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| Investigating synergistic action of molecular mechanisms of insecticide resistance in a Drosophila model framework  **Rafaela Panteleri1,2,3#, Mantha Lamprousi1, Caterina Katsanou3,4, Irene Varnava4, John Vontas2,5** and **Vassilis Douris1,4\***  1 Biomedical Research Institute, Foundation for Research and Technology-Hellas (BRI-FORTH), Ioannina  2 Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas (IMBB-FORTH), Heraklion  3 Dept. of Biology, University of Crete (UoC)  4 Dept. of Biological Applications and Technology, University of Ioannina  5 Pesticide Science Laboratory, Agricultural University of Athens  # Presenting author: Rafaela Panteleri, email: [rafaela\_panteleri@imbb.forth.gr](mailto:rafaela_panteleri@imbb.forth.gr)  \* Corresponding author: Vassilis Douris, email: [vdouris@bri.forth.gr](mailto:vdouris@bri.forth.gr) |

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 using CRISPR/Cas9 genome modification1 and heterologous GAL4/UAS overexpression of candidate detoxification genes for the validation of particular genes implied in resistance.

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 and conditional expression in the same genetic context, aiming to reconstruct resistance pathways in a susceptible genetic background, taking advantage of the unique available genetic toolkit and standard *Drosophila* genetics2. 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. The same model framework can be applied to investigate novel proposed resistance mechanisms that may act in a complementary fashion with standard detoxification mechanisms, such as chemosensory proteins binding different insecticide classes *in vivo*3.

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