The Southern California Drug Metabolism Discussion Group
Presents:

Mechanism-based Inactivation of Human Cytochromes P450

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The cytochrome P450s catalyze the metabolic activation of a wide variety of drugs and other xenobiotics to reactive intermediates which can covalently bind to cellular molecules ultimately leading to toxicity by a variety of different mechanisms. These reactive intermediates may also react with moieties in the P450 active sites that catalyze their formation to form covalent adducts that inactivate the P450 without ever leaving the active site, a process referred to as mechanism-based inactivation. The irreversible inactivation of the human P450s by drugs and other xenobiotics has resulted in a number of clinically significant drug-drug interactions and is of considerable importance in drug discovery and development. A variety of different types of drugs have been shown to undergo metabolic activation by P450s to very tight-binding or highly reactive intermediates that can inactivate the proteins by binding to the heme or to the apoprotein. Mechanism-based inactivators can be used to probe the active sites of P450s in their catalytically functional conformations. The identification of the site of modification, whether it is on the apoprotein or the heme prosthetic group, can provide valuable information regarding the three-dimensional structure of the active site. Recent advances in trapping procedures for the identification of reactive intermediates have greatly facilitated these types of studies. We have investigated the abilities of a wide variety of compounds to act as mechanism-based inactivators and determined the structural aspects and functional groups of several classes of molecules that lead to mechanism-based inactivation during metabolism by P450s. This presentation will focus on studies on the mechanism-based inactivation of human P450s, the trapping and identification of the reactive intermediates responsible for inactivation, and the determination of the sites of modification on the protein responsible for the loss of activity.

Tuesday, October 6, 2009

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

University of California, San Diego; Skaggs School of Pharmacy (La Jolla)

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 – F. Hollenberg, October 6, 2009, send payment with this form to:
5310 Eastgate Mall, San Diego, CA 92121

$20/person in advance or at the Door. Please make **CHECKS** payable to SCDMDG.

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