s1.m6.o1 **Structure of the human outer-mitochondrial membrane Monoamine Oxidase B at 1.7 Å resolution*.** Andrea Mattevi[a], Min Li[b], Frantisek Hubalek[b], Dale E. Edmondson[b] and Claudia Binda[a] , [a]*Department of Genetics and Microbiology, University of Pavia, Italy and* [b]*Department of Biochemistry and Chemistry, Emory University, Atlanta, GA. E-mail: mattevi@ipvgen.unipv.it*

Keywords: Neurotransmitters, Membrane Protein, Drug-Design

Monoamine oxidase B (MAO B) is an outer- mitochondrial membrane-bound flavoenzyme that is a well- known target for anti-depressant and neuroprotective drugs [1]. The 3 Å resolution structure of recombinant human MAO B originally determined was of the enzyme complex with pargyline, an irreversible inhibitor covalently bound to the N5 atom of flavin coenzyme [2]. The crystal structure shows that the enzyme is dimeric. Each monomer binds to the membrane via a C-terminal transmembrane helix and by apolar loops located at various positions in the sequence. The helix of each monomer protrudes from the basal face of the dimer with each helical axis approximately parallel to the molecular two-fold axis. This observation suggests that the dimer binds to the membrane with its two-fold axis perpendicular to the membrane plane, and the C-terminal helices inserted in the lipid bilayer. Substrate binding to the enzyme involves negotiating a loop covering a 290 $Å^3$ entrance apolar cavity before reaching an apolar 420 $Å^3$ substrate cavity where the flavin coenzyme is located. The 1.7 Å isatin-MAO B structure allowed a detailed examination of the enzyme's active site [3,4]. A novel reversible MAO B inhibitor which is found as a contaminant in polystyrene plastics (1,4-diphenyl-2-butene) binds in both the entrance and substrate cavities. The new structures show that Ile199 functions as a "gate" whose side chain rotation allows for either separation or fusion of the two cavities. GRID analysis shows a hydrophilic region in the substrate cavity near the flavin that may facilitate the binding of the substrate amine moiety.

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s1.m6.o2 **Structural studies of Imatinib in complex with its targets in CML and GIST: the molecular basis for selectivity and resistance.** Sandra W. Cowan-Jacob, *Novartis Institutes of Biomedical Research, Basel, Switzerland. E-mail: sandra.jacob@pharma.novartis.com*

Keywords: Kinase; Inhibition

Glivec™ (Imatinib, STI571) is a drug targeted against Bcr-Abl kinase for the treatment of chronic myelogenous leukemia (CML) and against cKit kinase for the treatment of gastrointestinal stromal tumors (GIST). The impressive response rate of patients treated with STI571 in the early phase of CML showed the feasibility of using ATP-competitive inhibitors in the chronic treatment of molecularly defined cancers. However, CML patients treated in the later phases (accelerated and blast crisis), tend to develop resistance and relapse. Resistance is now also being found in GIST patients.

The unique binding mode of STI571 to the kinase domain of the target is key to the excellent selectivity and thus tolerability of the drug, but it also the source of the susceptibility to resistance. STI571 binding is dependent on the conformational state of the protein and on contacts with residues that are not important for the function of the protein. Mutations that affect the conformational state or the binding site will therefore result in STI571 resistance. Although there are probably several different mechanisms leading to patient relapse, mutations are found in more than 50 % of cases.

Structural biology has been used to gain a better understanding of the role of these mutations in resistance. This provides a basis for the design of more potent inhibitors that might overcome or avoid the devlopment of resistance and the design of inhibitors that are active against mutants. However, it is unlikely that one single inhibitor will be effective and it will be necessary to use multiple compounds to target different conformations or different mutants of Abl kinase, or other downstream targets.