached to those from plants example.

Scientists agreed to a worldwide moratorium until a conference could be held to identify dangers and outline safety steps. They stopped work for six months until the conference was held in 1975, in Asilomar. Given the competitive nature of science and its global reach, it was an extraordinary accomplishment.

Today, recombinant DNA technology is no longer controversial when used to make medicines. It’s still opposed by some when used to genetically modify crops, because of unknown effects when unnatural DNA combinations escape into nature.

These crops haven’t been shown to harm anyone, and provide benefits such as resistance to pests and greater level of nutrients. Skeptics say harm could still occur when modified genes leak out of cultivated fields and mix with wild relatives of these crops.

That scenario is more likely to occur with gene drive technologies because they are designed to displace their natural counterparts. Scientists have devised safety measures, such as a reversible gene drive that erases the effect of the original one. But it’s unclear whether the reverse gene drive will work in nature as planned, or perhaps introduce its own complications.

Southern California-born

Workshop participant Omar Akbari of UC Riverside said the report took a comprehensive look at how gene drive technologies are to be evaluated and tested.

“You first test the gene drive systems in the laboratory, then in confined cage trials in a larger laboratory setting, then you move on to a field setting, which is also going to be confined, and then potentially a small island which is isolated to test the efficiency of the different systems ... and eventually move on to a city setting.”

Since Southern California is a hotbed of gene drive research, it was fitting to hold the meeting here, said JCVI’s Friedman.

A groundbreaking study on using gene drive to combat malaria was published last November (http://www.sandiegouniontribune.com/news/2015/nov/23/mosquitoes-bier-valentino-james/) by researchers led by gene drive experts Ethan Bier and Valentino Gantz of UC San Diego along with Anthony James of UC Irvine, an expert on mosquito-borne diseases.

The researchers modified a gene to block the malaria parasite, and successfully inserted it into the mosquito species Anopheles stephensi. This gene isn’t expected to harm the mosquitoes. Moreover, the altered gene spreads far faster than conventional breeding.

Bier and Gantz first introduced the possibility of using gene drives in mosquitoes in another study, published in March of last year (http://science.sciencemag.org/content/348/6233/442). They performed their work in fruit flies, establishing for the first time that a highly efficient approach to gene drive using the popular CRISPR/Cas9 gene editing technology works in animals.

Previous research led by George Church of Harvard Medical School first demonstrated the gene drive technology (http://biorxiv.org/content/early/2015/03/19/013896) in Saccharomyces cerevisiae, a species of yeast used in baking and brewing. Bier and Gantz extended that to animals with their fruit fly work. They've said the technology should work in most diploid

(https://en.wikipedia.org/wiki/Ploidy#Diploid) organisms.

Funding the science

As with humans, mosquitoes have two sets of genes, one inherited from each parent. If a mosquito with a modified gene mates with one with an unmodified counterpart, the modified gene does a search-and-replace on the unmodified ones. So the offspring of that union will have two copies of the gene, not just one. And with each subsequent generation, the number of genes in the population grows exponentially. The method is more than 99 percent effective in changing unmodified genes.

In theory, once such a modified gene establishes itself in a mosquito population in one locale, those mosquitoes could spread the gene to other populations, eventually encompassing all populations of that mosquito species in the world.

UC Riverside's Akbari put in a plug for more research dollars in Southern California to develop and test gene drive technologies.

"Developing these systems takes a lot of effort and time and they are very complex," Akbari said. "So funding the right groups would be important, and opening up larger collaborative efforts.

"In California we have a pretty good team of people working on this goal. We have Bruce Hay at Caltech, Tony James at UC Irvine, Ethan Bier, and me. We're all really close to each other, about an hour's drive of each lab. So I think having a collaborative grant where we could come together and work on these technologies would be really nice, and we don't have that yet."

Reactions

The report offers good advice, said Vanderbilt University's Elizabeth Heitman, co-chair of the committee that performed the National Academies report released in June.

"I am pleased with it," said Heitman, associate professor of medical ethics at Vanderbilt's Center for Biomedical Ethics and Society. "One of the conclusions that our committee reached was that there needs to be a lot of conversation about this ... Responsible science begins with the scientists."

Researchers need to talk among themselves about the best practices for advancing gene drive technologies, taking into account issues likely to develop as well as those of immediate concern, she said.

"This project, having come out of the conversations among researchers themselves in Southern California, really goes a long way to doing that," Heitman said.

The researchers reached many of the same conclusions reflected in the National Academies report, such as calling for the federal government to clarify how existing regulations apply to the new gene drive technologies, she said.

"One of the things new in this workshop report that we didn't address is the key question of how is anyone supposed to know what governance applies to their work. Their call for a single point of entry or single portal .... that's an interesting and potentially valuable recommendation."

Another virtue of the report is that it's written in "accessible" language, Heitman said. "It reads easily and the language is succinct."

Heitman said she has worked previously with some of the members of the committee that drew up the report, such as UC San Diego bioethicists Michael Kalichman and Mary Devereaux.

"These are people whose work I trust, " Heitman said