



The Southern California Drug Metabolism Discussion Group
Presents:

Regulation Of Intestinal CYP3A By VDR: Implications And Safety Of Oral Therapeutics

Dr. Kenneth Thummel, PhD

Professor and Chair
Department of Pharmaceutics
University of Washington
Seattle, Washington

Biotransformation of drugs and other xenobiotic molecules by hepatic and intestinal CYP3A4 can be a major determinant of the systemic bioavailability and clearance of orally administered drugs. The expression and function of CYP3A4 in these tissues is most likely influenced by multiple mechanisms of control, including those that involve endogenous and exogenous modifiers of gene transcription that exert their effects through activation of nuclear hormone receptors.

Through a series of cell-based and in-vivo studies we, and others, have shown that CYP3A4 expression within enterocytes of the small intestine may be activated through a vitamin D receptor mediated signaling pathway (5-8). Moreover, CYP3A4 can catalyze the catabolism of the most active receptor ligand, 1 α ,25-dihydroxy vitamin D₃, providing the possibility of feedback control of important genomic effects of the hormone in this tissue (9,10).

Two questions emerge from these observations:

1. Does variability in the VDR signaling pathway contribute to inter-individual differences in basal intestinal CYP3A4 expression?
2. Does modification of CYP3A4 expression by exogenous stimuli (e.g., drug activators of hPXR) affect the local disposition of vitamin D and, in turn, its genomic effects and contribute to adverse drug reactions?

In this presentation, the speaker will review evidence for the control of intestinal CYP3A4 by VDR and the proposed feedback control of vitamin D genomic effects through CYP3A4-dependent vitamin D metabolism. These issues will also be discussed in the broader context of understanding sources of inter-individual differences in both efficacious and adverse drug response.

Kenneth Thummel is Professor and Chair of the Department of Pharmaceutics, School of Pharmacy, University of Washington. He received a Bachelor of Science degree in Chemistry from Boise State University in 1981 and a Ph.D. in Pharmaceutical Science from the University of Washington in 1987. He completed a post-doctoral fellowship with Dr. John Schenkman at the University of Connecticut Health Science Center, studying in the field of cytochrome P450 structure and function. In 1989, he joined the faculty at the University of Washington and was promoted to the rank of Professor in 2001. In 1997, he was appointed to the Institute for Public Health Genetics, and currently serves as the program deputy director.

Wednesday, May 7, 2008

5:00 pm: Registration and Buffet Dinner

7:00 pm: Presentation Begins

Biogen Idec

5200 Research Place, San Diego, 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 - K. Thummel, May 7, 2008 send payment with this form to:
5310 Eastgate Mall, San Diego, CA 92121

\$15/person in Advance, \$15 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

Name(s) _____
Company _____
Address _____
Phone _____ E-mail _____
Attending _____ Amount Enclosed \$ _____