	Experiment title: STRUCTURE OF HUMAN KYNURENINE AMINOTRANSFERASE I	**Experiment number**: MX129
Beamline: ID14-EH4 ID14-EH2	**Date of experiment**: from:14/10/03 to:15/10/03 from 05/12/03 to:06/12/03	**Date of report**: 22th June 2004
Shifts: 4	**Local contact(s)**: Joanne McCarthy, Sofia Macedo	*Received at ESRF:*

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REPORT

Background – In mammals, the kynurenine pathway is the main route for the degradation of tryptophan exceeding anabolic needs. Cumulating clinical and experimental evidences, suggest that an imbalance in the local concentrations of the metabolites along this pathway in the CNS, could be responsible for the onset and the progression of a broad spectrum of neurological pathologies. In particular, increasing of kynurenic acid significantly correlates with schizophrenia and cognitive impairment, suggesting a key role for this metabolite in the pathophysiology of psychiatric disorders and mental retardation. The synthesis of kynurenic acid in the CNS is guaranteed by the irreversible transamination of L-kynurenine, catalyzed by kynurenine aminotransferases (KATs) which are regarded as important targets for the treatment of correlated neurological disorders.

Results - The crystal structure of human KAT I has been determined at 2.0 A resolution, and is shown in Fig. 1. The analysis of the enzyme active site for the PLP and PMP forms, as well as for the complex with phenylalanine, 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 kynurenine, paving the way for the rational design of kynuerine analogues of potential medical interest.

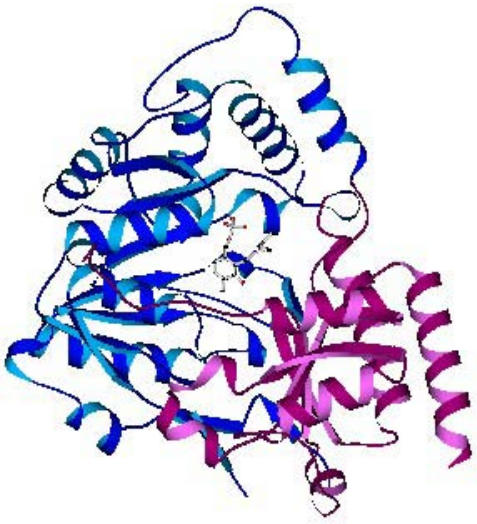

Figure 1: Ribbon representation of human kynurenine aminotransferase I in its PLP from

1. Franca Rossi, Qian Han, Jianyong Li, and Menico Rizzi. Structure of human kynurenine aminotransferase I, a key enzyme for the synthesis of the potent neuroactive compound kynurenic acid. (2004), submitted.