Quantitative Translational Safety: A 21st Century Approach for Predictive Assessment of Drug-Induced Hepatic and Renal Toxicities

- Overall attrition rates due to hepatotoxicity and nephrotoxicity – changes over the last decade?
- A mechanistic insight into organ specific toxicity is critical to circumventing safety issues that often limit the clinical use of approved drugs or may even lead to market withdrawal.
- Role of drug metabolizing enzymes and transporter – parent drug vs metabolites.
- Tissue-specific exposure of drugs/metabolites is a well-known determinant of organ-specific toxicities.
- Yet a major complexity in assessing the mechanistic basis of toxicity is that pathophysiological effects frequently are not apparent during short term drug exposure.
- Either sub-chronic or chronic drug exposure often is required for the toxicities to manifest and studies that provide the key results consume large amounts of time, effort, and resources.
- Thus, for early stage drug development and lead optimization there is increased reliance upon high throughput in vitro methods and
- the use of biomarkers that allow an earlier definition and identification of critical toxicities.
- Academia/Industry/FDA colleagues will share their perspectives on the state-of-the art in predictive organ-specific toxicities,
- advances in toxicogenomics/toxicoproteomics and toxicokinetics and factors that still limit the bridging of pre-clinical and clinical safety assessment.
Assessing Drug-Induced Liver Injury During Clinical Trials and Post-Marketing

- Paul B. Watkins, MD, is director of the Hamner-University of North Carolina Institute for Drug Safety Sciences.
- Professor of Medicine, Pharmacy and Public Health at the UNC Chapel Hill
- Trained clinical hepatologist
- Accomplished basic and translational investigator in drug metabolism and hepatotoxicity.
- Chair of both the Steering and Genetics Committees for the U.S. Drug-Induced Liver Injury Network (DILIN) (U01DK065201).
- One of the most frequently cited authors in the field of pharmacology according to www.ISIhighlycited.com.
- He is the recipient of numerous honors and awards including:
  - Therapeutic Frontiers Award from the American College of Pharmacy
  - election to the Association of American Physicians (AAP),
  - the 2013 Agilent Therapeutic Frontiers Award, and
  - 2015 Rawls-Palmer Award for Progress in Medicine from the American Society for Clinical Pharmacology and Therapeutics
Quantitative Translational Safety: A 21st Century Approach for Predictive Assessment of Drug-Induced Hepatic and Renal Toxicities

AGENDA: Pre-Lunch

**8:15 am–9:15 am**

*Assessing Drug-Induced Liver Injury During Clinical Trials and Post-Marketing*

Paul Watkins, M.S. Hamner Institutes for Health Sciences

**9:15 am –10:15 am**

*Contemporary Approaches and Challenges in Assessing Drug-Induced Hepatotoxicity*

Kim L. Brouwer, Ph.D. University of North Carolina at Chapel Hill

Beverage Break, 10:15 – 10:30 am

**10:30 am–11:30 am**

*Industry Perspectives on the State-of-the Art in Assessment of Drug-Induced Liver Injury*

Jonathan Maher, Ph.D., Genentech, Inc.

Lunch, 11:30 am–12:30 pm *Room W308*
Quantitative Translational Safety: A 21st Century Approach for Predictive Assessment of Drug-Induced Hepatic and Renal Toxicities

AGENDA: Post-Lunch

12.30: - 1.30 pm:
Defining a Translation Safety Strategy for Drug Induced Kidney Injury: The Role of Biomarkers in Drug Development
John-Michael Sauer, Ph.D., Critical Path Institute

Beverage Break, 1:45 – 1:30 pm

1:45 pm–2:45 pm
A Regulatory Perspective on Evaluating and Monitoring for Drug-Induced Kidney Injury in Drug Development
Aliza Thompson, M.D., U.S. Food and Drug Administration

2:45 pm–3:45 pm
Clinical Assessment of Renal Toxicity Risks: Key Considerations during Drug Development and Post-Marketing
Gary Friedman, Ph.D., Pfizer, Inc.

3:45 pm–4:00 pm
Panel Discussion
Moderator, John-Michael Sauer, Ph.D., Critical Path Institute
Contemporary Approaches and Challenges in Assessing Drug-Induced Hepatotoxicity

Kim L. Brouwer, Ph.D. University of North Carolina at Chapel Hill

• Associate Dean for Research and Graduate Education, UNC Eshelman School of Pharmacy, and Kenan Distinguished Professor in the School of Pharmacy and Curriculum in Toxicology at UNC-Chapel Hill.

• PharmD/PhD in Pharmaceutical Sciences/Pharmacokinetics from the University of Kentucky (UK) College of Pharmacy, and postdoctoral training in Pharmacology/Drug Metabolism in the UK College of Medicine.

• Dr. Brouwer directs an NIH-funded research program focused on hepatobiliary drug disposition, hepatic transport proteins, and development/refinement of in vitro models to predict in vivo hepatic drug disposition, drug interactions, and hepatotoxicity.

• Dr. Brouwer was founding Director of the UNC Pharmacokinetics/Pharmacodynamics Fellowship Program and is Co-PI of an NIH-funded T32 Clinical Pharmacology Postdoctoral Training Program.

• Dr. Brouwer is co-inventor of B-CLEAR® and is co-founder of Qualyst Transporter Solutions, a UNC spin-off company.

• Member of numerous Steering editorial boards, NIH study sections.

• Dr. Brouwer was recognized as an AAPS Fellow in 1998 and received the 2001 PhRMA Foundation Award in Excellence in Pharmaceutics. In 2009, Dr. Brouwer was named a Kenan Distinguished Professor, one of the highest honors bestowed on UNC faculty.
Industry Perspectives on the State-of-the Art in Assessment of Drug-Induced Liver Injury

Jonathan Maher, Ph.D

• Dr. Jonathan Maher is currently a project discovery toxicologist at Genentech, and supports multiple projects across several therapeutic areas.

• He was formerly employed as an investigative toxicologist at Abbott Labs/Abbvie for more than four years, and was intricately involved in DILI screening paradigms and biomarker development.

• Jon received his PhD in toxicology from the University of Kansas Medical Center, from the laboratory of Dr. Curtis Klaassen. Similarly he is a DABT-certified toxicologist, and has over 40 peer-reviewed publications, reviews, and book chapters.

• Member of the Critical Path Institute Hepatobiliary Working Group, and is the current co-chair of the BSEP Subteam, which is currently assessing the contributions of BSEP transporter inhibition to DILI.

• He serves on the editorial board of Toxicology and Applied Pharmacology, and has recently become an adjunct research assistant professor at the University of Arizona.