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Driving Out Pests with Genetic Engineering

by Timothy Erick | May 2018

If you keep fruit in the house, you have probably encountered fruit flies of the genus *Drosophila*. There are roughly 1,500 *Drosophila* species, most of which lay eggs on rotten fruit. Thus, once these tiny flies start buzzing around your fruit bowl, it is time to throw those bananas away. However, one particular species, *Drosophila suzukii*, lays eggs inside healthy fruit, which ruins the fruit before it can be eaten. Since entering the United States roughly 10 years ago, *D. suzukii* has had a devastating impact on the West Coast fruit industry. Thus, scientists and farmers have been trying desperately to figure out the best way to combat this pest.

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Insecticides provide only temporary protection against *D. suzukii* infestation. Genetic manipulation, on the other hand, offers the possibility of long-term population control. One potential strategy is to introduce harmful genetic mutations into wild *D. suzukii* populations. The main challenge is to get the mutation to spread, since harmful mutations tend to be self-limiting: natural selection will usually eliminate them. To overcome this problem, researchers at the University of California recently made something called a gene drive that was designed to propagate rapidly through *D. suzukii* populations in to introduce harmful genes that would kill off wild *D. suzukii*. The study was published in the *Proceedings of the National Academy of Sciences (PNAS)*, with Omar S. Akbari as the corresponding author.

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Spoiled Fruit

We like to think of humans as the dominant species on Earth. It is simultaneously humbling and frustrating when smaller, less intelligent organisms like insects take us down a peg. Mosquitoes, for instance, feed on our blood and infect us with disease-causing microorganisms. Other insects may not harm us directly, but instead attack our supply lines. A number of insect species lay their eggs in a variety of food crops. The resulting larvae eat the crops, spoiling them in the process. Collectively, insects ruin about a fifth of the world's food crops each year.

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***D. suzukii*, which is native to Japan, made its way to Hawaii in the 1980s, and eventually touched down in California in 2008. Since then, *D. suzukii* has spread not only throughout California but also across Oregon and Washington State. This particular fruit fly pokes a hole through the skin of ripening cherries, raspberries and other soft-skinned fruits, and lays its eggs inside. The hatching eggs ruin the fruit before it can be harvested.**

Invasive species are often particularly troublesome in this respect. When introduced to a new area, insects can spread like wildfire and disrupt the entire ecosystem. For instance, the spotted wing fruit fly, *D. suzukii*, which is native to Japan, made its way to Hawaii in the 1980s, and eventually touched down in California in 2008. Since then, *D. suzukii* has spread not only throughout California but also across Oregon and Washington State. This particular fruit fly pokes a hole through the skin of ripening cherries, raspberries and other soft-skinned fruits, and lays its eggs inside. The hatching eggs ruin the fruit before it can be harvested. Fruit cultivation is an important industry in the West Coast states, so the *D. suzukii* invasion has had a massive economic impact. Between 2009 and 2014, *D. suzukii* destroyed nearly $40 million worth of raspberries in California alone!

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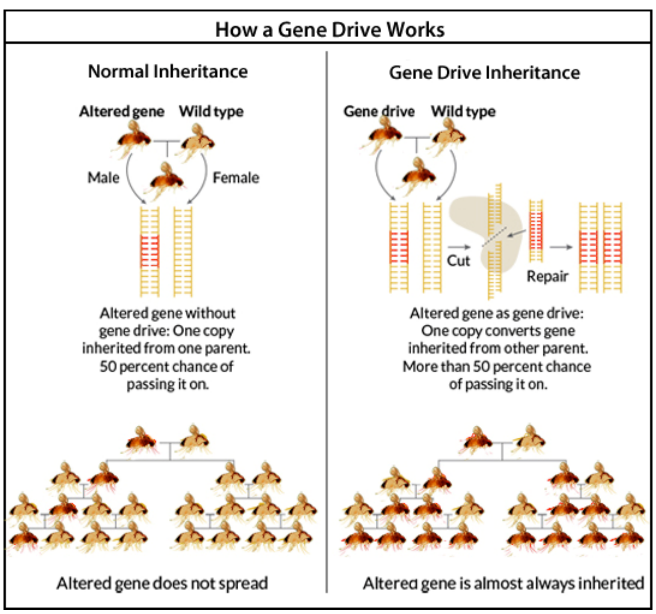
To prevent further losses, scientists and farmers are scrambling to protect fruit crops from *D. suzukii*. So far, the standard tactic of spraying crops with insecticides has proven only moderately effective. Most of the chemicals that kill *D. suzukii* soon lose their potency, which necessitates repeated sprayings. Fruit flies also reproduce rapidly, allowing them to quickly evolve resistance to insecticides. A different approach would be useful.

Scientists have already developed genetic techniques to reduce or eliminate populations of harmful insects. For instance, the sterile insect technique involves releasing sterile males into the wild, which then compete with normal males for mating opportunities. More recently, scientists have used genetic engineering technologies to produce male insects with germline mutations that only kill females. The modified males mate with normal females, and any resulting female embryos die before birth. Unfortunately, neither of these tactics has been tested in *D. Suzukii*. Moreover, these techniques require constant production and release of modified insects, which takes a lot of effort and money.

Toxic Genes

Akbari and his team of researchers sought to achieve self-perpetuating genetic control over wild *D. suzukii* populations. They did this by tailoring a gene drive to *D. suzukii*. A gene drive is a genetic sequence that forces its own inheritance, and thus spreads rapidly in sexually reproducing organisms. They made a particular type of gene drive called a *Medea* element.



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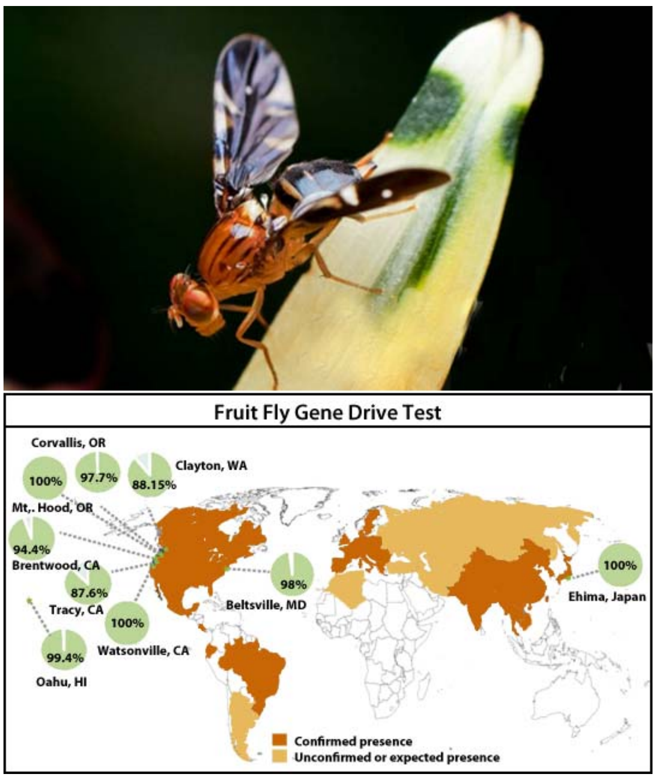
The researchers based their gene drive—the so-called *Medea* element—on a gene called *myd88*. In normal flies, pregnant females express the *myd88* gene and deposit it into the embryos. The gene drive works at the maternal and embryonic level. In essence, the alterations the researchers made disabled the gene from working at the maternal level but enabled it to work at the embryonic level. Pregnant females that have the gene drive are prevented from passing *myd88* on to their embryos the normal way. This means that all embryos of *Medea*-bearing mothers should die—and will die unless they inherit the *Medea* element. However, embryos that inherit the *Medea* element regain a functional copy of *myd88* with the element. So *Medea* takes away a necessary gene at the maternal level, but still manages to provide it to the embryos. In this way, *Medea* makes itself necessary for survival, and thus quickly spreads through a population.

The health of flies that inherit the *Medea* element will not be affected by the element itself. Rather, the researchers are hoping to use *Medea* as a delivery system to introduce additional genes to the flies that cause death under certain conditions. For instance, they could introduce a gene that makes the flies more vulnerable to a certain insecticide chemical, or that causes them to die when the weather gets hot. But to use *Medea* for such purposes, the researchers first needed to see if it would spread through a wild *D. suzukii* population as intended.



Top: Lee Chee Keong/EyeEm/Getty Images; Bottom: Buchman, A., et al./*PNAS*/M. Bank

To test their gene drive, the researchers mated *Medea*-heterozygous *D. suzukii* females with wild-type (normal) males for several generations. Six generations of these crosses produced 97.7% *Medea*-positive offspring. In contrast, a normal gene would be inherited by only 50% of offspring. However, an ideal *Medea* element would reach 100% inheritance in a population; 97.7% indicated the presence of resistance. The researchers tested the *Medea* element in nine different *D. suzukii* populations from around the world. Some populations inherited the drive at 100%, whereas for others the rate was lower than 90%.

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100%, whereas for others the rate was lower than 90%. This suggested that some wild populations have natural resistance to *Medea* inheritance.

The Resistance

To try to understand the mechanisms of Medea resistance, the researchers sequenced the *myd88* gene in the different *D. suzukii* populations. They observed a variety of *myd88* mutations, some of which corresponded to lower *Medea* inheritance rates. Resistant populations featured mutations that inhibited the anti-*myd88* toxin gene, helping to explain the decreased inheritance of the *Medea* element in these flies. Hence, the researchers concluded that natural genetic variation could be a barrier to *Medea* spread.

The team wanted to learn more about the extent to which natural resistance might prevent the *Medea* element from spreading in the wild. They set up different ratios of *Medea*-bearing and wild-type males with wild-type females in order to simulate the release of *Medea*-bearing males into the wild. They then observed the inheritance of *Medea* over several generations. When the ratio of *Medea*-bearing to wild-type males was 50% or lower, the *Medea* sequence disappeared from the population after nine generations. In fact, the researchers found that no less than a 90% ratio of *Medea*-bearing males to wild-type males was necessary for *Medea* to become established. The researchers also performed mathematical modeling, which confirmed that a release of 90% *Medea*-bearing males into an area would be necessary for *Medea* to gain a foothold there. Even then, the gene drive would be eliminated from the population after roughly 20 generations. These results indicated that a gene drive can remain susceptible to natural selection. Tailoring the *myd88* toxin genes to different *D. suzukii* populations might help the gene drive spread more easily.

Eventually, the researchers hope to use a *Medea* gene drive to introduce additional genes to kill off *D. suzukii*. The goal of this study was merely to determine if a *Medea* gene drive could be made to spread through wild populations. The researchers mostly succeeded, although they encountered some heavy resistance from Mother Nature. Natural selection is a powerful force; although we are learning how to temporarily circumvent it, we cannot yet fully overcome it.

Discussion Questions

Why would natural selection favor resistance to gene drives like the *Medea* element?

Can you think of any natural genetic sequences that are similar to the human-made *Medea*?

Journal Abstracts and Articles

(Researchers' own descriptions of their work, summary or full-text, on scientific journal websites.)

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Keywords

Drosophila suzukii, *D. suzukii*, gene drive, *Medea*, *myd88*, Omar S. Akbari

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