PS04.12.15 RATIONAL DESIGN OF SULFONAMIDE INHIBITOR SPECIFIC FOR HUMAN CARBONIC ANHYDRASE I ISOZYME. Sugoto Chakravarty, Sunil Ghose, A. Bannerjee, K. K. Kannan, Bhabha Atomic Research Centre, Bombay - 400 085, India

Rational design of N - unsubstituted sulfonamide drugs which inhibit specifically a particular human carbonic anhydrase isozyme is of immense importance. From the refined crystal structures of human carbonic anhydrase I (HCAI) - sulfonamide complexes and subsequent molecular dynamics simulations, we have proposed a new sulfonamide inhibitor with stronger inhibition against HCAI. From the 2Å refined structures of three heterocyclic and aromatic sulfonamides complexed to HCAI the active site loop of L198, T199 and H200 was identified to be important for binding of the drug molecules (Chakravarty & Kannan, (1994). J. Mol. Biol., **243**, 298 - 309). The general features of binding of sulfonamides to HCAI were also revealed. The components of interaction energy which correlate well with the known inhibition constants for six sulfonamide complexes of both HCAI and HCAII were then

obtained using molecular dynamics simulations of XPLOR (Chakravarty, (1995). Ph.D. thesis, University of Bombay, India). Further simulations on nineteen other sulfonamide complexes whose crystal structures were not known, clearly revealed that the loop region comprising of L198, T199, H200, P201 and P202 were crucial for the design of HCAI - specific sulfonamide inhibitors. Several substituted aromatic and benzene sulfonamides were then docked into the active sites of the isozymes to optimise the interactions with these loop residues. Stereospecific substitution of methyl imidazole group in benzene sulfonamide resulted in strong interactions between the imidazole groups of the inhibitor and His 200 as observed from the energy minimised structure of the complex. Since His 200 is non - conserved between HCAI and HCAII, this indicated that the inhibitor would be more specific against HCAI. Energy minimisation of the resultant complex confirmed it. Further substitution of an alkyl chain resulted in additional stable non - bonded interactions with another non conserved active site residue Ala / Val 121. The compound BARCZM1 has been synthesised (Ghosh et al.; To be published) and is being characterized for its inhibitory properties the details of which will be presented.