



Experiment title:
STRUCTURE mosquito 3-hydroxykynurenine
transaminase

**Experiment
number:**
MX394

Beamline:
ID14-2

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REPORT

Background – Spontaneous oxidation of 3-hydroxykynurenine (3-HK), a metabolic intermediate of the tryptophan degradation pathway, elicits a remarkable oxidative stress response in animals tissues. In the yellow fever mosquito *Aedes aegypti* the excess of this toxic metabolic intermediate is efficiently removed by a specific 3-HK transaminase, which converts 3-HK into the more stable compound xanthurenic acid (XA). In anopheline mosquitoes transmitting malaria XA may play an important role in *Plasmodium* gametocytes maturation and fertility. Recombinant *A. gambiae* 3-HK transaminase is a dimeric pyridoxal-5-phosphate dependent enzyme, showing a comparable catalytic efficiency for both 3-hydroxykynurenine and its immediate catabolic precursor kynurenine. This study may be useful for the identification of 3-HK transaminase inhibitors of potential interest as malaria transmission-blocking drugs or effective insecticides. We have obtained well diffracting crystals of both *A. gambiae* and *A. aegypti* 3HKT in the PLOP form and in complex with a newly synthesized inhibitors.

Results – The crystal structure of *A. gambiae* and *A. aegypti* 3HKT have been determined at 2.4 Å and 1.8 Å resolution respectively (1,2). The analysis of the active site, for the PLP and for the complex with a competitive inhibitors, reveals the presence of a crown of aromatic residues surrounding the substrate binding site, unraveling the molecular determinants responsible for the exquisite specificity shown by the enzyme for 3-hydroxykynureine, paving the way for the synthesis of specific inhibitors of the mosquito enzyme.

1. Rossi F, Garavaglia S and Rizzi M (2005). Structure of *Anopheles gambiae* 3-hydroxykynurenine transaminase a key enzyme for *Plasmodium* gametogenesis (Submitted)
2. Franca Rossi, Qian Han, Junsuo Li, Jianyong Li, and Menico Rizzi (2005). Structure of the detoxifying enzyme 3-hydroxykynurenine transaminase from *Aedes aegypti*. (Submitted)