Molecular modeling of human flavin-containing monooxygenase 3

Gianluca Catucci, Sheila Sadeghi, Olivier Friard and Gianfranco Gilardi
Department of Human and Animal Biology, University of Torino, Italy

Human flavin-containing monooxygenase 3 (hFMO3) is a hepatic phase-1 drug metabolising enzyme. To date, the tertiary structure of hFMO3 has not been solved and therefore molecular modeling attempts have tried to assign a structural/functional role to the predicted secondary structure elements of the polypeptide. Here we present a 3D model of this enzyme generated by ab-initio and homology modeling using the bacterial FMO structure as template (30% homologous). The model was energy minimized and refined.

Docking experiments were carried out using the DRUGBANK database (3987 molecules). The docking output produced putative binding energies for each of the drugs. Known marker substrates of hFMO3 such as sulindac, tamoxifen, ranitidine and cimetidine showed binding energies of 8.55, 7.97, 7.16 and 5.04 Kcal/mol, respectively. As lower binding energies imply a weak interaction while higher ones suggest putative inhibitors of the hFMO3, the values here reported give indication of the range within which substrates are comprised. This is the first step towards an in vitro screening of new chemical entities against hFMO3 for the benefit of pharmaceutical research.