The Southern California Drug Metabolism Discussion Group
Presents:

Characterization of Substrate/Inhibitor Binding to Drug-Metabolizing Cytochrome P450 Monooxygenases using X-ray Crystallography

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Cytochrome P450 monooxygenases determine the rate of clearance for many drugs, and metabolic clearance by P450s can limit the bioavailability and efficacy of new molecular entities. Although each of the major drug-metabolizing P450's exhibits a broad capacity to recognize structurally diverse compounds, they make distinct contributions to drug clearance that reflect underlying structural differences between the enzymes that shape substrate and inhibitor recognition. This is evident from comparative analyses of x-ray crystal structures for the predominant P450s in human liver, 3A4, 1A2, 2C9, 2C19, 2C8, 2D6, 2A6, 2A13 and 2E1, which contribute substantially to drug clearance. The largely hydrophobic substrate binding cavities differ greatly in size from >1500 Å3 for 3A4 and 2C8 to <300 Å3 for 2A6 and 2E1. Although trends in substrate profiles for each enzyme generally correspond well to cavity volumes, it is also clear that relatively small substrates can be efficiently oxidized by enzymes with much larger active site cavities. This reflects several mechanisms that include specific interactions that position the molecule appropriately for catalysis, differential changes in active site hydration, and occupancy of the active site by more than one substrate molecule such that one molecule facilitates oxidation of the other. Conversely, structures obtained for individual P450's complexed with structurally distinct substrates demonstrate active site plasticity, which can adapt in response to specific substrates. Together, these structures provide a basis for modeling the interactions of P450's with compounds of interest.

Tuesday, September 30, 2008

5:00 pm: Registration/Buffet
7:00 pm: Presentation Begins

Salk Institute for Biological Studies, Frederic de Hoffmann Auditorium
10010 North Torrey Pines Road, La Jolla, CA

Price: $15 Registration (includes buffet dinner and soft drinks / beer / wine)

The SCDMDG was established in 2003 as a forum for Southern California scientists working in drug metabolism in both academic and industrial settings to meet and discuss issues and share information for the public good.

Space is Limited— Please Register Early to Guarantee Your Attendance!

To Register for SCDMDG – E. Johnson, September 30, 2008, send payment with this form to:
5310 Eastgate Mall, San Diego, CA 92121

$15/person in advance or at the Door. Please make **CHECKS** payable to SCDMDG.

For more information ▪·phone 858.458.9305 ▪·e-mail: registration@scdmdg.org ▪·website www.scdmdg.org

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