



Dissecting insecticide resistance via genetic manipulation and genome modification in *Drosophila*

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ABSTRACT

The protection of agricultural production, as well as the prevention of vector borne diseases, largely relies on the control of insect populations with the use of insecticides. However, insects display an intriguing ability to develop resistance. Our research aims at the investigation of the mechanisms inducing resistant phenotypes using several experimental approaches; among these, genetic transformation and genome modification in model species like *Drosophila* has played a pivotal role in the understanding of the role of individual alleles and the determination of specific insecticides' mode of action. Certain examples include the investigation of the contribution of specific mutations in target-site resistance phenotypes (in genes like chitin synthase¹, ryanodine receptor, ACCase and voltage-gated sodium channels²) using CRISPR/Cas9 genome modification. Furthermore, the heterologous GAL4/UAS overexpression of candidate detoxification genes, facilitated by *Drosophila* genetic transformation, is invaluable for the validation of particular genes implied in resistance. Among recent examples, the contribution of individual cytochrome P450s in insecticide detoxification in major agricultural pests was investigated³.

The versatility of these tools is demonstrated by the ability to devise *ad hoc* strategies in order to test hypotheses where the emergence of resistance may involve several different mechanisms. Such cases may be dissected in-depth with the combined use of genome modification, conditional expression and/or knock-down (via RNAi) in the same genetic context, aiming to reconstruct resistance pathways in a susceptible genetic background, taking advantage the unique available genetic toolkit and standard *Drosophila* genetics. Despite certain limitations, this approach greatly enhances our ability to investigate insecticide resistance in a fashion complementary to standard pipelines investigating resistance in the field and classical forward genetics. Engineered "super-resistant" *Drosophila* lines, bearing simultaneously several resistance genes and/or mutations and showing striking resistance phenotype against classical insecticides, can eventually be used to test the anti-resistance potential of novel candidate insecticidal compounds, synergists etc.

REFERENCES

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