

Commentary

Invading an invasive species: Gene-drive systems in the malaria vector mosquito, *Anopheles stephensi*

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DESCRIPTION

The Indo-Pakistan mosquito, *Anopheles stephensi*, is a vector of human malaria on the Asian subcontinent where it is responsible for significant pathogen transmission in urban environments (Hati 1997, Thomas et al., 2017). It has recently invaded and appears established in Northeastern Africa with a high likelihood of moving to major urban areas throughout the continent (Tadesse et al., 2022, Sinka et al., 2020). Similar to the major African vector mosquitoes, *An. stephensi* shows a high degree of adaptability and accommodation to man-made environments and likewise exhibits resistance to commonly-used insecticides (Enayati et al., 2020, Safi et al., 2017). As a consequence, it is a proposed target for new genetic tools to control transmission of the Plasmodium parasites. It is a focus of efforts to develop population modifications strains designed to prevent transmission of the parasites (Carballar-Lejarazú et al., 2017, Isaacs et al., 2012).

DISCUSSION

Population modification technology require a gene-drive system, a mechanism for rapidly introducing beneficial, anti-parasite genes into wild populations and *An. stephensi* was the first system published in which this was developed (Gantz et al., 2015). This system could drive anti-parasite genes into ~99% of progeny when the parent was a male, but only about 60-70% of the time when the parent was a female. A significant fraction of 'drive-resistant' alleles was generated in females that subsequently interfered with gene-drive dynamics in the female germline.

Researchers at the University of California (UC), Irvine, along with colleagues at UC Berkeley and UC San Diego, have developed a highly-efficient, second-generation gene drive system for *An. Stephensi* (Adolfi et al., 2020). The failure to drive efficiently through females was solved by equipping the gene drive system with a functional copy of the gene into which the drive inserts (the *kynurenine hydroxylase [kh]* gene, which encodes an enzyme required for eye-pigment production). Females of the strain used in this study that are homozygous for disruptions of the *kh* gene exhibit reduced survival and reproductive output following a bloodmeal resulting in population extinctions in some small cage trials (Pham et al., 2019). However, lower release ratios of gene drive-to-wild type males resulted in a dampening of the drive dynamics and selection for mosquitoes with functional drive-resistant alleles that lacked the gene-drive system and maintained the populations. The "recoded" *kh*-drive does not cause the adverse female post-blood feeding phenotypes and benefits from a phenomenon designated 'lethal/sterile mosaicism, demonstrated first in the vinegar fly, *Drosophila melanogaster* (Guichard et al., 2019). The two effects, recoding the *kh* target gene and lethal/sterile mosaicism, result in a strong and consistent drive in small cage population modification trials and maintain >95% of the mosquitoes carrying the gene-drive system. This approach of targeting a gene-drive system to an essential gene (for viability or fertility) and complementing the disruption with a recoded gene to restore function may provide a general approach to the drive-resistant allele problem through females (Kormos et al., 2020).

CONCLUSION

Genetic modification strategies are new technologies and it is incumbent on the developers to provide open and honest

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communications with potential end-users and all stakeholders. Towards that end, we are pursuing a relationship-based model to ensure that the necessary information is available and understood by the decision-makers who ultimately will be responsible for the use of these technologies.

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