Dominant lethal systems for genetic control of mosquito populations

Luke Alphey[1,2*], Hoang Kim Phuc[1], Morten H. Andreasen[1], Céline Vass[1], Matthew J. Epton[1], Gavin Pape[1], Guoliang Fu[2], Sarah Scaife[2], Christl A. Donnelly[3], Paul G. Coleman[2,4] and Helen White-Cooper[1].

[1]Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK.
[2]Oxitec Limited, 71 Milton Park, Oxford OX14 4RX, UK
[3]Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, Norfolk Place, London, W2 1PG, UK
[4]Department of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK
*: corresponding author, email: `luke.alphey@zoo.ox.ac.uk`

Recent advances in insect genetic engineering have opened up new possibilities in the genetic control of insect vectors of human diseases. Key advances include the genetic transformation of *Aedes, Anopheles* and *Culex* mosquitoes, and the sequencing of the *Anopheles gambiae* genome. We are currently attempting to engineer repressible dominant lethal genes or genetic systems into mosquitoes, using *Aedes* (*Stegomyia*) *aegypti* as our model mosquito and *Drosophila melanogaster* as our genetic test-bed. The primary applied goal of the programme is to develop usable area-wide population control methods based on the Sterile Insect Technique, an approach we call RIDL (Release of Insects carrying a Dominant Lethal)[1,2]. For this purpose, we are attempting to develop genetic systems with the following properties:

Genetic marker

A genetic marker is useful not only to isolate the initial transformant, but also to discriminate between released and wild adults in a mass-release program without having to resort to PCR or other molecular methods. Therefore, a marker that can be readily scored in adults would be helpful. DsRed2 under the control of the *Drosophila Actin5C* promoter comes close to this; it is easily scored in live larvae and pupae of *Aedes aegypti*, and in dissected adults. Other markers are also available. If only males are released, the requirement for an adult marker may be less important.

Repressible dominant lethality (non-sex-specific)

An area-wide control program based on mass-release of mosquitoes would preferably not release large numbers of biting females. Some form of sex-separation is therefore required. For *Anopheles* mosquitoes, this will presumably require a genetic sexing mechanism (see below), but for *Aedes aegypti* physical sex separation based on pupal size can be very effective, as shown in trial programmes in the 1970s. A critical problem with SIT-type control methods for mosquitoes is sterilisation. Early trials found that pupal irradiation compromised the adults, while adult irradiation is problematic in practice. Chemosterilisation was used instead, but greater concern about toxic residues would make this difficult today. Use of a strain homozygous for a non-sex-specific dominant lethal can potentially overcome this problem[2,3]. We are therefore constructing such strains, using the tetracycline-repressible gene expression system[4] to allow us to repress the lethal effect with dietary tetracycline[5]. Where density-dependent effects are significant, engineering the time of death to be after the density-dependent phase, rather than before, should be beneficial. We have explored this by mathematical modelling and find that such manipulation of the time of death can be highly advantageous.

Genetic sexing mechanisms

In many cases it is important to release only males, rather than a mixed population of males and females. There are two main reasons for this: the adult females may be hazardous and/or co-releasing females may inhibit dispersal of males. Physical sex-separation methods are available for *Aedes aegypti*, however this is not the case for Anophelines. We are therefore developing genetic sexing methods. We have achieved considerable success with *Drosophila* and tephritid fruit flies and are currently attempting to translate this to mosquitoes.

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