

Monday, June 14

MORNING COURSES 9:00 am – 12:00 pm

(SC1) Reactive Metabolites in Drug Discovery and Development-A Critical Examination of the Issues

You will obtain a perspective on the variety of factors necessary to make informed decisions regarding reactive metabolites.

- Analytical approaches to detect and characterize reactive metabolites
- Bioactivation pathways that lead to reactive metabolites
- Toxicophores and Structural Alerts
- Evidence linking reactive metabolites and Idiosyncratic drug toxicity
- Reactive metabolites and covalent protein binding

Course Instructor:

John C.L. Erve, Ph.D., DABT, Principal Research Scientist II, Drug Safety Metabolism, Wyeth Research

(SC2) Animal Models of Pain: Progress and Challenges

Due to frustration with translational progress, animal models of pain are currently being reconsidered. This course will cover:

- Implementation of classical models of acute, tonic and chronic pain
- Limitations of these classical models
- Refinement of classical models via a consideration of modulatory factors (sex, genetics, testing environment, social modulation)
- Development of new animal models (e.g., operant methods, spontaneous behaviors)

Course Instructor:

Jeffrey S. Mogil, Ph.D., E.P.Taylor Professor of Pain Studies, McGill University

(SC3) Translating Safety Biomarkers from the Lab to the Clinic

The course offers a unique and practical perspective for successfully translating the pre-clinical work done for testing and validating safety biomarkers to the clinic.

- Design and implementation of studies to identify new biomarkers
- Designing clinical studies to test and validate biomarkers
- Clinical methodologies for cost-effective and reliable decision-making
- Bridging the gap between pre-clinical and clinical findings
- Practical considerations when using biomarkers in the clinic
- Points to consider for a successful transfer from the lab to the clinic

Course Instructor:

Stephen Furlong, Ph.D., Safety Science Lead, U.S., Patient Safety, AstraZeneca

William B. Mattes, Ph.D., DABT, Independent Consultant, PharmPoint Consulting

(SC4) Use of Stem Cells for Safety Screening

The course provides new insights into the use of embryonic and pluripotent stem cells for drug safety testing, especially cardiac safety.

- Differentiation of human stem cells into cardiac myocytes
- Comparison of electrophysiology and pharmacology
- Overcoming technical challenges related to working with stem cells
- Methodologies to maintain and use stem cells for predictive safety testing

Course Instructors:

Craig T. January, M.D., Ph.D., Professor, Medicine and Physiology, Division of Cardiovascular Medicine, University of Wisconsin-Madison
Timothy J. Kamp M.D., Ph.D., Professor of Medicine and Physiology and Director, Stem Cell and Regenerative Medicine, University of Wisconsin School of Medicine and Public Health

Dany Salvail, Ph.D., Director, Pharmacology, Cardiac Safety and Toxicity, IPS Therapeutique, Inc.

Steven L. Stice, Ph.D., Professor, Director, Regenerative Bioscience Center, University of Georgia

AFTERNOON COURSES 2:00 pm – 5:00 pm

(SC5) Dealing with the Blood-Brain Barrier

You will obtain a perspective on the variety of factors necessary to make informed decisions regarding blood-brain barrier.

- The physiological basis for the "barrier" nature of the BBB
- Experimental approaches (*in vitro/in vivo*) that are available for screening for brain penetration
- Medicinal chemistry perspective on *in vitro/in silico* approaches for optimizing CNS penetration
- Multi-parameter optimization (MPO) for CNS penetration
- *in vivo* examples where all these concepts are applied together, e.g., consideration of free fractions in various compartments in relation to *in vitro* pharmacology values
- Projecting human receptor occupancies considering species differences in affinity, free fraction
- Exposure targeting for biomarker studies

Course Instructors:

Douglas Spracklin, Ph.D., Director, Pharmacokinetics, Dynamics & Metabolism, Pfizer, Inc.

Christopher L. Shaffer, Ph.D., Associate Research Fellow, Pharmacokinetics, Dynamics & Metabolism, Pfizer, Inc.

Travis T. Wager, Ph.D., Associate Research Fellow, Neuroscience Discovery Medicinal Chemistry, Pfizer, Inc.

Lisa Plitnick, Ph.D., Senior Investigator, Biologics Safety Assessment, Merck & Co. Inc.

(SC6) Addressing Safety Concerns for Biological Drugs

The course offers guidance from experts in the field on what is being used and looked at for early safety assessments for biological molecules and how these early predictions are then being applied for clinical testing.

- Overview of challenges pertaining to the safety of biologics
- Tools, markers and assays for early safety predictions
- Assessing immunogenicity, PK/PD and off-target effects
- Regulatory guidelines and their interpretations
- Criteria for determining what needs to be tested and when

Course Instructors:

Gary Gintant, Ph.D., Senior Group Leader, Department of Integrative Pharmacology, Abbott Laboratories

Lauren Black, Ph.D., Senior Scientific Advisor, Charles River Laboratories

Noël Dybdal, Ph.D., D.V.M., Associate Director, Principal Scientist, Safety Assessment, Genentech, Inc.

(SC8) Mechanistic Insights into Cardiotoxicity

The course offers detailed information about some of the genetic and physiological factors that trigger cellular pathways leading to cardiac injury and failure.

- Genetics, physiology and risks in human heart failure
- Mechanisms underlying sex differences in ion channel expression and their role in arrhythmia phenotype
- Sex differences in the severity of ischemic injuries and in general, the effects of sex steroids in metabolic injuries

Course Instructors:

Barry London, M.D., Ph.D., Professor of Medicine and Chief, Division of Cardiology, University of Pittsburgh School of Medicine

Guy Salama, Ph.D., Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine

Kenneth S. Korach, Ph.D., Director, Environmental Disease and Medicine Program; Chief, Laboratory of Reproductive and Developmental Toxicology, NIEHS/NIH

Wednesday, June 16

6:00 – 9:00 pm (Dinner will be served)

(SC9) Mechanistic Insights into Hepatotoxicity

The course is designed for both pre-clinical and clinical scientists looking to better understand the mechanisms underlying drug-induced liver injury or DILI, to help in the development of early predictive technologies for hepatotoxicity including mechanism-based assays. It provides an overview of cellular pathways involved in:

- Mitochondrial dysfunction and Oxidative stress
- Inflammation
- Excessive generation of reactive metabolites
- Inhibition of bile salt efflux protein and involvement of hepatic transporters
in drug-induced hepatotoxicity

Course Instructors:

Amit S. Kalgutkar, Ph.D., Research Fellow, Pharmacokinetics, Dynamics and Metabolism Department, Pfizer Global R&D

José E. Manautou, Ph.D., Associate Professor of Toxicology, Department of Pharmaceutical Sciences, University of Connecticut

Ivan Rusyn, M.D., Ph.D., Associate Professor of Environmental Science and Engineering, University of North Carolina

Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D