

Easy DNA Editing Will Remake the World. Buckle Up.

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Any gene typically has just a 50–50 chance of getting passed on. Either the offspring gets a copy from Mom or a copy from Dad. But in 1957 biologists found exceptions to that rule, genes that literally manipulated cell division and forced themselves into a larger number of offspring than chance alone would have allowed.

A decade ago, an evolutionary geneticist named Austin Burt proposed a sneaky way to use these “selfish genes.” He suggested tethering one to a separate gene—one that you wanted to propagate through an entire population. If it worked, you’d be able to drive the gene into every individual in a given area. Your gene of interest graduates from public transit to a limousine in a motorcade, speeding through a population in flagrant disregard of heredity’s traffic laws. Burt suggested using this “gene drive” to alter mosquitoes that spread malaria, which kills around a million people every year. It’s a good idea. In fact, other researchers are already using other methods to modify mosquitoes to resist the *Plasmodium* parasite that causes malaria and to be less fertile, reducing their numbers in the wild. But engineered mosquitoes are expensive. If researchers don’t keep topping up the mutants, the normals soon recapture control of the ecosystem.

Push those modifications through with a gene drive and the normal mosquitoes wouldn’t stand a chance. The problem is, inserting the gene drive into the mosquitoes was impossible. Until Crispr-Cas9 came along.



Emmanuelle Charpentier did early work on Crispr. Baerbel Schmidt

Today, behind a set of four locked and sealed doors in a lab at the Harvard School of Public Health, a special set of mosquito larvae of the African species *Anopheles gambiae* wriggle near the surface of shallow tubs of water. These aren't normal *Anopheles*, though. The lab is working on using Crispr to insert malaria-resistant gene

drives into their genomes. It hasn't worked yet, but if it does ... well, consider this from the mosquitoes' point of view. This project isn't about reengineering one of them. It's about reengineering them all.

Kevin Esvelt, the evolutionary engineer who initiated the project, knows how serious this work is. The basic process could wipe out any species. Scientists will have to study the mosquitoes for years to make sure that the gene drives can't be passed on to other species of mosquitoes. And they want to know what happens to bats and other insect-eating predators if the drives make mosquitoes extinct. "I am responsible for opening a can of worms when it comes to gene drives," Esvelt says, "and that is why I try to ensure that scientists are taking precautions and showing themselves to be worthy of the public's trust—maybe we're not, but I want to do my damndest to try."

Esvelt talked all this over with his adviser—Church, who also worked with Zhang. Together they decided to publish their gene-drive idea before it was actually successful. They wanted to lay out their precautionary measures, way beyond five nested doors. Gene drive research, they wrote, should take place in locations where the species of study isn't native, making it less likely that escapees would take root. And they also proposed a way to turn the gene drive off when an engineered individual mated with a wild counterpart—a genetic sunset clause. Esvelt filed for a patent on Crispr gene drives, partly, he says, to block companies that might not take the same precautions.

Within a year, and without seeing Esvelt's papers, biologists at UC San Diego had used Crispr to insert gene drives into fruit flies—they called them "mutagenic chain reactions." They had done their research in a chamber behind five doors, but the other precautions weren't there. Church said the San Diego researchers had gone "a step too far"—big talk from a scientist who says he plans to use Crispr to bring back an extinct woolly mammoth by deriving genes from frozen corpses and injecting them into elephant embryos. (Church says tinkering with one woolly mammoth is way less scary than messing with whole populations of rapidly reproducing insects. "I'm afraid of everything," he says. "I encourage people to be as creative in thinking about the unintended consequences of their work as the intended.")

Ethan Bier, who worked on the San Diego fly study, agrees that gene drives come with risks. But he points out that Esvelt's mosquitoes don't have the genetic barrier Esvelt himself advocates. (To be fair, that would defeat the purpose of a gene drive.) And the ecological barrier, he says, is nonsense. "In Boston you have hot and humid summers, so sure, tropical mosquitoes may not be native, but they can certainly survive," Bier says. "If a pregnant female got out, she and her progeny could reproduce in a puddle, fly to ships in the Boston Harbor, and get on a boat to Brazil."

These problems don't end with mosquitoes. One of Crispr's strengths is that it works on every living thing. That kind of power makes Doudna feel like she opened Pandora's box. Use Crispr to treat, say, Huntington's disease—a debilitating neurological disorder—in the womb, when an embryo is just a ball of cells? Perhaps. But the same method could also possibly alter less medically relevant genes, like the ones that make skin

wrinkle. “We haven’t had the time, as a community, to discuss the ethics and safety,” Doudna says, “and, frankly, whether there is any real clinical benefit of this versus other ways of dealing with genetic disease.”

Researchers in China announced they had used Crispr to edit human embryos.

That’s why she convened the meeting in Napa. All the same problems of recombinant DNA that the Asilomar attendees tried to grapple with are still there—more pressing now than ever. And if the scientists don’t figure out how to handle them, some other regulatory body might. Few researchers, Baltimore included, want to see Congress making laws about science. “Legislation is unforgiving,” he says. “Once you pass it, it is very hard to undo.”

In other words, if biologists don’t start thinking about ethics, the taxpayers who fund their research might do the thinking for them.

All of that only matters if every scientist is on board. A month after the Napa conference, researchers at Sun Yat-sen University in Guangzhou, China, announced they had used Crispr to edit human embryos. Specifically they were looking to correct mutations in the gene that causes beta thalassemia, a disorder that interferes with a person’s ability to make healthy red blood cells.

The work wasn’t successful—Crispr, it turns out, didn’t target genes as well in embryos as it does in isolated cells. The Chinese researchers tried to skirt the ethical implications of their work by using nonviable embryos, which is to say they could never have been brought to term. But the work attracted attention. A month later, the US National Academy of Sciences announced that it would create a set of recommendations for scientists, policymakers, and regulatory agencies on when, if ever, embryonic engineering might be permissible. Another National Academy report will focus on gene drives. Though those recommendations don’t carry the weight of law, federal funding in part determines what science gets done, and agencies that fund research around the world often abide by the academy’s guidelines.

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