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Gene Drives Offer New Hope Against Diseases and Crop Pests

By Nicholas Wade
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Biologists in the United States and Europe are developing a revolutionary genetic technique that promises to provide an unprecedented degree of control over insect-borne diseases and crop pests.

The technique involves a mechanism called a gene drive system, which propels a gene of choice throughout a population. No gene drives have yet been tested in the wild, but in laboratory organisms like the fruit fly, they have converted almost the entire population to carry the favored version of a gene.

Gene drives "could potentially prevent the spread of disease, support agriculture by reversing pesticide and herbicide resistance in insects and weeds, and control damaging invasive species," a group of Harvard biologists wrote last year in the journal eLIFE.

A much discussed application of gene drives would help rid the world of pest-borne diseases like malaria, dengue fever and Lyme disease.

A gene drive designed to render a population extinct is known as a crash drive. A crash drive being developed for mosquitoes consists of a gene engineered into the Y chromosome that shreds the X chromosome in the cells that make the mosquito's sperm, thus ensuring that all progeny are male. Unless the drive itself is damaged through mutation, the number of females would be expected to dwindle each generation until the population collapses.

Biologists led by Andrea Crisanti and Tony Nolan at Imperial College London reported this month in the journal Nature Biotechnology their development of mosquitoes with gene drives that disrupt three genes for female fertility, each of which acts at a different stage of egg formation. Because the female mosquitoes are infertile only when a copy is inherited from both parents, the gene drives would be thoroughly disseminated through a population before taking their toll. They could "suppress mosquito populations to levels that do not support malaria transmission," the authors wrote.

The mosquitoes are not yet ready for release. Because natural selection will heavily favor any wild mosquitoes that acquire resistance to the gene drives, the researchers need to prevent such resistance from arising. One approach would be to target two or three sites in the same fertility gene, giving natural selection a much higher barrier to overcome.

Another approach is to endow mosquitoes with genes that make them resistant to the malaria parasite. Last month, biologists at the Irvine and San Diego campuses of the University of California reported introducing a gene drive with a cargo of malaria-resistance genes into mosquitoes. Such genes, if successfully propelled throughout a wild mosquito population, would render a region free of the malarial parasite, which could no longer spread via mosquito bites.

In agriculture, biologists envisage gene drive systems that could destroy or modify insect pests, and reverse genetic resistance to pesticides in species that had acquired it. Gene drives may also be used to squelch populations of harmful invasive species like rats.

Gene drives have two major technical limitations. They will work only in sexually reproducing species, which effectively rules out bacteria. Second, they spread significantly only in species that reproduce quickly, meaning they would be of no practical use in elephants or people.

Because no gene drive organisms have yet been released, biologists cannot yet assess how well they will work and what degree of risk they may pose.

The issue of risk, rather than effectiveness, has dominated discussion for the last several months. Biologists are eager to see the benefits of the technology realized, and wish to avoid any consequences that might erode public confidence or get gene drive systems off on the wrong foot, as has happened with genetically modified foods. Several articles published in the last few months propose specific safety precautions and call for full public discussion of gene drives, along with speedy regulation.

Because a single escaped organism carrying a gene drive system "could alter a substantial fraction of the wild population with unpredictable ecological consequences, the decision to deploy a gene drive must be made collectively by society," a group of scientists, led by George M. Church of Harvard Medical School, said in Nature Biotechnology last month.

A Gene Editing Advance

A gene drive refers to any process that biases the usual pattern of Mendelian inheritance, in which a gene has a 50 percent chance of making it to the next generation. Several gene drive processes exist in nature but are hard to manipulate.

In 2003, Austin Burt, a biologist at a branch of Imperial College London in Sunninghill, England, essentially laid out the whole theory of gene drives and their possible applications based on natural gene drives known as homing endonucleases. "Clearly, the technology described here is not to be used lightly," he concluded. "Given the suffering caused by some species, neither is it obviously one to be ignored."

James Gathany/Centers for Disease Control and Prevention

An endonuclease is an enzyme that cuts at a specific site the DNA of the chromosome with which its gene's own chromosome is paired. Because DNA breaks are very threatening to genome integrity, cells rush to repair them, often by using the other chromosome of a pair as a template. In doing so, they copy the gene for the endonuclease into the joint made between the two broken ends of the cut chromosome. If this repair occurs in a germ line cell, both eggs and sperm will carry the endonuclease gene together with any cargo genes that genetic engineers may have attached to it.

Because it is hard to change the natural site at which a homing endonuclease cuts DNA, Dr. Burt's proposed gene drive systems could not easily be put into practice. All that changed three years ago with the invention of Crispr-Cas9 gene editing. The technique is based on a natural system that evolved in bacteria as a defense against invading viruses.

The bacteria store DNA samples from these invasive viruses in a DNA library, called Crispr, that is part of their genome. When a virus attacks, endonucleases such Cas9 (Cas stands for Crispr-associated) are primed by the Crispr library to cut viral DNA of the same sequence.

After recovering from their amazement that organisms as small as bacteria possessed an adaptive immune system, biologists realized that they could take over the Cas9 endonuclease and make it cut DNA at any site of their choosing by providing it with a synthetic guide sequence instead of one from the Crispr library. The use of Crispr-Cas9 for genome editing was first published in 2012 by Jennifer Doudna of the University of California, Berkeley, and Emmanuelle Charpentier, now at the Max Planck Institute for Infection Biology in Berlin. But Feng Zhang, of the Broad Institute in Cambridge, Mass., was the first to file a patent, which Berkeley lawyers are challenging.

The Crispr-Cas9 technique gives biologists unprecedented power to edit DNA. With the ability to cut DNA at a specific site, they can let the cell's DNA repair machinery paste in new sequences, usually a gene of interest, in the process of annealing the two cut ends of the DNA molecule.

Uncertain Ecological Effect

In April, two biologists at the University of California, San Diego, Valentino M. Gantz and Ethan Bier, caused a stir with a gene drive system that carried a gene for albinism into laboratory fruit flies. Their drive was astonishingly efficient: Within two generations, some 97 percent of the fruit flies had been rendered pale by the mutation. Although gene drives may not spread so quickly in natural populations, which are more variable, the experiment demonstrated the vast potential of the method for modifying pest populations.

With the Crispr-Cas9 technique, laboratories all over the world, including many with no experience in confining potentially hazardous organisms, could now generate gene drive systems. A flurry of articles urging caution began to appear from other biologists, who noted that if a fruit fly with a gene drive system escaped

from a laboratory, it could affect fruit flies worldwide. In an article in Science in August, Dr. Church and others recommended steps for avoiding accidental release, including having more than one confinement strategy. With strong safeguards, they wrote, “we hope to build a foundation of public trust for potential future applications.”

A harder issue than containment is how to assess the ecological effect of gene drive systems. Even something as apparently benign as eliminating mosquitoes could have ecological effects “because mosquitoes interact with other species,” said Kevin Esvelt, a biochemist at Harvard. Dr. Burt, however, noted in an interview that there are more than 800 species of mosquitoes in Africa, and eliminating the group of species that carries malaria was “unlikely to have a cascading effect,” even though the possibility should be looked at. Dr. Burt said he is also unable to think of any disadvantage to humans or to mosquitoes in eliminating the malaria parasite that preys on both.

Another concern is that a gene drive system may have unintended consequences, by making its target species more pathogenic or by spreading to other species. A suggested approach to this problem is to proceed in careful stages, releasing a gene drive system first in a caged population of target insects, and then in an isolated habitat like an island, if possible, before any major release into the wild.

A Plan for Backing Out

It may seem that once a gene drive system is released, it can never be recalled. But this may not be entirely true. Biologists are working on the concepts of “reversal drives” and “immunizing drives.” A reversal drive would cut out an errant drive and restore the target organism almost to its previous state. An immunizing drive would attack and pre-emptively change the DNA sequence targeted by the rogue drive.

A group of biologists proposed last year that before any gene drive system is released into the environment, its designers should prepare a standby reversal drive. But critics suggested that the availability of reversal drives might make people overconfident — and in any case, they might not work as advertised.

“If your first drive doesn’t work as intended, are you sure your second drive will work?” Dr. Burt said.

The power over nature that gene drive systems promise is a responsibility that surely no biologist takes lightly. But people already exert control over nature with a slew of toxic pesticides and herbicides that are a heavy burden on the environment. Gene drive systems offer a much more specific and less harmful approach, at least in principle, toward attaining the same goals.

Risks aside, there is no guarantee that gene drives will work as well in the field as they do in the laboratory. Wild populations of mosquitoes, say, may have much genetic variation at the target site of a gene drive system. Those with a variant target site would escape the drive and might have a selective advantage over it.

Resistance will arise, as to any change that reduces a species’s fitness. But biologists could respond by releasing many drives into a wild population, each assigned to a different target. Even if a drive comes to dominate a whole population, biologists expect it will eventually be eliminated by fitter genes. But a response would be to keep releasing new drives.

“I think we’ll be able to make this work,” Dr. Burt said.

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