

# 2007 Distinguished Scholars in Toxicology Lecture Series

Hosted by  
The Center for Integrative Toxicology  
In cooperation with  
The Department of Pharmacology and Toxicology

Wednesday, January 31, 2007

**Jose Manautou, Ph.D.**

Department of Pharmaceutical Sciences  
University of Connecticut

**“Changes in Expression of  
Hepatobiliary Transport Proteins  
as a Compensatory Response  
to Drug-Induced Hepatotoxicity”**

Wednesday, March 14, 2007

**David Sherr, Ph.D.**

Department of Environmental Health,  
Boston University, School of Public Health

**“The Role of the AHR, an Environmental Chemical  
Receptor, in Mammary Tumor Growth and Invasion”**

12 noon to 1 p.m.

**B448-9 Life Sciences Building**

## **Manautou Lecture Abstract**

Drug-induced liver injury impairs hepatobiliary function and results in altered xenobiotic disposition. Our laboratory has carried out a comprehensive temporal characterization of the expression of multiple mouse uptake and efflux drug transporters following acetaminophen and carbon tetrachloride exposure. Our studies have shown that hepatotoxic doses of acetaminophen and carbon tetrachloride decrease mRNA and protein levels of uptake drug transporters (organic anion transport proteins, Oatps, and sodium-taurocholate co-transporting polypeptide, Ntcp), while increasing the levels of efflux transporters (multidrug resistance-associated proteins, Mrps). Zonal analysis demonstrates induction of Mrp isoforms 3 and 4 (Mrp3 and Mrp4) in centrilobular hepatocytes. Furthermore, Mrp4 immunochemical staining is localized to cells undergoing active replication adjacent to injured zones. Both Mrp3 and 4 are efflux transporters located in the basolateral membrane of hepatocytes and they mediate the elimination of endogenous compounds and xenobiotics into sinusoidal blood. Administration of a second, higher dose of acetaminophen to mice at 48 hr after the initial dose resulted in lower hepatotoxicity, which is a phenomenon known as autoprotection. This autoprotection is seen in association with a much more robust induction in Mrp4 expression. From these studies we have hypothesized that up-regulation of efflux transporters (particularly Mrp4) is a protective mechanism that minimizes accumulation of potentially toxic chemicals in hepatocytes and may also be a mechanism for enhanced paracrine signaling within the liver during recovery from injury. More recently, we have investigated regulatory factors underlying these changes in transport protein expression. Our focus has been on the transcription factor nuclear factor E2-related factor 2 (Nrf2) and on signaling molecules originating from Kupffer cells. Nrf2 is activated during periods of oxidative stress and is responsible for the transcriptional regulation of multiple antioxidant and detoxification genes, while Kupffer cell function is known to influence the susceptibility of the liver to chemical toxicants. Studies with Nrf2 knockout mice demonstrate that the up-regulation of Mrp3 and Mrp4 by APAP is dependent on Nrf2 expression. Similarly, mice depleted of Kupffer cells by treatment with liposomal clodronate show an impaired capacity to increase expression of some Mrp proteins in response APAP treatment. Collectively, these findings provide insightful information on the regulation of hepatobiliary transporters expression in mice during drug-induced liver injury. Further studies are necessary to establish the functional consequences of altered transporter levels during hepatotoxicity.

## **Biographical Information**

Jose Manautou is associate professor of toxicology in the Department of Pharmaceutical Sciences at the University of Connecticut. His research interests are in biochemical and molecular mechanisms of hepatotoxicity. Specifically, he is interested in studying the role of multidrug resistance proteins in the hepatobiliary disposition of toxicants. His laboratory also investigates changes in expression of transport proteins in response to chemical liver injury as well as the hepatoprotective effects of peroxisome proliferators. Dr. Manautou has served as Councilor of the Society of Toxicology and is a former Councilor of the SOT's Mechanisms Specialty Section. He was the 2006 recipient of the SOT Achievement Award for significant contributions to the field of toxicology. Most recently, Dr. Manautou served as a member of the National Research Council Committee Assessing the Human Health Risks of Trichloroethylene and has been appointed Associate Editor for the journal Toxicology and Applied Pharmacology. Dr. Manautou is currently a member of the NIH XNDA study section. He received his Ph.D. in pharmacology and toxicology from the Purdue University School of Pharmacy and his postdoctoral training in toxicology at the University of Connecticut. He also conducted sabbatical research at the Academic Medical Center of the University of Amsterdam.