Veille citoyenne d'information sur les OGM et les semences

# Male mosquitoes genetically modified to produce poison

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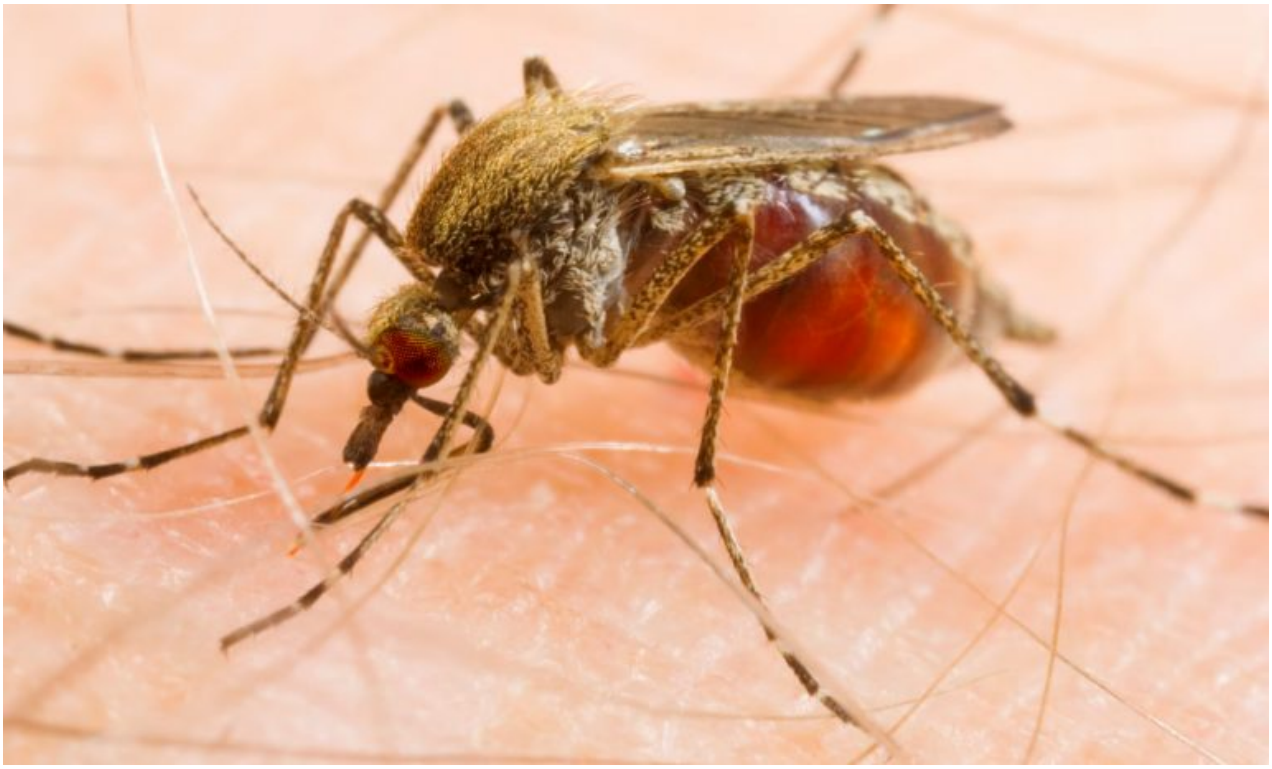
Mosquitoes carry pathogens that cause diseases such as malaria and dengue fever, and are therefore known as vector-borne diseases. As part of the fight against these mosquitoes, researchers at Macquarie University (Australia) are considering a new genetic strategy. The idea is to genetically modify male mosquitoes so that their sperm produce molecules that will poison female mosquitoes.



Scott Smith

Mosquito-borne diseases are mainly controlled by "*mechanical*" methods (mosquito netting, stagnant water management) or chemical methods (repellents, insecticides). These methods are still used today. However, it has been observed that insecticides are losing their effectiveness: mosquitoes have acquired a strong resistance to many molecules. It is against this backdrop that the idea of rendering male mosquitoes sterile has emerged, a strategy we have already discussed extensively in our columns. Sterility can be achieved by irradiation or transgenesis. But, as we have

also pointed out, the results have not been encouraging. Australian researchers are proposing a new approach: transferring a spider or sea anemone genetic sequence encoding a toxic molecule into male mosquitoes, so that they produce it in their sperm.

## Insects that poison their fellow creatures

For the time being, researchers at Macquarie University (Australia) have not genetically modified mosquitoes but male *Drosop?ila melanogaster* flies, as detailed in an article published in *Nature Communications*[i]. *Drosophila* is a well-known laboratory model, often used as a precursor to research on other insects. In their project, the researchers wanted to express venom proteins in the "*accessory glands*" of male *Drosophila*, the glands where seminal fluid proteins are produced. These proteins are derived from two living organisms: a Brazilian spider (*Phoneutria nigriventer*) and the sea anemone (*Anemonia sulcata*). This choice is based on the theory that the proteins encoded by the spider or sea anemone transgenes will not pass into the males' hemolymph (the equivalent of blood) and will therefore not be toxic to these transgenic flies. The transgene is injected into the insects' eggs and, in theory, will only be expressed as a toxic protein in the insects' seminal glands.

The idea is that transgenic males mate with wild females and the latter "*receive*" venom via the seminal fluid. In short, the males poison the females. In concrete terms, the toxic proteins must be of low molecular weight if they are to pass from the female's sexual organs to vital organs: "*It has been demonstrated in* Drosophila melanogaster *that several low molecular weight (seminal fluid proteins) can pass through the female reproductive tract and enter the circulatory system (haemolymph), and even to act on receptors in the central nervous system*". Once in the central nervous system, these venoms target specific receptors and thus have a neurotoxic effect. The researchers found that in mosquitoes, these seminal fluid proteins "*also act on receptors found within the CNS, with 30% of radiolabelled Culex SFP localising to the female head and thorax*". Theoretically, males would not be affected by this leakage of toxic molecules from seminal vesicles to nerve receptors.

The article points out that this approach reduces "*the median lifespan of mated females by 37 ? 64% compared to controls mated to wild type males*". Using mathematical models, the authors also compared the performance of this strategy with that of the sterile male insect by irradiation, *Wolbachia*[ii] or transgenesis: "*These results suggest that compared to [the Oxitec strategy (fsRIDL)], TMT* (toxic male technique) *may reduce the incidence of blood feeding during the release period by a further 40–60% under most scenarios, which has significant epidemiological implications*". To achieve a significant rate of females dying during mating, the authors specify that their toxic males must be fertile... Paradoxically, they also state that "*sterilisation of the males to mitigate the risk of transgene escape*" will probably be required. But all this is based, again, on estimates and mathematical models, and no one knows what might actually happen once these genetically modified toxic males are widely disseminated in the environment.

The researchers point out that males are not affected by the venom because the chosen transgenic protein acts on a targeted receptor, which is not present in the male reproductive system. They also claim that the chosen venom proteins cannot interact with receptors present in mammals. In fact, not all poisoned females die, so the survivors can continue to bite and transmit the venom to mammals...

## Female mosquitoes targeted

For the authors of the study, the advantage of their strategy over the sterility strategy used in previous techniques is that it targets not the offspring between modified males and wild females, but wild females directly. They write: "*for example, wild female* Ae. aegypti *have a median adult lifespan of 2–3 weeks, will typically mate within 24–48 h of emerging, and on average will take 0.63–0.76 blood meals per day. Females that mate with (genetic biocontrol technologies) males may not produce viable offspring, but they can continue to spread disease or damage crops*".

However, the question of mosquito resistance to these poisons cannot be ruled out. The researchers' strategy is designed to circumvent the acquisition of pesticide resistance in mosquitoes, but it too could be circumvented. As the authors of the study put it: "*Co-expression of multiple toxins could help to mitigate the emergence of resistance alleles, as well as potentially resulting in synergistic toxicity from affecting multiple ion channel targets*"[iii].

## Other unanswered questions

The researchers consider that the impact of these venoms on the mosquito's natural predators, such as birds, bats and certain amphibians, also needs to be determined. The authors are reassuring, immediately pointing out that "*the oral toxicity of venom proteins is typically between 1 and 2 orders of magnitude lower than when they are directly injected, and venom proteins can be selected which have greater toxicity for the target species relative to natural predators*". Again, this is theory. These GM mosquitoes have not been studied under real conditions in a complex ecosystem.

In an article in the British newspaper *The Guardian*[iv], Professor Philip Weinstein, an infectious disease researcher at the University of Adelaide (Australia), who was not involved in the study, is reported having said that "*an ideal solution would be to control the insects without eradicating them, given that mosquitoes were pollinators and an important food source for fish and bats*". There is also the question of the purpose of these genetic technologies. Vector-borne diseases are fatal in certain socio-political contexts, and for children under the age of five who are often malnourished at the same time. The implementation of water management systems and the fight against insecurity and poverty are important elements not to be neglected. While eradicating mosquitoes is not desirable, achieving this objective seems impossible today.

i Beach, S.J., Maselko, « M. Recombinant venom proteins in insect seminal fluid reduce female lifespan », *Nat Commun* 16, 219 (2025).

ii Technically, the sterility is obtained by inoculating *Wolbachia* bacteria to mosquito, see : Christophe Noisette , « Google also eradicates mosquito », *Inf'OGM*, 27 July 2017 (in french) ; Christophe Noisette, « Wolbachia : the bacteria which renders mosquito inoffensiv », *Inf'OGM, le journal*, n°158, January / March 2020 (in french).

iii An ion channel is a membrane protein that allows the high-speed passage of one or more ions. Ion channels are present in the membrane of all cells.

iv Petra Stock, « Male mosquitoes to be genetically engineered to poison females with semen in Australian research », *The Guardian*, 7 janvier 2025.

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