

Functional Characterisation of *Anopheles gambiae* P450 Reductase

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In collaboration with Dr. Paine at Ninewells Hospital, Dundee, we have started the study of genes involved in P450 metabolism in *Anopheles*. These studies are critical in understanding the role of specific genes in insecticide metabolism in mosquitoes.

Growing resistance of the mosquito *Anopheles gambiae* to insecticides is hampering malaria eradication programs and new tools to control diseases transmitted by insects are eagerly sought. Cytochrome P450s are a superfamily of hemoproteins, important in the metabolism of both xenobiotic and endogenous compounds, and known to be involved in insecticide resistance. Their catalysis in the endoplasmic reticulum is dependant on the redox partner NADPH cytochrome P450 reductase (POR). We report the major sites of mosquito POR expression to be oenocytes, midgut epithelia and head appendages. Furthermore, POR gene silencing by RNAi enhances sensitivity of adult mosquitoes to the insecticide, permethrin; confirming a role of the p450 system in pyrethroid metabolism. In parallel, we demonstrate that RNAi does not affect POR expression to the same extent in all tissues. POR expression is drastically reduced in the oenocytes, and to a lesser extent in midgut epithelia, but POR content in the head is unchanged. Finally, a first direct comparison of insect POR activity with known homologues reveals unexpected differences in the binding of inhibitors, 2', 5'-ADP and diphenyliodonium chloride (DPI). These differences may open a new route for the development of selective insecticides or insecticide synergists.