Target Malaria’s step-by-step development pathway

A phased pathway to develop a novel genetic approach for malaria control

Target Malaria is working to develop and share novel genetic technologies to help control malaria in Sub-Saharan Africa. We aim to do so by developing modified mosquitoes that carry a genetic trait that will result in the reduction of malaria mosquito populations and that could complement existing methods of malaria control. Reducing the number of mosquitoes that can transmit the malaria parasite would result in fewer malaria infections.

Malaria is quite different compared to these diseases. In sub-Saharan Africa, malaria is mainly rural, covering large areas and regions that are often difficult to access. This geographical setting makes it difficult to rely on large scale interventions that need to be repeated over time. For dengue, for instance, much of the burden is in cities so it is possible to control the dengue mosquitoes by doing multiple releases of modified mosquitoes, enough to “swamp” the population and control it. In Africa, it would be impractical to carry out these interventions at a national or regional scale because it would mean repeatedly producing and releasing very large numbers of mosquitoes. It would not be cost effective and therefore not sustainable.

Target Malaria is seeking a long-term, sustainable and cost-effective solution to eradicate malaria. Our research is building on these precedents to develop gene drive approaches, which would allow the intended modification to become established in a target population over a relatively short period of time, thus reducing that population’s ability to reproduce. This would help to decrease the population of the malaria vector, the *Anopheles* mosquitoes, and therefore result in a reduction in the number of malaria infections in sub-Saharan Africa.
While there are precedents and experience to draw on, gene drive approaches are a novel area of research that require a stepwise development pathway. Target Malaria is progressing through several phases of iterative research to enable its stakeholders and national authorities in the countries concerned to gain understanding of this new field of research and its potential.

Target Malaria’s approach draws on the guidance developed by WHO, as well as expert views from national academies, regulatory bodies, other scientists and researchers who are working in this field. We have adopted a phased approach to our technology development and are constantly re-evaluating the best pathway based on the information we gather from our work, advances made by other research teams, and new guidance from experts and authorities.

Non gene drive male bias mosquitoes

Another step in our phased development pathway has been the development of a mosquito that could successfully mate and produce offspring, but in which the genetic modification would only persist for some time before disappearing⁶. The strain(s) would hence be “self-limiting” in the sense that the modification does not persist for a very long time. This strain does not carry the gene drive element that biases inheritance. This means approximately 50% of the offspring have the genetic modification as would be expected by Mendelian inheritance. The male mosquitoes carry a modification that causes them to produce almost exclusively males offspring, biasing the ratio of the targeted mosquito population towards males (male mosquitoes do not bite and therefore do not transmit malaria).

While also an interim step that does not involve gene drives, it is useful to have strains where the modification persists for longer in order to provide additional information on how the genetically modified mosquitoes behave in a natural setting over an extended period of time. It is also an important intermediate step for stakeholders to learn more about genetic modification and for regulatory authorities to consider how they want to manage future research in this field. This strain of mosquitoes has undergone laboratry evaluation in the UK, Italy and the United States. It has been imported to Burkina Faso in 2022.

Prior to any regulatory approval for a field evaluation, a comprehensive risk assessment would be performed by the Target Malaria risk team as well as third parties, including quantitative analysis and levels of certainty, as has been recommended in global fora.

Non gene drive sterile male mosquitoes

Our development pathway started with a sterile male mosquito as proof of principle in the laboratory in 2008⁴. The males were genetically modified to be sterile, so they could not have any progeny. These mosquitoes were not intended to be a viable tool for controlling malaria, because they would not provide the long-term or cost-effective benefits that malaria control requires. However, their development was an important step to gain knowledge, start a dialogue with stakeholders and provide a strain of mosquitoes that we could use to evaluate our process, procedures and preparedness.

The genetically modified sterile male mosquitoes, like all our strains, were subject to evaluation in small cages (30cm x 30cm) and then large environmental cages (up to 9.2m)⁵ in laboratories in the UK and Italy as well as further safety and risk assessments, before being imported by the team at the Institut de Recherche en Sciences de la Santé (IRSS) in Burkina Faso, under permits granted by Burkina Faso’s National Biosafety Authority, the Agence Nationale de Biosécurité (ANB). The team worked with the genetically modified sterile male strain for over a year in contained laboratories before conducting a small-scale controlled field release in 2019, under additional permits and with the agreement of the local communities involved. The team at Malaria Research Training Center (MRTC) in Mali was also granted a contained use permit by the Malian National Biosafety Committee, under the Ministry of the Environment. There was no release in Mali.

The work on the sterile male was concluded in 2021 for the whole project.
Self-Sustaining gene drive mosquitoes

Our ultimate goal is a new vector control tool for malaria. To achieve this goal, we are developing a mosquito strain, which involves a gene drive that biases its inheritance and is self-sustaining. Malaria is predominantly a rural disease, which has remained most entrenched in African countries with populations spread over large areas and often with less well-developed transport and public health infrastructures. The complexity and cost of carrying out repeat interventions (such as spraying and bed net distributions), combined with issues of growing resistance to insecticide and anti-malarial drugs, are threatening to reverse progress towards malaria elimination.

Gene drive approaches, because of their self-sustaining nature, could - in conjunction with existing tools - offer long-term, sustainable and cost-effective methods to control *Anopheles* mosquito populations. We are currently investigating several options, the two most promising are:

1) A gene drive strain with fertile males that produce predominantly male offspring, leading to a distortion in the sex ratio and biased inheritance of the gene drive element in the targeted mosquito population;

2) A genetically modified strain with fertile males carrying a gene that will spread through the mosquito population and cause females that inherit the gene from both parents to be sterile.

Both approaches would lead to a reduction in the mosquito populations that are the main malaria vectors. We are making good progress, but these approaches are still in the discovery stages in our laboratories in the UK and Italy.

Although we are developing the approaches separately, it may also be possible to combine the two approaches for use in the fight against malaria. The project’s achievements so far on development and evaluation of self-sustaining genetically modified mosquitoes have been published in peer reviewed scientific journals.

2. IEA: https://www.iaea.org/newscenter/presreleases/iaeas-helps-burkina-faso-scale-up-fight-against-tsetse-flies