Die Gene, die ich rief

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The genes that I called

Scientists want to eradicate Malaria or Zika with the help of Gene Drives. This new technology could turn entire ecosystems upside down. Evolution becomes controllable.

BY JULIA GROSS

What if it was possible to eradicate malaria forever within the next five years? If we managed to dramatically reduce diseases like Dengue, yellow fever or Zika? What if we were able to start giving up pesticides in just five years, and save many endangered species, too?

These are not fantasies, but the serious projectiona of biochemist Kevin Esvelt, who's working at Harvard and MIT. Esvelt co-discovered the technology that may possibly make all of this reality: the "Gene Drive", which in German means something like "genetic impulse" or "swing".

"Gene drives are fundamentally different from everything we are able to do today. They can change whole ecosystems", says Esvelt. "Our society has never been faced with such a powerful, disrupting technology." With gene drives it becomes possible to control evolution, bypassing the Mendelian laws most people remember from their biology classes.

According to Mendel's doctrine the offspring of organisms that reproduce sexually usually receive one set of chromosomes from the father and one from the mother. Both sets contain blueprints for the same body features, for example eye color - but in different variants. Depending on what variations are combined in the fertilized egg, some offspring might inherit a feature from the mother, some from the father, and some even from of the grandparents.

With a synthetic gene drive it's different. The technology turbo-charges the inheritance patterns of manipulated genes. As a consequence almost all descendants carry only one, desired variant of a gene. The same applies to all following generations and therefore sooner or later for the entire population.

Just several hundred mosquitoes engineered with a gene drive would, for example, be enough to change an entire mosquito population typically living in or next to an African village. This is a huge difference to the use of irradiated, sterile insects or mosquitoes that have been genetically modified the traditional way. These need to be released in large quantities again and again in order to influence the gene pool of a population.

Introducing gene drives into living organisms became feasible because of the discovery of genome editing with CRISPR/Cas 9, a revolutionary method to precisely cut and replace parts of DNA in cells. To engineer a gene drive, scientists edit the desired gene in sperm cells or eggs and simultanously insert CRISPR / Cas-9 blueprint into their genomes. It's like placing the hammer next to the nail. Once the egg is fertilized, the Cas-9 protein cuts the unwanted gene variant from the second set of chromosomes. The cell's own repair mechanism fills the gap by copying the first, the manipulated gene. An organism growing from that fertilized egg ends up with two identical copies of the altered gene, which are now also being passed to all its descendants. Every time one of them reproduces and thus a different gene variant ist added during fertilization, the CRISPR/Cas-9 system is going to remove it.

The idea of gene drives has been circulating in the scientific community for decades. But the proper tool to do it has been missing until CRISPR became available. And like all things connected with CRISPR, gene drive research is developing rapidly. Kevin Esvelt and some of his Harvard colleagues first suggested using CRISPR for gene drives in July 2014. Only eight months later two biologists did just that with drosophila, fruit flies. In December 2015 and January 2016 research groups from UC Irvine and Imperial College published the introduction of a gene drive into Anopheles, the bug that spreads malaria.

Anthony James and his co-workers from southern California created mosquitoes that are no longer capable of transmitting Plasmodium, the parasite that causes malaria. Austin Burt and Andrea Crisanti from the UK developed an Anopheles strain that reproduces far less successful than the wild type. „I don't think that this will eliminate all mosquitoes in the world or that this is the magic weapon against malaria", points out Anthony James. „But gene drives may be one of many tools to eradicate malaria. For example, in regions where the disease has been pushed back successfully, it might help to keep it that way."

As for the question who will be the first to establish a gene drive in Aedes aegypti and Aedes albopictus, the tiger mosquitoes which not only transmit Zika, but also epidemiologically far more important diseases like yellow fever, dengue or chikungunya, the race is on. "We could probably have a gene drive in Aedes within twelve months", says Anthony James. "However, this would have to be tested in the laboratory first, followed by cage trials in the field. What happens after that depends on the regulatory environment. "

Mosquitoes are by no means the only creatures targeted by researchers. "I'm sure it's possible to introduce a gene drive in pretty much any species with this method," says Kevin Esvelt. "In men or elephants, with their long generation times, it just doesn't make any sense at all. But otherwise?" Mice and rats are probably not a problem. And just recently Esvelt talked with scientists from Australia about eradicating cane toads, an invasive species threatening the unique wildlife down under.

The list is endless. Invasive species, and Aedes mosquitoes count as one in most parts of the worlds, cause problems in many places. Agricultural pests like diamondback moths, olive fruit flies or spotted-wing drosophila cost farmers billions every year, plus they regularly develop resistance to existing measures.

Bees in turn could use genetic support to defend themselves against mites and environmental toxins. For each of these problems there could in theory be a customized gene drive-solution that leads to the death of some species or introduces certain traits or takes away others. That’s the reason Kevin Esvelt named his recently established research group at MIT "Sculpting Evolution", the equivalent in German meaning something like „shape the evolution“.

But what if genetically modified organisms mutate to an undesired variation - and proliferate uncontrollably? What if modified genes are transferred to other species? What if the decline of certain species has unforeseen consequences for ecosystems? If terrorists use the technology to spread pathogens?

"That’s exactly why we should start discussing nows," says Kevin Esvelt. "We have to think about what kind of risks we want to take in exchange for exactly what benefits." The biochemist fears a single error in a lab somewhere in the world could have a devastating effect on the relationship between science and society.

Many of these concerns are justified. It’s been proven in some cases that different species can exchange genes. Nobody can predict the outcome if this happened to a gene drive, although Anthony James thinks this could be avoided if a gene drive was restricted to e.g. mosquito-specific genes.

Many scientists think that the threat of terrorism is exaggerated, simply because the effort needed would be so high. Nevertheless, FBI, the Pentagon and the United Nations Office for biological weapons already dealt with the technology.

Another big question mark is hanging over possible environmental consequences of gene drive insects released into the wild. "This has clearly not been explored enough yet," says Kevin Esvelt. Many entomologists are convinced that no one would miss Aedes or Anopheles mosquitoes because there are plenty of other insects that can fill their ecological niche. This, however, doesn’t apply everywhere, as long-term observations of the Research Institute Tour du Valat in the French Camargue show. Since 2006 parts of this protected wetland area are being sprayed with bacterial spores that specifically kill only the larvae of two mosquito species kill - a similar effect, as if a mosquito population was reduced by introduction of a gene drive. "We showed that housemartins raise about 30 percent less chicks because they had to switch to less energy-dense swarming ants as food without these mosquitoes" says Brigitte Poulin, Assistant Director at Tour du Valat. The scientists also observed a decrease in the number of spiders, dragonflies, and seven out of 50 monitored waterfowl species. The results suggest that environmental consequences of a release of gene drive-organisms need to be examined individually on a case-by-case base.

So what would our society deem worth to save 750.000 lives per year that would otherwise fall victims of mosquito-borne diseases? Would it be okay to sacrifice a few spiders or birds – and where is the limit? Also there’s no legal framework governing the release of gene drive-organisms yet. If a public authority had to decide about a release proposal today, official would probably apply the rules for genetically modified seeds. But these rules by no means cover problems that may arise with gene drives.

The scientists working in the field are clearly committed to transparency and public dialogue. In the end of February they want to discuss at a meeting how to proceed and possibly talk about voluntary restrictions. But what about those people who do not intend to abide by such agreements?

Just last December, a similar event took place in which scientists argued against CRISPR-controlled interventions in the human germ line. But they had been superseded by reality already eight months before, when researchers in China conducted those very experiments. Something similar might very well happen with gene drives.