GENOMICS

Targeted nucleases fight malaria

Genome engineering skews the sex ratio of malaria-carrying mosquitoes heavily toward males and leads to a population crash.

One way to control population size is by sex distortion: if the reproductive balance for a species is driven to produce mostly males, the population will die out in a few generations. Research groups led by Nikolai Windbichler and Andrea Crisanti at Imperial College London sought to apply this strategy to reduce populations of *Anopheles gambiae*, the mosquito species that transfers malaria parasites to humans.

Both Windbichler and Crisanti are mosquito geneticists. In 2004, when the project received funding from the Gates Foundation, they invited Barry Stoddard from the Fred Hutchinson Cancer Center to join the team for his expertise in protein and genome engineering. Stoddard engineered a homing endonuclease to cleave essential ribosomal genes on the X chromosome during spermatogenesis in male mosquitoes. The enzyme shreds the paternal X chromosome and ensures that predominantly Y-bearing sperm are produced.

The first endonuclease the team tried was so stable that it persisted also in male sperm and targeted the maternally derived X chromosome in the zygote, leaving no viable embryos. It took a deliberately destabilized version of the enzyme to show the desired activity in male gametes only.

Transgenic mosquito lines expressing this endonuclease displayed the expected sex ratio distortion of up to 97% male progeny after 4–6 generations. The work was carried out in laboratory settings with inbred *A. gambiae* strains, and the next step will be to perform cage tests in several African countries and mate the transgenic males with indigenous wild-type *A. gambiae* strains. Stoddard sees this as crucial for testing the method, and he plans to partner with African researchers to share expertise and support educational efforts.

Ultimately the project will involve releasing the genetically modified organisms into the wild, and this elicits concerns about unintended consequences. Although horizontal gene transfer of the endonuclease to other mosquito species is theoretically an issue, Stoddard points out that such transfers work on a much longer timescale than their strategy, which sees a population crash after several generations. He also predicts that total eradication of *A. gambiae* may not be necessary: even a reduction in mosquito populations for a few months would have an impact on malaria.

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RESEARCH PAPERS
Galizi, R. *et al.* A synthetic sex ratio distortion system for the control of the human malaria mosquito. *Nat. Commun.* **5**, 3977 (2014).