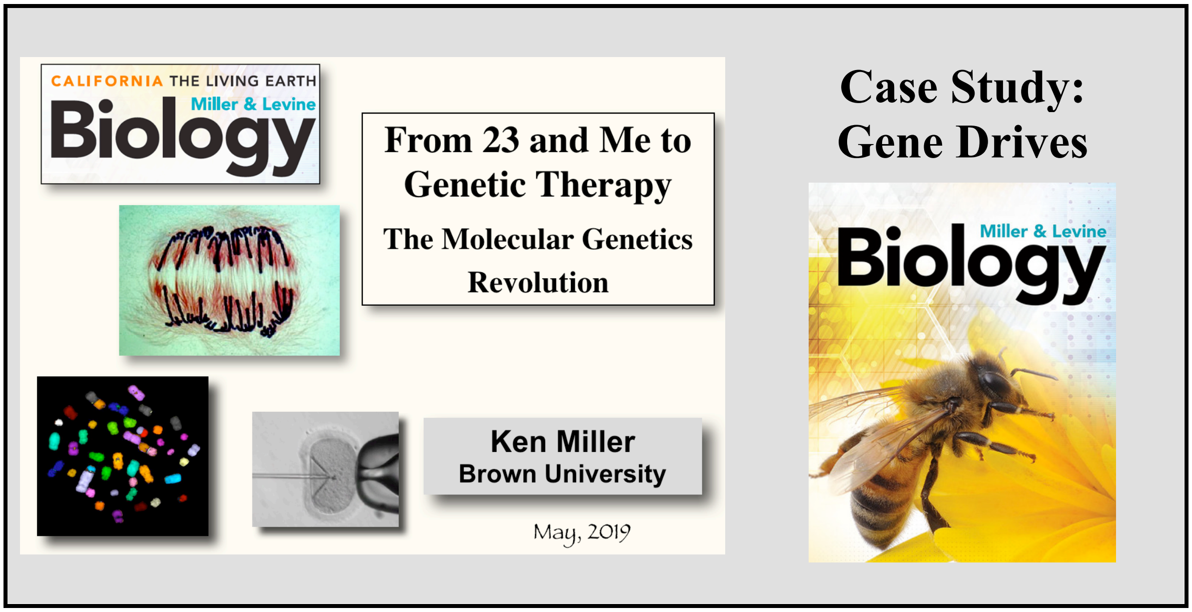
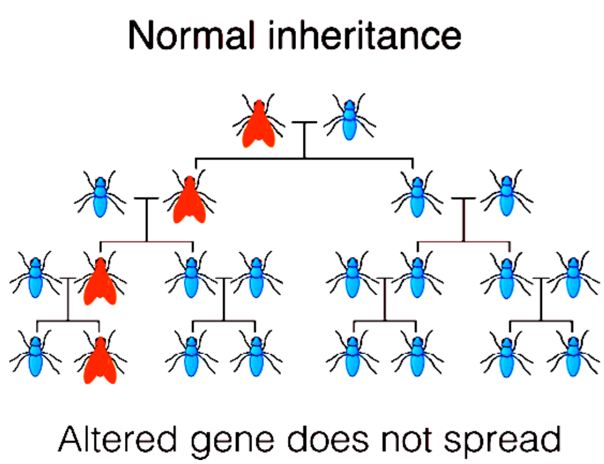


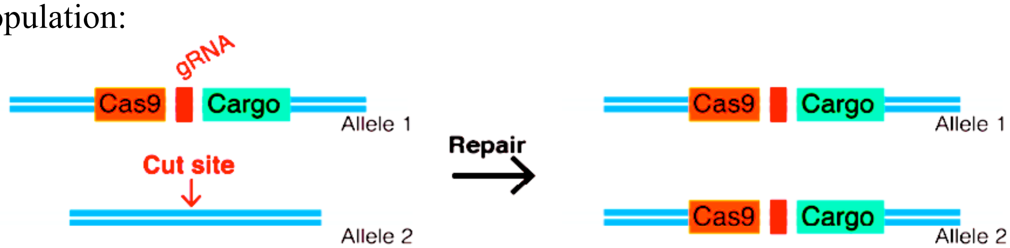
Gene Drives:

For decades, biologists have dreamed of a way to control serious, disease-carrying pests such as mosquitoes that would not involve poisons, chemical pesticides, or other drastic techniques. One longstanding idea would be to breed defective genes into a population in the hopes of weakening or even eliminating the pest. Unfortunately, such ideas are limited by the usual rules of Mendelian genetics, shown here:

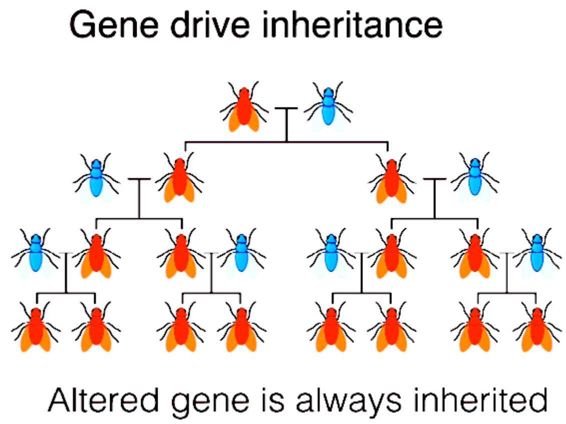


Once a gene is inserted into a population, there is no way to ensure its spread, and if it places the organism at a disadvantage for survival or reproduction, natural selection will gradually eliminate it.

CRISPR, however, makes it possible to insert a construct into a population that actually engineers its own spread through the population:



The technique is simple enough. A construct is inserted into one chromosomes that actually targets the other chromosome in a diploid cell, then cuts, and inserts a copy of itself in the homologous chromosome. As a result, the "cargo" gene, which may weaken, sterilize, or even kill the host, gradually spreads through the population. Once the gene drive has gone to work, it alters the genetic composition of the host population in a way that enables it to be controlled, altered, or even eliminated. One might hope, for example, to introduce a gene drive in the mosquitoes that spread malaria that might make it impossible for the *Plasmodium* parasite to survive within them, breaking the life cycle of the microbe. More children are killed yearly by malaria than any other infectious disease, which means that controlling or eliminating it should be one of the highest public health priorities, worldwide.



Proof of Concept

Experiments in a number of laboratories have shown that gene drives do indeed work in captive populations of *Anopheles*, the mosquito that carries malaria. One powerful strategy is to use the drive to spread a gene that suppresses the development of female mosquitoes. In one recent laboratory study, the gene drive construct spread through the insects so rapidly that the entire population collapsed within 8 generations, unable to produce enough female mosquitoes to sustain itself.

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Study: Gene Drive Wipes Out Lab Mosquitoes

No females were produced after eight generations, causing the population to collapse.

Sep 24, 2018
ASHLEY YEAGER

802 161

A gene drive has successfully caused the collapse of a malaria-carrying mosquito population in the lab, researches report today (September 24) in *Nature Biotechnology*. This is the first time a gene drive—a genetic element that ensures its own inheritance—has caused a population of mosquitoes to self-destruct, a result that holds promise for combating malaria.

ABOVE: *Anopheles gambiae* mosquito
WIKIMEDIA, CDC/JAMES GATHANY

"This breakthrough shows that gene drive can work, providing hope in the fight against a disease that has plagued mankind for centuries," study coauthor Andrea Crisanti, a molecular parasitologist at Imperial College London, says in a university statement.

The hope would be to released laboratory-engineered mosquitoes into heavily infected areas, suppressing or even eliminating the insect vectors and preventing the spread of malaria. Similar techniques could be used against other insect-borne diseases, such as Zika virus and dengue fever.

Should We Go Ahead?

Maybe. But consider this excerpt from Scientific American (9/14/18) describing some of the issues that should be addressed before releasing this promising genetic tool into the wild:

https://www.scientificamerican.com/article/gene-drive1/

> The Defense Advanced Research Projects Agency (DARPA) is among the investors who are enthusiastic about the technology. It has poured $100 million into gene-drive research aimed at fighting mosquito-borne disease and invasive rodents. The Bill & Melinda Gates Foundation has invested $75 million in a research consortium working on gene drive to combat malaria.
>
> Despite all the promise, gene drives raise many concerns. Might they inadvertently jump to, and disrupt, other species in the wild? What are the risks of eliminating selected species from an ecosystem? Could malevolent parties use gene drives as a weapon to, say, interfere with agriculture?
>
> In an effort to avoid such dire prospects, one team has invented a switch that must be turned on by delivery of a particular substance before the gene drive will work. In parallel, multiple groups of scientists are working on protocols to guide progression through each stage of gene-drive testing. In 2016, for instance, the U.S. National Academies of Sciences, Engineering, and Medicine reviewed the research and made recommendations for responsible practices. And in 2018 a large, international working group laid out a road map for handling research from lab studies through releases in the field. The group (some of whose meetings were attended by observers from DARPA, the Gates Foundation or other agencies) modeled its recommendations on gene drive's use to control malaria in Africa, where, it says, the public health benefit would probably be greatest.
>
> Beyond limiting the risks of the technology itself, many investigators also want to avoid incidents and missteps that could lead to public or policy backlash. In a 2017 essay about the potential use of gene drive for eliminating pest mammals, Kevin M. Esvelt of the Massachusetts Institute of Technology and Neil J. Gemmell of the University of Otago in New Zealand fretted that an international incident could set back research by a decade or more. "For malaria alone," they predicted, "the cost of that delay could be measured in millions of otherwise preventable deaths."

Questions for discussion:

Are CRISPR Gene Drives Without Risk?

While CRISPR constructs can be engineered to target a highly specific region of DNA, as these laboratory experiments have shown, there is also a possibility of so-called “off target” effects. In other words, at a certain very low frequency, the system may cause unintended DNA breaks which may be repaired in unpredictable ways. Should we hold back on releasing such tools into the wild, knowing that if something does go wrong along these lines, at present there would be no way to “recall” them from nature?

The genome editor CRISPR can be used to engineer female lab mice that have increased odds of passing down a specific gene to offspring. ISTOCK.COM/GORKEMDEMIR

‘Gene drive’ passes first test in mammals, speeding up inheritance in mice

By Jon Cohen | Jul. 10, 2018 , 1:50 PM

Are they Truly Safe and Effective?

We know that gene drives work in laboratory populations. However, in the absence of a field test, we cannot be sure that they will have the intended effect in a wild population. Are they additional tests that should be done before we conclude that genetically engineered mosquitoes should be released into the wild?

Could Resistance be a Problem?

Virtually every insect and pest control system ever implemented has eventually resulted in the evolution of resistance within the population for which control has been sought. Is that a possibility here, too? And if resistance to the gene drive mechanism does emerge, what form might it take?

Could There be Ecological Side Effects?

Although we rightly regard mosquitoes (and rats, for that matter) as disease-carrying pests, they are nonetheless part of the ecosystems in which they reside and play a part, as all organisms do, in food webs and ecosystem goods and services. Can we be confident that a highly-effective gene drive would not have unexpected ecological consequences for other organisms that might depend upon the very pests we seek to eliminate?