Drug Safety Summit

Early, Efficient and Effective Tools for Predicting Drug-Induced Adverse Events

Monitoring Cardiotoxicity
Predicting Hepatotoxicity
Detecting Nephrotoxicity
Early ADME/DMPK Predictions

FEATURED SPEAKERS

Thomas Force, M.D.
Professor of Medicine and Clinical Director of the Center for Translational Medicine, Thomas Jefferson University

Stephen Furlong, Ph.D.

Paul B. Watkins, M.D.
Director, Hamner-UNC Institute for Drug Safety Sciences, Verne S. Caviness Distinguished Professor of Medicine, University of North Carolina at Chapel Hill

SHORT COURSES

Monday, June 6

- Use of Stem Cells for Safety Screening
- Advanced Topics in Drug Metabolism
- Translating Safety Biomarkers from the Lab to the Clinic
- Addressing Safety Concerns for Biological Drugs

Wednesday, June 8

- Mechanistic Insights into Hepatotoxicity

World Pharma Congress
Promising Assays and Technologies for Better Pre-Clinical Predictions

Cambridge Healthtech Institute

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CHI’s **World Pharma Congress 2011** encompasses a broad spectrum of topics that are very important and relevant to scientists in academia as well as those in the pharmaceutical and biotechnology industry. Building on last year’s focus on the pre-clinical aspects of drug discovery and development, the congress has now expanded the coverage of each of its three summits by adding two new conferences to the program. The conferences all offer informative and pragmatic viewpoints for tackling issues relevant to chemists, biologists, pharmacologists, toxicologists and clinicians alike. Each conference features presentations, interactive panels and technology talks that cover the very latest on the topic, both on the scientific and the technical side. The World Pharma Congress continues to offer attendees and exhibitors ample opportunity to network, brain-storm and collaborate on various fronts.

## WORLD PHARMA CONGRESS CONFERENCE-AT-A-GLANCE

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*Separate registration required, please see page 3 for details.

## SPONSORSHIP AND EXHIBITOR INFORMATION

CHI offers comprehensive sponsorship packages which include presentation opportunities, exhibit space, branding, as well as the use of the pre and post show delegate list. Sponsorships allow you to achieve your objectives before, during, and long after the event. Any sponsorship can be customized to meet with your company’s needs and budget.

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**For information, contact:**

**Suzanne Carroll**

**Manager, Business Development**

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2 | World Pharma Congress
WJC Short Courses*

MONDAY, JUNE 6 (9 AM - 12 PM)

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., operand methods, spontaneous behaviors)
Course Instructor:
Jeffrey S. Mogil, Ph.D., E.P. Taylor Professor of Pain Studies, McGill University

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 Instructor:
Emile Nuwaysir, VP and COO, Cellular Dynamic Intl.

ADVANCED TOPICS IN DRUG METABOLISM
The purpose of this course is to cover advanced topics related to drug metabolism with a focus on newer developments in the field.
- In vitro tools to study drug metabolism
- New biotransformation pathways including some that lead to reactive metabolites
- Evidence linking reactive metabolites and idiosyncratic drug toxicity
- In silico tools to predict metabolism
Course Instructor:
John C. Erve, Ph.D., Investigator III, Analytical Sciences, Novartis Institutes for Biomedical Research

MONDAY, JUNE 6 (2 PM - 5 PM)

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

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 and off-target effects
- Regulatory guidelines and their interpretations
- Criteria for determining what needs to be tested and when
Course Instructors:
Lisa M. Plitnick, Ph.D., Senior Investigator, Safety Assessment, Merck & Co., Inc.
Noël Dybdal, Ph.D., D.V.M., Associate Director, Principal Scientist, Safety Assessment, Genentech, Inc.
Vivek Kadambi, Ph.D., Senior Director, Drug Safety Evaluation, Millennium, The Takeda Oncology Company
Lauren E. Black, Ph.D., Senior Scientific Advisor, Navigators, Charles River Laboratories

WEDNESDAY, JUNE 8 (6 PM - 9 PM)

MOLECULAR IMAGING IN DRUG DISCOVERY AND DEVELOPMENT: BACK TO BASICS.
This course will provide knowledge needed to choose the appropriate imaging modality for a pre-clinical study and the basic requirements for generation of imaging agents for optical, MRI, and nuclear imaging. It will consist of two parts:
- Strengths and limitations of imaging modalities
- Imaging agent design and synthesis
Chairperson: Dr. Matthew Leevy, Carestream Molecular Imaging
Course Instructors:
Thomas Krucker, Ph.D., Head, Molecular Imaging, Global Imaging Group, Novartis Institutes for Biomedical Research, Inc.
Hisataka Kobayashi, M.D., Ph.D., Chief Scientist, Molecular Imaging Program, NCI/NIH
Vania Kenanova, Ph.D., Head, Pre-clinical PET/SPECT/CT Imaging Laboratory, Novartis Institutes for Biomedical Research, Inc.

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:
Dylan P. Hartley, Ph.D., Senior Scientist, Investigative Toxicology, Genentech, Inc.
José E. Manautou, Ph.D., Associate Professor of Toxicology, Department of Pharmaceutical Sciences, University of Connecticut
Robert A. Roth, Ph.D., DABT, Professor, Pharmacology and Toxicology, Director, Graduate Program in Environmental and Integrative Toxicological Sciences, Michigan State University
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

*Separate Registration Required
TUESDAY, JUNE 7

7:45 am Registration and Morning Coffee

EARLY IN VITRO MODELS AND MARKERS FOR CARDIAC SAFETY PREDICTIONS

8:45 Chairperson’s Opening Remarks
Peter Hoffmann, M.D., Ph.D., Executive Director, Pre-Clinical Safety, Novartis Institutes for BioMedical Research

8:55 Expanding in vitro Biochemical and Cellular Models for Earlier Drug Safety Assessment
Mary Ellen Cvijic, Ph.D., Principal Scientist, Lead Evaluation, Molecular Sciences and Candidate Optimization, Bristol-Myers Squibb Co.
We have developed a high-throughput in vitro assay panel including target classes such as GPCRs, kinases, transporters, ion channels, and nuclear hormone receptors to determine which critical targets can be used to best flag potential cardiac liability issues before compounds advance to in vivo or late-stage drug safety evaluation. We have investigated which in vitro assays offer more sensitive and physiologically-relevant read-outs for assessing compound safety profiles and have identified current gaps in harnessing state-of-art technology platforms. We can now address how to establish a comprehensive pharmacologic liability tool kit for structure liability relationship studies and how to build connectivity between cause and effect.

9:25 Stem Cell Cardiomyocyte Screening
Craig T. January, M.D., Ph.D., Professor, Medicine and Physiology, Division of Cardiovascular Medicine, University of Wisconsin, Madison

9:55 Networking Coffee Break

10:25 Development of Translatable Biomarkers for Cardiovascular Safety
Jennifer Colangelo, Ph.D., Associate Director, Drug Safety R&D, Pfizer Global Research and Development
Safety biomarkers are an integral part of the decision-making process for drug development at all stages, aiding in compound selection for early pre-clinical studies and ensuring patient safety in clinical trials. Mass spectrometry is one of the critical tools for safety biomarker discovery, development and deployment, providing assays that are often easily translatable between species. This presentation will provide examples of mass spectrometry applications to the development of biomarkers for drug-induced cardiovascular toxicity, including MS-based metabolomics for biomarker discovery and stable label approaches for the quantitation of novel proteins.

10:55 Pre-Clinical Strategies for De-Risking the Potential of Cardiovascular Toxicity
Peter Hoffmann, M.D., Ph.D., Executive Director, Pre-Clinical Safety and Co-Chair, Translational Cardiovascular Advisory Team, Novartis Institutes for BioMedical Research
The introduction of in vitro and in vivo cardiovascular safety tests as suggested by guidelines S7A and S7B was successful in preventing acute and catastrophic effects in Phase 1 studies, primarily in healthy male volunteers. On the contrary, recent experiences show that the manifestation of human cardiovascular adverse effects during late stage clinical development or post-marketing is poorly predicted. The presentation summarizes current status and emerging trends of preclinical strategies for de-risking the potential of cardiovascular toxicity in the target population, e.g., diabetic patients.

11:25 Biologicals and Cardiac Toxicity Risk: Relating Toxicity to Mechanism of Action
Noël Dybdal, Ph.D., D.V.M., D.A.C.V.P., Associate Director, Principal Scientist, Safety Assessment, Genentech, Inc.
High molecular weight biological therapeutics in general and monoclonal antibodies specifically are highly targeted in their activity and risk of off-target toxicity is low. Adverse cardiovascular effects associated with these drugs to-date result from on-target pharmacology and relate to their mechanism of action. Species specificity of biologics presents challenges that limit the extent to which cardiovascular toxicity risk can be assessed preclinically. However, novel approaches including in vitro strategies are increasingly offering better opportunities for focused safety assessments. This presentation will include case studies as examples of preclinical cardiac toxicity assessments for biologicals of various types.

11:55 Multiplex Biomarker Assays for Kidney and Liver Toxicity
Pankaj Oberoi Ph.D., Director of Scientific Services & Director of Qualified Kit Development, Meso Scale Discovery
Protein expression fingerprints of various biological samples can be used for measuring drug efficacy and toxicity and for target selection. Multiplexing has the advantage of rapidly measuring levels of multiple analytes from a limited sample volume, which is critical for preclinical and clinical studies where samples are precious and often limited. There are numerous challenges to overcome during the development and validation of biomarker assays and these challenges are magnified when considering multiplex biomarker assays. Meso SCALE DISCOVERY® is focused on the development and validation of multiplex biomarker assays to serve the safety biomarker community. A description of novel assays for human and rat kidney biomarkers as well as rat liver biomarkers will be discussed.

12:25 pm Luncheon Presentation II
(Sponsorship Opportunity Available)

CHALLENGES CORRELATING IN VITRO AND IN VIVO DATA

1:30 Chairperson’s Remarks
Vivek Kadambi, Ph.D., Senior Director, Drug Safety Evaluation, Millennium, The Takeda Oncology Company

1:35 Evolving Trends in Pre-Clinical Cardiovascular Safety: Gazing into the Crystal Ball
Gary Gintant, Ph.D., Senior Group Leader, Integrative Pharmacology, Global Pharmaceutical Research & Development, Abbott Laboratories
Increasing emphasis on the safety of novel drug candidates demands more efficient discovery and development efforts with a balanced focus on risk/benefit considerations. This goal will be realized only with a) early “frontloading” of appropriate assays to derisk compounds early in discovery, b) an understanding of the strengths and limitations of present (and evolving) assays, and c) an appreciation of present and emerging cardiac safety issues within the context of drug efficacy in development. This presentation will provide some instructive preclinical examples of where we have succeeded present-day gaps in our understanding, and future challenges for pre-clinical cardiac safety.

2:05 Does it Help or Hurt to Know Cardiovascular Biology?
Douglas B. Sawyer, M.D., Ph.D., Lisa M. Jacobson Professor of Medicine and Chief, Cardiovascular Division, Vanderbilt University Medical Center
Cardiotoxicity

5:35 - 6:30 Happy Hour in the Exhibit Hall

Evaluation, Millennium, The Takeda Oncology Company
Moderator: Vivek Kadambi, Ph.D., Senior Director, Drug Safety

Between the Worlds
In Vivo

5:05 PANEL DISCUSSION: Minimizing the Disconnect
Between the *In Vitro* and *In Vivo* Worlds
Moderator: Vivek Kadambi, Ph.D., Senior Director, Drug Safety Evaluation, Millennium, The Takeda Oncology Company

5:35 - 6:30 Happy Hour in the Exhibit Hall

MITOCHONDRIAL INVOLVEMENT IN CARDIAC, RENAL AND LIVER TOXICITY
*(Joint session for Cardiotoxicity and Nephrotoxicity tracks)*

8:30 Chairperson’s Remarks
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

8:40 Introduction to Mitochondrial Function and Drug-Induced Dysfunction
James Dykens, Ph.D., CEO, EyeCyte Therapeutics
Mitochondria typically produce more than 90% of the ATP in aerobically poised cells, plus the majority of potentially injurious, free radicals. Inhibition of the electron transfer system, or the uncoupling of the membrane potential it generates from phosphorylation, reduces the bioenergetic capacity of the cell. Many drugs have direct and deleterious mitochondrial effects that contribute to the etiology of idiopathic drug-induced organ toxicity. These off-target effects are a function of compound chemistry, but also of genetic diversity in plasma membrane transporters that facilitate bio-accumulate of drugs into the mitochondria. Emerging animal models will be discussed with an emphasis on hepatotoxicity.

9:10 Tales of Broken Mitochondria: Drug-Induced Cardiac Mitochondrionopathy
Paulo Oliveira, Ph.D., Group Leader, Mitochondrial Toxicology and Disease, Center for Neuroscience and Cell Biology, University of Coimbra, Portugal and Visiting Research Associate, University of Minnesota Medical School
Drug-induced cardiac mitochondrial dysfunction can progressively result in organ degeneration. Classical examples of drug-induced cardiac mitochondrialopathy include nucleoside reverse transcriptase inhibitors, local anesthetics and anthracyclines. Doroxubicin (adriamycin, DOX) is a clear case study of a well known pharmaceutical that can lead to progressive degeneration of cardiac mitochondrial function. DOX is a potent anthracycline anti-neoplastic agent, whose clinical use is limited by a dose-dependent and cumulative cardiotoxicity, with a clear mitochondrial component. In this case, protection of cardiac mitochondrial function during DOX treatment appears to be critical for preventing the maintenance of the myocyte bioenergetics.

9:40 Automate the Detection and Quantitative Characterization of Pathological Changes - Benefits of Digital Pathology in Drug Development
Curtis Adams, Ph.D., Senior Product Manager, Life Sciences, Aperio
Aperio’s digital pathology and whole-slide image analysis tools facilitate research in drug discovery. Discover how pathologists can improve measurement of morphological changes, work across international boundaries, and better communicate tissue toxicity results.

10:10 Networking Coffee Break in the Exhibit Hall

10:50 Mitochondrial Homeostasis in Acute Kidney Injury
Rick Schnellmann, Ph.D., Professor, Chair, Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy
Mitochondrial damage is a major contributor to the initiation of tubular cell injury and the progression of acute kidney injury (AKI) produced by...
drugs, toxicants, and ischemia. To understand the role of mitochondria in organ damage and repair, we think that mitochondria need to be examined holistically by measuring mitochondrial homeostasis. This includes changes in mitochondrial loss, fission/fusion, mitophagy, and biogenesis over time. Using this approach, temporal differences in mitochondrial loss, dynamics and biogenesis were observed with mitochondrial loss occurring early and changes in mitochondrial fission/fusion and biogenesis occurring later after AKI.

11:20 Mechanistic Insights into Mitochondrial-Based Organ Toxicity
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

Previous speakers have elucidated in detail on the contribution of mitochondrial impairment to different organ toxicities. It is apparent that in order to avoid late stage attrition due to mitochondrial toxicity, early predictive screens need to be deployed early in the drug discovery process. Here I will show organelle and cell-based HTS applicable screens to detect such liabilities. I will describe the screens using examples from different drug classes such as antidiabetics/antilipidemics, antivirals, antibiotics, and NSAIDs.

11:50 PANEL DISCUSSION: Strategies for Assessing Mitochondrial Involvement in Drug-Induced Organ Toxicities
Moderator: Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

12:20 pm End of Conference
Methodology for Predicting Hepatotoxicity

This also applies to children. Children are not simply small adults and it follows that children may exhibit differential sensitivity to drug-induced adverse events. This applies to drug-induced liver injury (DILI). As an embryo develops, leading to the birth of a child, and eventually maturation into an adult, the human body goes through many different development phases. Various factors involved with the developmental phases may make the developing human more or less susceptible to DILI when compared to adults. This presentation will review the major developmental phases of the maturing liver with an emphasis on phases that may pose unique sensitivities to DILI.

Toxicology, Fluofarma

Efforts to develop new biomarkers for IDILI have been largely unsuccessful due to limitations such as, incomplete understanding of the mechanisms, lack of effective in-vitro models, absence of universally accepted animal models, and often, lacking scientific exchange between clinicians and basic science researchers. One important prerequisite for the facilitation of new IDILI biomarkers is enhanced understanding on the types of questions that can and should be addressed. This presentation will outline pertinent clinical issues that could theoretically be addressed by specific diagnostic or predictive biomarkers.

Arie Regev, M.D., Hepatology Consultant and Chair, Liver and GI Safety Advisory Committee, Global Patient Safety, Eli Lilly and Company

Over the last several years, some pharmaceutical companies have successfully used genome wide association (GWA) to find genetic susceptibility loci for hepatotoxicity observed in clinical trials. In one case, this approach has lead to a proposal to reintroduce with routine genetic testing a drug that has been withdrawn from worldwide markets due to DILI. Genotyping data from the largest DILI genebanks (the International Severe Adverse Events Consortium and the U.S. based Drug Induced Liver Injury Network) have been recently pooled. GWA analysis of this dataset, which reflects DILI due to over 200 different drugs, is providing fresh insight into mechanisms underlying DILI and should inform the hunt for epigenetic and environmental factors underlying DILI.

Paul B. Watkins, M.D., Director, Hammer-UNC Institute for Drug Safety Sciences, Verne S. Caviness Distinguished Professor of Medicine, University of North Carolina at Chapel Hill

Drug-induced liver injury (DILI) is the adverse drug event that most frequently leads to termination of clinical development programs and regulatory actions on drugs. A predictive model has been developed based on physiological processes involved in DILI. The model initially focuses on acetaminophen and includes multiple scales, spanning from the organ/tissue level to the molecular and cellular levels. The model accurately reproduced acetaminophen pharmacokinetic and other measures for rats, mice, and humans. The use of N-acetyl-cysteine (NAC) as a treatment for acetaminophen overdose was analyzed to predict optimal use. Finally, the model successfully predicted the species differences in hepatotoxicity of methapyrilene using in vitro to in vivo extrapolation.

3:00 Development of a New High Content Methodology for Predicting Hepatotoxicity

Marion Zanese, Ph.D., Group Leader, Predictive Toxicology, Fluofarma

Drug-induced liver injury is a major issue during drug development process. However, there remains a shortage of early models to predict in vivo hepatotoxicity satisfactorily. We present here an optimized predictive methodology which relies on high-throughput flow cytometry applied to different cellular models (cell lines, primary rat hepatocytes and cryopreserved human hepatocytes).

3:30 Networking Refreshment Break in the Exhibit Hall

4:30 Pediatric Drug Induced Liver Injury- Children Are Not Just Small Adults

William Salminen, Ph.D., DABT, Director, Center for Hepatotoxicity, U.S. FDA, National Center for Toxicological Research

Children are not simply small adults and it follows that children may exhibit differential sensitivity to drug-induced adverse events. This also applies to
MECHANISMS UNDERLYING HEPATOTOXICITY

10:45 Prediction of Immune-Mediated Drug-Induced Liver Injury in Pre-Clinical Drug Development
Tsuyoshi Yokoi, Ph.D., Professor, Drug Metabolism and Toxicology, Kanazawa University

Drug-induced liver injury (DILI) is a major problem in drug development and clinical drug therapy. The pathogenesis of DILI usually involves the participation of the parent drug or metabolites that either directly affect the cell biochemistry or elicit an immune response. However, in most cases the mechanisms are still unknown, thus it is difficult to predict and prevent these reactions. Recently, we demonstrated that halothane- and alpha-naphthylisothiocyanate (ANIT)-induced liver injury is mediated by interleukin-17 in mice, and carbamazepine-induced liver injury also mediated by IL-17. Dicloxacillin-, methimazole-, and flutamide-induced liver injury is mediated by IL-4. Continued advances in our understanding of immune-mediated DILI will lead to earlier prediction of hepatotoxic potential of drug under development.

11:15 Hepatoprotective Effect of Peroxisome Proliferators is Associated with Induction of Vanin-1 Gene Expression
Jose E. Manautou, Ph.D., Associate Professor of Toxicology, Pharmaceutical Sciences, University of Connecticut

Clofibrate (CBF) is a peroxisome proliferator, hypolipidemic drug that affords protection against acetaminophen (APAP) hepatotoxicity. The mechanism of this protection is still unknown but thought to be dependent on peroxisome proliferator-activated receptor alpha (PPARα) function. A gene array analysis revealed that the expression of Vanin 1 (Vnn1) is greatly increased in animals exhibiting CBF-mediated resistance to APAP toxicity. This presentation in vivo and in vitro approaches to examine the role of Vnn1 in APAP hepatotoxicity and hepatoprotection by CFB, and for the development of new therapeutics approaches to minimize acute liver failure produced by APAP overdose will be discussed.

11:45 Luncheon Presentations (Sponsorship Opportunities Available) or Lunch on Your Own

EARLY PRE-CLINICAL PREDICTIONS OF LIVER INJURY

JUNE 8 - 9, 2011

3rd Annual
New Assays and Tools for Predicting Hepatotoxicity

A modest inflammatory stress in animal models can render the liver sensitive to injury from numerous drugs that cause idiosyncratic toxicity in humans. This enhanced sensitivity is associated with expression of proinflammatory cytokines, other mediators of inflammation and with enhanced sensitivity of hepatocytes to their damaging influence. In particular, prolonged generation of tumor necrosis factor-alpha (TNF) appears to be important for the development of injury. Understanding mechanisms of drug-inflammation interactions could lead to models to predict preclinically the potential of some drug candidates to cause idiosyncratic liver injury in humans.

10:00 Networking Coffee Break in the Exhibit Hall

1:55 In vitro Strategies: High Content Mechanistic Screening, Mitochondrial Toxicity, and Transporter Assessment
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

In recent years we have developed several assays that can be deployed early in the drug discovery process. These include 1. An oxygen consumption assay for mitochondrial toxicity, 2. Several assays for ERs tress and 3. A High Content Mechanistic Screening approach for multiple assay endpoints in the presence and absence of cytokine addition. Here, I will describe these screens using examples of hepatotoxic drugs. I will discuss advantages and limitations of each in vitro screen with respect to predicting hepatotoxicity.

2:25 Ice Cream Refreshment Break in the Exhibit Hall

3:05 Approaching Hepatotoxicity in Drug Discovery as a Lead Optimization Problem
Dylan P. Hartley, Ph.D., Senior Scientist, Investigative Toxicology, Genentech, Inc.

Given the demands on drug discovery teams to produce molecules devoid of hepatotoxicity, toxicologists are now integral members of these teams with new responsibilities geared toward lead optimization. Toxicologists are now expected to assess risk for hepatotoxicity in a compound in predictive manner, or ascribe a mechanism to early hepatotoxicity findings, link the findings to an offending moiety within the structure, and define the chemical lead optimization path. Structure-based strategies to predict and/or attenuate hepatotoxicity will be presented with respect to various hepatotoxic signals.

3:35 The Utility of Emerging Biomarkers of Liver Injury in Pre-Clinical and Clinical Drug Development
Shellie Schomaker, Principal Scientist, Drug Safety R&D, Pfizer, Inc.

While alanine aminotransferase (ALT) activity remains the gold standard biomarker of liver injury, the correlation between increased ALT levels and morphological liver findings is rather imperfect. These discrepancies could be due to adaptive responses, altered liver membrane permeability, extrahepatic injury, or treatment-related effects on ALT enzyme activity. This presentation will focus on an evaluation of malate dehydrogenase, purine nucleoside phosphorylase and glutamate dehydrogenase for the detection of liver injury when ALT activity is limited and will demonstrate the utility of this alternative biomarker approach for improving confidence.

4:05 From Mild Pre-Clinical Transaminase Elevations to Idiosyncratic Liver Injury in One Easy Lesson
Paul Vancutsem, D.V.M., Ph.D., Director, Pre-Clinical Safety; Senior Member, Novartis Internal Liver Experts Team, Novartis Pharmaceuticals

Even if we do not fully understand idiosyncratic liver injury (IDILI), it appears to necessitate events involving an often subtle local liver insult, an immune system imbalance and a specific genetic make-up (HLA alleles). Integration of these traditionally unconnected areas of toxicology will lead to an improved prediction of IDILI. This presentation proposes a template for integration using a pragmatic approach.

4:35 End of Conference

Present a poster and save $50!
Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by April 22, 2011.

Reasons you should present your research poster at this conference:
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Detecting Nephrotoxicity Using Early Markers and Imaging Tools

TUESDAY, JUNE 7

7:45 am Registration and Morning Coffee

UNDERSTANDING MECHANISMS OF NEPHROTOXICITY

8:45 Chairperson’s Opening Remarks

8:55 Cisplatin Nephrotoxicity and Renal Protective Strategies
Navjotsingh Pabla, Ph.D., Postdoctoral Fellow, Department of Cellular Biology and Anatomy, Medical College of Georgia/Georgia Health Sciences University

Cisplatin, a widely used chemotherapy drug, has major side effects in normal tissues, notably nephrotoxicity in kidneys. Research during last few years has delineated several signaling pathways leading to renal tubular damage and kidney injury in cisplatin nephrotoxicity, including a rapid DNA damage response. Importantly, cisplatin may activate different signaling pathways in normal tissues and tumors. Targeting these pathways may uncover clinically effective strategies for kidney protection without diminishing the chemotherapy efficacy of cisplatin in tumors.

9:25 Primary Cell Cultures from Human and Rat Proximal Tubule as Models to Study Mechanisms of Acute Kidney Injury
Lawrence H. Lash, Ph.D., Professor, Associate Chair, Pharmacology, School of Medicine, Wayne State University

Our laboratory has developed several in vitro models from rat and human kidney, using both non-specific toxic chemicals and specific nephrotoxicants, including halogenated solvents, analgesics, and antibiotics. One focus has been the metabolism and toxicity of the halogenated solvent trichloroethylene (TCE), which is a significant environmental contaminant that has the kidney as one target organ. Molecular approaches and proteomics have been integrated into our in vitro toxicity models to explore the role of specific proteins and examine the influence of disease processes, such as diabetic nephropathy and reduced nephron mass, on renal toxicological responses.

9:55 Networking Coffee Break

MONITORING AND ASSESSING KIDNEY INJURY

10:25 Current Use of Renal Biomarkers in Early Drug Development
Diann Weddle, Ph.D., D.V.M., Senior Pathologist, Pre-Clinical Safety, Abbott Laboratories

An overview of renal toxicology will be presented including a discussion of use and limitations of current biomarkers. Key concepts will be further emphasized through case examples. Within the last year, the Predictive Safety Testing Consortium’s Nephrotoxicity Working Group submitted a qualification package for multiple renal biomarkers to the FDA and EMEA and received clearance for limited use in nonclinical and clinical drug development. Conclusions and recommendations from the submission will be summarized.

10:55 Pre-Clinical Biomarkers of Nephrotoxicity: Applications in Drug Discovery and Development
Eric Blomme, D.V.M., Ph.D., D.A.C.V.P., Senior Project Leader, Abbott Laboratories

This presentation will build upon the preceding presentation discussing the current use of renal biomarkers in early drug development. Specifically, several case examples will be used to illustrate how biomarkers of renal toxicity can be applied in drug discovery and development to increase probability of success and make better decisions on compounds at earlier stages. Data on performance characteristics for several of these biomarkers in rats will be presented.

11:25 Integrative Assessment of Drug-Induced Kidney Function Changes and Acute Injury Using an Automated Blood Sampling and Telemetry (ABST) System
Yafei Chen, M.D., M.S., Scientist Safety Pharmacology, Global Safety Assessment, AstraZeneca Pharmaceuticals

~20% of hospital admissions are caused by nephrotoxic drugs due to acute kidney injury. Current preclinical methods are insufficient to detect and predict drug-induced changes in kidney function and/or kidney injury (DIKI). We will describe an integrated pharma-cology platform representing a convergence of automated blood sampling with telemetry (ABST) for simultaneous assessment of cardiovascular, renal hemodynamic and excretory functions, and nephron site-specific DIKI biomarkers in surgically prepared conscious rats. This integrated preclinical approach provides multiple translational markers for risk management in early clinical development.

11:55 Luncheon Presentations (Sponsorship Opportunities Available) or Lunch On Your Own

KIDNEY MARKERS: FROM BENCH TO BEDSIDE

1:30 pm Chairperson’s Remarks
W. Brian Reeves, M.D., F.A.C.P., Chief, Division of Nephrology, Professor and Vice Chair, Medicine, Penn State College of Medicine

1:35 FEATURED PRESENTATION: Establishing the Context for Introducing New Safety Biomarkers into Clinical Trials

There has been rapid progress in developing new safety biomarkers for monitoring organ toxicity. Some of these new markers have already been qualified for use in supporting pre-clinical studies. Efforts to qualify these new safety biomarkers for use in human clinical trials are also underway. This presentation will explore recent experiences with organ-specific markers and strategies and challenges for progressing these markers for support of clinical trials.

2:05 Clinical Evaluation and Qualification of Kidney Safety Biomarkers: A Collaboration between Two Consortia
Maria Vassileva, Ph.D., Scientific Program Manager, The Biomarkers Consortium, Foundation for the NIH

The Biomarkers Consortium (BC), a public private partnership managed by the Foundation for the NIH, is preparing to launch an important project expected to generate the data needed to advance the regulatory acceptance of new biomarkers appropriate for monitoring kidney safety in the clinic, and reaching alignment on how these biomarkers could improve clinical diagnoses of drug-induced acute kidney injury during drug development and patient therapy with aminoglycosides in patients with cystic fibrosis and cisplatin in patients with head and neck cancer. This project is a collaboration between the BC and the Predictive Safety Testing Consortium of the Critical Path Institute.

2:35 Urinary Cytokines as Biomarkers of Nephrotoxicity
W. Brian Reeves, M.D., F.A.C.P., Chief, Division of Nephrology, Professor and Vice Chair, Medicine, Penn State College of Medicine

Inflammation is a critical component of drug-induced acute kidney injury. In response to injury, renal epithelial cells elaborate a variety of chemokines and cytokines which alter epithelial cell function and also lead to the recruitment and/or activation of inflammatory cells in the kidney. Levels of cytokines increase in the urine early after kidney injury and may provide a window to the inflammatory processes ongoing within the kidney.

3:05 Sponsored Presentations (Opportunities Available)

3:35 Grand Opening Refreshment Break in the Exhibit Hall
4:35 Rapid Point-of-Care GFR: Technique, Diagnostic and Therapeutic Advantages
Bruce A. Molitoris, M.D., Director, Division of Nephrology and Professor of Medicine, Indiana University

Glomerular filtration rate (GFR) is the most important measure of kidney function. Although many ways exist to measure GFR, there is no acceptable rapid point-of-care technique. Therefore, we have developed a fluorescent based ratiometric technique in dogs and pigs using an LED-based detection device and an intravenous optical catheter by using a non-filterable large red fluorescent dextran and a small kidney freely filterable FITC dextran. In less than one hour accurate GFRs are obtained in many conditions including acute kidney injury (AKI). We believe this has clinically important diagnostic and therapeutic advantages in AKI and chronic kidney disease.

5:05 PANEL DISCUSSION: Renal Injury Markers and How Effectively Can They Be Used?
Moderator: W. Brian Reeves, M.D., F.A.C.P., Chief, Nephrology; Professor and Vice Chair, Medicine, Penn State College of Medicine

5:35 - 6:30 Happy Hour in the Exhibit Hall

WEDNESDAY, JUNE 8

7:30 am Continental Breakfast Breakout Discussions
Breakout Discussion Topics:
- Biomarkers for Organ Toxicity and Their Effective Use in Pre-Clinical and Clinical Development
- Monitoring Mitochondria and Their Impact on Organ Toxicities

MITOCHONDRIAL INVOLVEMENT IN CARDIAC, RENAL AND LIVER TOXICITY
(Joint session for Cardiotoxicity and Nephrotoxicity tracks)

8:30 am Chairperson’s Remarks
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

8:40 Introduction to Mitochondrial Function and Drug-Induced Dysfunction
James Dykens, Ph.D., CEO, EyeCyte Therapeutics

Mitochondria typically produce more than 90% of the ATP in aerobically poised cells, plus the majority of potentially injurious, free radicals. Inhibition of the electron transfer system, or the uncoupling of the mitochondrial potential it generates from phosphorylation, reduce the bioenergetic capacity of the cell. Many drugs have direct and deleterious mitochondrial effects that contribute to the etiology of idiosyncratic drug-induced organ toxicity. These off-target effects are a function of compound chemistry, but also of genetic diversity in plasma membrane transporters that facilitate bio-accumulate of drugs into the mitochondria. Emerging animal models will be discussed with an emphasis on hepatotoxicity.

9:10 Tales of Broken Mitochondria: Drug-Induced Cardiac Mitochondrionopathy
Paulo Oliveira, Ph.D., Group Leader, Mitochondrial Toxicology and Disease, Center for Neuroscience and Cell Biology, University of Coimbra, Portugal and Visiting Research Associate, University of Minnesota Medical School

Drug-induced cardiac mitochondrial dysfunction can progressively result in organ degeneration. Classical examples of drug-induced cardiac mito toxicity include nucleoside reverse transcriptase inhibitors, local anesthetics and anthracyclines. Doxorubicin (adriamycin, DOX) is a clear case study of a well known pharmaceutical that can lead to progressive degeneration of cardiac mitochondrial function. DOX is a potent anthracycline anti-neoplastic agent, whose clinical use is limited by a dose-dependent and cumulative cardiotoxicity, with a clear mitochondrial component. In this case, protection of cardiac mitochondrial function during DOX treatment appears to be critical for preventing the maintenance of the myocyte bioenergetics.

9:40 Sponsored Presentations (Opportunities Available)

10:10 Networking Coffee Break in the Exhibit Hall

10:50 Mitochondrial Homeostasis in Acute Kidney Injury
Rick Schnellmann, Ph.D., Professor, Chair, Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy

Mitochondrial damage is a major contributor to the initiation of tubular cell injury and the progression of acute kidney injury (AKI) produced by drugs, toxins, and ischemia. To understand the role of mitochondria in organ damage and repair, we think that mitochondria need to be examined holistically by measuring mitochondrial homeostasis. This includes changes in mitochondrial loss, fission/fusion, mitophagy, and biogenesis over time. Using this approach, temporal differences in mitochondrial loss, dynamics and biogenesis were observed with mitochondrial loss occurring early and changes in mitochondrial fission/fusion and biogenesis occurring later after AKI.

11:20 Mechanistic Insights into Mitochondrial-Based Organ Toxicity
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

Previous speakers have elucidated in detail on the contribution of mitochondrial impairment to different organ toxicities. It is apparent that in order to avoid late stage attrition due to mitochondrial toxicity, early predictive screens need to be deployed early in the drug discovery process. Here I will show organelle and cell-based HTS applicable screens to detect such liabilities. I will describe the screens using examples from different drug classes such as anti-diabetics/antilipidemics, antivirals, antibiotics, and NSAIDs.

11:50 PANEL: Strategies for Assessing Mitochondrial Involvement in Drug-Induced Organ Toxicities
Moderator: Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global R&D

12:20 pm End of Conference
Environmental, interpreting DDI results according to regulatory guidance, and predicting the magnitude of in vivo DDIs based upon in vitro data.

THURSDAY, JUNE 9

7:20 am Continental Breakfast Breakout Discussions
Breakout Discussion Topics:
- Utilization of Genotoxic Data for Effective Risk Assessments
- Emerging Trends in ADME/DMPK Testing

TACKLING GENOTOXICITY ISSUES

8:20 Chairperson’s Remarks
Martha Moore, Ph.D., Director, Division of Genetic and Molecular Toxicology, U.S. FDA, National Center for Toxicological Research

8:30 Genetic Toxicity Concepts and Strategies for Small Molecule Lead Optimization
Dolores Diaz, Ph.D., DABT, Investigative Toxicology, Genentech, Inc.
Genotoxicity is a critical component of the safety assessment strategy for small molecule drug development. As a field, genotoxicity is a complex discipline with unique challenges. This presentation will provide an overview of relevant genotoxicity concepts and mechanism and a discussion of genotoxicity assays (including limitations), with emphasis in practical applications in pharmaceutical drug development. Screening strategies for genotoxicity lead optimization and their rationale will be discussed, as well as investigative approaches around positive findings.

9:00 Early Genotoxicity Assessment: From HTS to Regulatory Testing
Stephan Kirchner, Ph.D., Predictive Toxicology & Emerging Technologies, Lab Head, Genotoxicology, Phototoxicity, F. Hoffmann-La Roche Ltd.
Indicator assays to predict genotoxic liabilities have high throughput and require very small amounts of compound. However, they are limited by lower predictivity for the outcome of regulatory OECD guideline assays. In order to screen more products at the low quantities, while keeping excellent predictivity, an integrated strategy relying on in silico assessment, high throughput approaches and automation of regulatory-like assays will be discussed and contrasted within the context of supporting the early development of drug candidates.

9:30 Going Beyond the Standard Genetic Toxicology Battery
Pamela L. Heard, Ph.D., Principal Scientist, Drug Safety R&D, Genetic Toxicology CoE, Pfizer Global Research & Development
The standard in vitro genotoxicity test battery was designed to be a sensitive screen to assess the genotoxic hazard of a chemical or drug. However, the tests often show limited specificity. Positive results in these assays demonstrate the intrinsic genotoxic activity of a chemical or drug but do not provide insight into its genotoxic mechanism of action. Over the past several years our laboratory has focused on establishing a series of follow-up assays designed to demonstrate a possible mechanism of action for a drug candidate that has tested positive in the standard tests. This presentation will discuss the follow-up options.

10:00 Networking Coffee Break in the Exhibit Hall
11:15 PANEL DISCUSSION: New Strategies for Genotoxic Risk Assessments
Moderator: Martha Moore, Ph.D., Director, Division of Genetic and Molecular Toxicology, U.S. FDA, National Center for Toxicological Research

11:45 Luncheon Presentations (Sponsorship Opportunities Available) or Lunch On Your Own

EARLY PRE-CLINICAL PREDICTIONS OF LIVER INJURY

1:15 pm Chairperson’s Remarks
Eric Blomme, D.V.M., Ph.D., D.A.C.V.P., Sr Project Leader, Abbott Labs

1:25 Current Toolbox for the Prediction of Hepatotoxicity
Eric Blomme, D.V.M., Ph.D., D.A.C.V.P., Sr Project Leader, Abbott Labs
This presentation will provide an overview of the current status of several technologies used to improve hepatotoxicity prediction during drug discovery. Examples will be used to illustrate the strengths, limitations and optimal application of these technologies during lead optimization and candidate selection.

1:55 In vitro Strategies: High Content Mechanistic Screening, Mitochondrial Toxicity, and Transporter Assessment

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

2:25 Ice Cream Refreshment Break in the Exhibit Hall

3:05 Approaching Hepatotoxicity in Drug Discovery as a Lead Optimization Problem
Dylan P. Hartley, Ph.D., Senior Scientist, Investigative Toxicology, Genentech, Inc.
Given the demands on drug discovery teams to produce molecules devoid of hepatotoxicity, toxicologists are now integral members of these teams with new responsibilities geared toward lead optimization. Toxicologists are now expected to assess risk for hepatotoxicity in a compound in predictive manner, or ascribe a mechanism to early hepatotoxicity findings. Examples will be used to illustrate the strengths and limitations of the various technologies used as a part of a risk assessment.

3:35 The Utility of Emerging Biomarkers of Liver Injury in Pre-Clinical and Clinical Drug Development
Shelli Schomaker, Principal Scientist, Drug Safety R&D, Pfizer, Inc.
While alanine aminotransferase (ALT) activity remains the gold standard biomarker of liver injury, the correlation between increased ALT levels and morphological liver findings is rather imperfect. These discrepancies could be due to adaptive responses, altered liver membrane permeability, extrahepatic injury, or treatment-related effects on ALT enzyme activity. This presentation will focus on an evaluation of malate dehydrogenase, purine nucleoside phosphorylase and glutamate dehydrogenase for the detection of liver injury when ALT activity is limited and will demonstrate the utility of this alternative biomarker approach for improving confidence.

4:05 From Mild Pre-Clinical Transaminase Elevations to Idiosyncratic Liver Injury in One Easy Lesson
Paul Vancutsem, D.V.M., Ph.D., Director, Pre-Clinical Safety and Senior Member of Novartis Internal Liver Experts Team, Novartis Pharmaceuticals
Even if we do not fully understand idiosyncratic liver injury (IDILI), it appears to necessitate events involving an often subtle local liver insult, an immune system imbalance and a specific genetic make-up (HLA alleles). Integration of these traditionally unconnected areas of toxicology will lead to an improved prediction of IDILI. This presentation proposes a template for integration using a pragmatic approach.

4:35 End of Conference
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**SAFETY SUMMIT**

- June 7 - 8
- Cardiotoxicity
- Nephrotoxicity
- June 8 - 9
- Hepatotoxicity
- ADME/DMPK Predictions

**DISCOVERY SUMMIT**

- June 7 - 8
- Pain
- Alzheimer’s Disease
- June 8 - 9
- Parkinson’s Disease
- In Vivo Molecular Imaging

**SCREENING SUMMIT**

- June 7 - 8
- Tools and Technologies for HTS
- June 8 - 9
- Cell-Based Screening

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