Revolutionary biotech to combat deadly diseases

Gene drives based on CRISPR-Cas9 are being used to genetically modify mosquito breeding patterns

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In 2003, Austin Burt, a researcher at Imperial College London, proposed a radical idea that had the potential to fundamentally reshape the natural world, and in the process, rid humanity of some of its worst ailments. While scientists had long been able to alter the genetics of domestic organisms, such attempts in the wild required releases of modified organisms so large they made the proposition unfeasible.

One study found that to have a chance of significantly altering the gene pool of a wild population of mosquitoes, ten times the number of the local population would have to be released. For a species that can number in the millions within a few square miles, this presents a real challenge. Usually, a gene in one individual has a 50 per cent chance of being passed on to the next generation. Most animals, humans included, have two copies of most of their genes, one set inherited through the chromosomes from their mother and one set from their father. So, if a relatively small population of modified organisms is introduced into a wild population, over time the modified genes become less common in the population.

Burt's suggestion, however, was revolutionary. He proposed to artificially rig the genetic lottery so that a desired trait could spread through a wild population at an exponential rate. So fast, in fact, that it could potentially affect every member of a population in less than 20 generations. To do this he proposed fitting an organism with a piece of DNA called a gene drive.

While genetic modification traditionally focuses on inserting the instructions for a desirable trait into an organism, a gene drive also inserts the genetic recipe to cut a neighbouring chromosome. It inserts a copy of the modified gene and the instructions for the gene drive into the gap. For example, if a modified male mated with an unmodified female, the gene drive would replace the female's unmodified gene with the male's modified version (and the gene drive) in their offspring. The offspring would then, in effect, inherit two versions of the desired male's gene, instead of one from each parent. This means that, in theory, instead of the usual 50 per cent chance of inheritance, the modified gene has a 100 per cent chance of passing into the next generation and, because the gene drive is also inherited, every generation after that inherits the gene too.

This is an exciting idea, but hard to put into practice, because all available methods were only able to cut chromosomes in places that were unsuitable for the new gene to copy itself into – until 2012. A revolutionary new gene editing technology called CRISPR-Cas9 became available. Gene drives based on Cas9 can be designed to cut anywhere on a chromosome, ensuring that the new gene can be inserted in just the right place for it to be effective. We are within touching distance of being able to modify entire wild populations of organisms.One use for the technology would be to tackle diseases that rely on animals to spread, known as vector borne diseases. The World Health Organization estimates that these account for around 17 per cent of all infections worldwide, amounting to 700 000 deaths and almost 100 million non-fatal cases annually, including devastating diseases such as Dengue and Zika. The largest single killer is malaria, transmitted by several species of mosquito and responsible for an average of 400 000 deaths per year. The vast majority of victims are children under the age of five.

This has lead to significant investment from health organizations and NGOs including the Bill and Melinda Gates Foundation-backed Target Malaria campaign, which hopes to eradicate malaria in part by using gene drives.Target Malaria and the Gates Foundation have so far given $100million to researchers at Imperial College working on several gene drives in *Anopheles gambia*e – one of the most prevalent malaria carrying species of mosquito. One of these gene drives would cause only male mosquitos to be born and another would cause all the females to be sterile.

This September, the team published an article in the journal *Nature Biotechnology* showing that they could drive a small caged population of the mosquitoes to extinction, a result that in theory could be replicated in the wild. The same could be applied to mosquitoes carrying other devastating conditions such as Zika or West Nile Fever. Moreover, while most of the work carried out so far has been limited to mosquitoes, the same principles can be applied to other carriers of disease such as Lyme-carrying tics, or Dengue-carrying Tsetse flies, potentially eradicating the diseases responsible for almost a fifth of annual infections, saving hundreds of thousands of lives annually.Careful thought will have to be applied to avoid unintended side effects of ecological manipulations at such a large scale. But the promise of this technology if applied in the right way is hugely exciting.

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