TESTBIOTECH Background **17 - 9 - 2018**

A potential future scenario: gene drive mosquitoes

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Testbiotech´s work is based on exacting scientific standards, but in our video on 'gene drive' mosquitoes we go beyond what can be considered to be scientific knowledge. Using the medium of 'scientific fiction' we explore a possible future scenario: the story starts with a mysterious incident that happens in around 2040 and unfolds step by step from there.

So why was this clip produced? What is the reality? What is the future scenario?

Why have we made this video?
Currently, there are highly dynamic and ongoing developments in the field of genetic engineering. New tools, such as the 'DNA scissors' (nuclease) CRISPR-Cas, have become much cheaper and more efficient than previous methods. This means that many more plants and animals can be genetically engineered within shorter periods of times than has been the case until now. The potential for engineering the genome now goes far beyond the first generation methods of genetic engineering, and radical changes in genetic traits have become feasible. One extreme example is a so-called 'gene drive': this is intended to genetically manipulate whole natural populations of insects, wild plants and mammals. Our video is about such a 'gene drive'.

What is the function of a 'gene drive'?
The 'gene drive' in our video is based on the application of the nuclease ('gene scissors') CRISPR-Cas. The 'gene scissors' are used to open up DNA at a specific gene site and thereby change its structure. In this case, in order to create a 'gene drive', the gene generating the 'gene scissors' is itself anchored in the genome.

The 'gene scissors' consist of an enzyme (protein). The enzyme is produced in the cells through the additionally inserted gene. This means that ultimately the process of genetic engineering becomes inherited and self-replicating in following generations – the enzyme self-replicates in every generation thereafter. If, for example, due to sexual reproduction, the targeted gene is reintroduced into the genome of the offspring in its natural variants, the 'gene scissors' will 'recognise' this region as their 'target' and CRISPR will activate to change this gene site in the way it is programmed for. As a result, all offspring will homozygously inherit the new genetic trait and the new genes will spread faster throughout the population as they would do naturally.

Consequently, these mechanisms not only change genetic traits but also the pattern of inheritance. The process of genetic engineering is no longer embedded in laboratory conditions. It becomes a self-organising process outside of human control and opens up a whole new dimension of risk. Our

video shows one possible risk.

Why is 'gene drive' such an important issue for the general public?
Throughout history mankind has bred plants and animals, in particular, for agricultural purposes; or people have sought to make changes through genetic engineering. Now, however, with 'gene-drive', a tool has been developed that can be used to genetically engineer wild species, and which can ultimately lead to the manipulation of the 'germline' in biodiversity.

There are two basic strategies underlying the development of 'gene drive': (1) to change traits in natural populations, and eventually replace them as it were with genetically engineered versions. (2) To decimate or eradicate natural populations.

The specific risks and ethical questions inherent in these developments have led the international community within the framework of the Convention on Biological Diversity (CBD) to address this issue: considering the many species already wiped out through human activity, the ethical question arises as to whether we are justified in targeted eradication or genetic engineering of whole species as we see fit. In addition, there is the question of specific risks for people and the environment: How predictable are the outcomes for 'gene drive' and which adverse effects might occur?

There is already huge interest in 'gene drive' applications, they are no longer just a theoretical concept. Research conducted in 2017 shows a wide network to which lobby groups, academic institutions and experts from state authorities belong. Amongst others, the Bill & Melinda Gates-Foundation is active in this area. They have e.g. instructed a specialist agency to exert their influence on public opinion and the drafting of future regulation for 'gene drive'.

Published documents also show the involvement of the US military in the development of 'gene drive'. The US military Defense Advanced Research Projects Agency (DARPA) is involved in financing 'gene drive' research in Germany: a laboratory in Goettingen carried out experiments with 'gene drive' in flies. Safety standards in this case were inadequate to exclude and prevent the escape of the genetically engineered flies.

Why have we chosen these mosquitoes as an example?
There are currently several ongoing 'gene drive' experiments. Amongst others, experiments have already been carried out with mosquitoes, flies, rodents and yeast. Basically, it can be said that that 'mutagenic chain reactions' can indeed be established. These applications are far from being entirely concerned with disease prevention, they are also targeted at agriculture and intervention in ecosystems.

A lot of this activity is directed at a mosquito species that transmits malaria, *Anopheles*. The consortium Target Malaria, which is, amongst others, supported by the Gates-Foundation, is planning projects in several regions of Africa where malaria is known to be a particular problem. In 2018, the government of Burkina Faso approved field trials with genetically engineered mosquitoes that do not as yet carry a gene drive, but they are meant as a first step towards such releases.

Various approaches are being considered in regard to malaria transmitting mosquitoes. One is about whether to decimate or eradicate the mosquitoes. Other projects are researching changes in the biological traits of the mosquitoes so that they can no longer transmit the disease. Our video shows mosquitoes that are to be genetically engineered so that they no longer transmit malaria.

Our example touches on complex ethical questions. Combating malaria is undoubtably a pressing

issue. However, uncontrolled releases of 'gene drive' organisms carry significant risks and, therefore, raise ethical questions about our responsibility for future generations.

How plausible is this future scenario?
The video starts by showing people suffering from fever after being bitten by a genetically engineered mosquito. It shows how (1) success in fighting malaria was only temporary after the release of 'gene drive' mosquitoes. It goes on to say that (2) the 'gene drive' was transferred to another species and (3) the mosquitoes were able to spread throughout Germany due to climate change. This is (4) where people bitten by the mosquitoes were becoming ill.

How plausible is such a scenario? Step by step:

(1) From experiments conducted in the laboratory, it is known that a 'gene drive' can in following generations lose its function either partially or completely. One reason, amongst others, is a technical deficiency in the 'gene-scissor'. The parasite (Plasmodium) causing malaria could adapt to the genetically engineered mosquitoes, and possibly be increasingly transmitted through other mosquito species. There are, therefore, a number of reasons why the release of 'gene drive' mosquitoes might ultimately fail even though the gene constructs do indeed spread through the mosquito population.

(2) There are several species of *Anopheles* which can cross breed. This means that the 'gene drive' can be transferred from one species to another. Once the 'gene drive' has been transferred to another species there may be interaction with natural genes in the receiving species that had not been observed in the original species. Unexpected interactions between the additionally inserted genes and natural genes have been described several times. It is known that the function of specific genes can be influenced by the genetic background of the receiving organism.

(3) Mosquitoes that are able to transmit malaria could spread to Germany. In the past, malaria was widespread in Europe. Climate change could contribute to increasing numbers of mosquitoes here. In 2018, there were several reports about mosquitoes occurring in the EU that can transmit the West Nile virus.

(4) There are naturally occurring enzymes in the saliva of mosquitoes that can cause itching after being bitten. In our example, the composition of these enzymes has been changed in such a way that bites can cause high fever in people. The reason for this are the interactions between the additionally inserted genes and the genome of the mosquitoes as mentioned above.

No-one can actually predict whether such a scenario will become reality. However, it is not impossible.

Is Testbiotech scaremongering?
The video is intended as an attempt to start wide and informed debate. Civil society should be given the opportunity to take part in a wide debate on the new developments in genetic engineering. How can we make sure that genetically engineered organisms do not spread uncontrolled into natural populations and seriously damage human health and biodiversity, which might no longer be reversible?

Testbiotech believes that we need binding international regulations to prevent releases of genetically engineered organisms that can spread without sufficient control. Such regulations are fully in

accordance with the regulatory framework of the EU which gives high priority to the precautionary principle.

We look forward to an informed and controversial debate.

Please watch the video: https://www.testbiotech.org/en/limits-to-biotech/videos

Further information:
Gene Drive Basic-paper: http://www.testbiotech.org/en/limits-to-biotech/gene-drive/basic_paper

Gates Foundation lobby campaign for the release of genetically engineered mosquitoes carrying a gene drive: http://www.testbiotech.org/en/press-release/gates-foundation-lobby-campaign-release-genetically-engineered-mosquitoes-carrying