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ETS-2011

9th International Conference on Early Toxicity Screening:
Transporters and Drug Toxicity
June 9-10, 2011

Red Lion Hotel on Fifth Avenue; Seattle, WA, USA

REGISTRATION DISCOUNT UNTIL MAY 6, 2011

ISC, INC.

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ETS-2011 MEDIA PARTNER

Featuring Experts from the Following Institutions: APSciences, Inc and IVAL LLC; Bristol Myers Squibb; Duke University; GlaxoSmithKline; Merck & Co., Inc.; Optivia Biotechnology, Inc.; Pfizer Global Research And Development; Qualyst, Inc.; Simulations Plus, Inc.; SOLVO Biotechnology; XenoTech, LLC.; University of Arizona; University of North Carolina at Chapel Hill; University of Tokyo; University of Washington.

ETS-2011 is a bi-yearly event with emphasis on promising approaches and challenges in the accurate prediction of adverse drug effects during drug development. This year's theme will be transporters and drug toxicity, with academic and industrial experts presenting data. Topics covered will be under the categories of Scientific Concepts of Transporters and Drug Interactions; Clinical Evidence of Transporter-related Drug Toxicity; and Experimental Approaches for Transporter-related Drug toxicity.

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Organizing Chairs:

Albert P. Li, APSciences/In Vitro ADMET Laboratories, LLC
Jash Unadkat, University of Washington
Christopher MacLauchlin, GlaxoSmithKline

Early Toxicity Screening-ETS-2011

Thursday, June 9, 2011

8:00 AM – 9:00 AM – REGISTRATION

Session I:**Scientific Concepts of Transporters and Drug Interactions**

Chair: Jash Unadkat

9:00 AM – 9:10 AM – Opening Remarks- Albert P. Li

9:10 AM – 9:50 AM

Keynote Presentation: Transporters on the Target Organs and Clearance Organs are Responsible for Drug Induced Toxicities

(*Yuichi Sugiyama, University of Tokyo; Tokyo, Japan*) The changes in pharmacokinetics due to genetic polymorphisms and drug-drug interactions involving transporters can often cause an adverse effect. For example, the decrease in the function of influx transporters, OATPs expressed in the liver cells enhanced statins induced myopathy due to the increase in drug exposure in the circulating blood and muscle cells. I will also focus on the role of transporters in the neutropenia caused by anticancer drugs based on our most recent studies.

9:50 AM – 10:30 AM

The Role of Nucleoside Transporters in Drug Toxicity

(*Jash Unadkat, University of Washington; Seattle, WA*) Transporters can constitute the rate-limiting step in the entry of drugs to their site of efficacy and/or toxicity. This site may be the cell cytoplasmic compartment or an intracellular organelle such as the mitochondria. In this case, the absence and presence of the transporter in the cell membrane or the membrane of the organelle, and its level of expression can significantly determine the efficacy and/or toxicity of the drug. Using nucleoside transporters as examples, I will show how the expression of such transporters in the plasma and mitochondrial membrane can significantly affect the efficacy and toxicity of nucleoside drugs such as ribavirin, ganciclovir and filgrastim. Supported by NIH GM5447

10:30 AM - 11:00 AM – BREAK

11:00 AM – 11:40 AM

Differences in Transporter-mediated Tissue Accumulation between Two Structurally Similar Antiparasitic Agents may Contribute to Differences in Toxicity Potential

(*Mary Paine, University of North Carolina at Chapel Hill; Chapel Hill, NC*) Clinical development of pafuramidine, a prodrug of the antiparasitic agent furamidine, was discontinued due to unforeseen, delayed kidney toxicity observed during an expanded phase I safety study. Preclinical studies demonstrated that the active metabolite of an efficacious, structurally similar prodrug accumulates in tissues, including kidney, markedly less than furamidine. Differences in transporter-mediated

active uptake/efflux between these two compounds may contribute to differences in tissue accumulation and potentially, risk of toxicity.

11:40 AM – 12:00 PM – PANEL DISCUSSION – SESSION I

12:00 PM – 2:00 PM – LUNCH BREAK

Session II:**Clinical Evidence of Transporter-related Drug Toxicity**

Chair: Christopher MacLauchlin

2:00 PM – 2:40 PM

Clinical Efficacy and Toxicity of Lapatinib: Deciphering the Role of Transporters (*Christopher MacLauchlin, GlaxoSmithKline; Research Triangle Park, NC*) Transporters can be effective barriers to drug exposure, the rate determining step in the uptake and/or excretion of a compound or metabolite, and a cause of drug-drug interactions or toxicity. Deciphering the role that drug transporters have on disposition and toxicity is driving a surge in transport-related research activities within drug metabolism and pharmaceutical sciences. An integrated approach of evaluating data from pharmacokinetic, mass balance, whole-body autoradiography, in situ perfusion experiments and in vitro studies were used to decipher key roles that specific transporters have in the disposition, efficacy, drug interactions and toxicity of Lapatinib, a dual tyrosine kinase inhibitor for the treatment of breast cancer. This work has been a crucial investigative activity that has had important consequences for the treatment of brain tumors in breast cancer patients, basic understanding of ABC transporters expressed in the blood-brain barrier on the CNS disposition of drugs, and a mechanistic understanding of Lapatinib hepatotoxicity.

2:40 PM – 3:20 PM

SLCO1B1*5 Genetic Variant and Statin-Induced Myopathy

(*Deepak Voora, Duke University; Durham, NC*) Despite their proven safety in clinical trials, it is the consensus that statins can cause a range of musculoskeletal side effects that range from the mild, but common, myalgia to the severe, but rare, rhabdomyolysis. Recently, genome-wide and candidate-gene approaches have identified genetic variants in the SLCO1B1 hepatic transporter as being key risk factors for not only, the development of statin-induced side effects, but also nonadherence to statin medications. These genetic effects appear to also be statin-specific, thus laying the groundwork for a genotype guided statin therapy to reduce side effects, to improve adherence, and, ultimately, to reduce cardiovascular risk.

3:20 PM – 3:50 PM – BREAK

3:50 PM – 4:30 PM

HIV Protease Inhibitors and the Metabolic Syndrome: Role of Glucose Transport Inhibition

(*Oliver Flint, Bristol Myers Squibb; Princeton, NJ*) The Metabolic Syndrome is a cluster of cardiovascular risk factors used widely in the diagnosis of patients with metabolic disease, such as Type 2 diabetes. The most important pathophysiological factors underlying this diagnosis are dysregulation of lipid and glucose metabolism. Reports of symptoms in HIV patients identifiable with the Metabolic Syndrome followed the introduction of treatment with drug cocktails of the first-generation nucleoside analogues (NRTIs) and the second-generation protease inhibitors (PIs). This treatment prolonged life

sufficiently for symptoms of metabolic disease to emerge. Multiple tissues are involved in the etiology of the syndrome including adipose, muscle, liver and pancreas. Clinical and in vitro studies using cells from the target tissues have helped elucidate the underlying molecular mechanism. Our in vitro studies indicate that PIs inhibit lipid synthesis in adipocytes, induce lipid synthesis in hepatocytes, and inhibit insulin secretion from pancreatic beta cells. The tissue-selectivity and degree of change observed depend on the PI. The fundamental regulatory mechanism disrupted in cells that remove glucose from the circulation, including adipocytes and muscle cells, is inhibition of the insulin-dependent glucose transporter, GLUT4. We have been able to confirm this in clinical insulin clamp studies in human subjects with lopinavir and other PIs, and also in vitro in adipocytes. Structure activity studies reveal that the peptidomimetic core of protease inhibitors is key to the inhibition of glucose transport. The PIs also inhibit insulin release from beta cells by a yet different mechanism, inhibiting calcium transport into the cell in a manner similar to the calcium channel blockers nisoldipine or diltiazem.

4:30 PM – 5:10 PM

Efflux transporter Inhibition and Hepatotoxicity of HER2 Tyrosine Kinase Inhibitors (*Bo Feng, Pfizer Global Research & Development; Groton, CT*) Pfizer compound, CP-724,714, a potent and selective orally active HER2 tyrosine kinase inhibitor, was discontinued from clinical development due to unexpected hepatotoxicity in cancer patients. The direct cytotoxic effect, hepatobiliary disposition of CP-724,714, and its inhibition of active canalicular transport of bile constituents were evaluated in established human hepatocyte models and in vitro transporter systems. The data suggest that inhibition of hepatic efflux transporters contributed to hepatic accumulation of drug and bile constituents leading to hepatocellular injury and hepatobiliary cholestasis.

5:10 PM – PANEL DISCUSSION SESSION II

END OF DAY

Friday, June 10, 2011 – DAY 2 – ETS-2011

8:00 AM – 9:00 AM – REGISTRATION

**Session III:
Experimental Approaches for Transporter-
related Drug toxicity
Chair: Albert P. Li**

9:00 AM – 9:40 AM

Transporters and Drug Toxicity during Drug Development (*Mathew Pletcher, Pfizer Global Research & Development; Groton, CT*) Drug-induced organ toxicity is a persistent problem in drug development, as it is the primary cause of late stage attrition for the majority of failed therapeutic molecules. Prescreening newly synthesized compounds in vitro for effects on pathways and mechanisms linked to drug toxicity provides an opportunity to predict some of these negative in vivo outcomes. These models, though, are incomplete because they ignore the factors that regulate in vivo accumulation and distribution of drugs, the primary determinant of the organ-specificity of toxicity. Understanding the role of various transporters and transporter families in organ distribution of therapeutic compounds

and incorporating that knowledge into our in vitro tools will greatly aid in the predictive power and ultimate utility of early safety screening.

9:40 AM – 10:20 AM

Role of Transporters of Toxicity of Biologics (*Loi Cho-Ming, Pfizer Global Research & Development; San Diego, CA*) Transporters may be more important than drug metabolizing enzymes as determinants of tissue drug concentrations for biologics than for small molecules. The potential involvement of transporters in the toxicity of biologic therapeutics will be discussed.

10:20 AM – 10:50 AM – BREAK

10:50 AM – 11:30 AM

Potential for Increased Risk of Adverse Drug Reactions due to Alterations in Transporter Function in Human and Experimental Fatty Liver Disease (*Nathan Cherrington, University of Arizona; Tucson, AZ*) Numerous adverse drug reactions result from the inability of a patient to metabolize and eliminate the standard dose of a drug. Non-alcoholic steatohepatitis alters the expression of specific drug metabolizing enzymes and transporters which alters the pharmacokinetics of numerous drugs, thereby increasing the risk of adverse reactions in patients with the disease. This talk will highlight some of the molecular mechanisms involved in human and rodent models of non-alcoholic steatohepatitis and demonstrate the potential for increased risk of toxicity using animal models.

11:30 AM – 12:10 PM

Approach to Predict OATP-mediated drug-drug interactions: Industry Case Studies (*Xiaoyan Chu, Merck & Co., Inc.; Rahway, NJ*) Organic anion transporting polypeptide OATPs are major uptake transporters expressed in human liver, which are responsible for hepatic uptake of many endogenous compounds and clinically used drugs, such as HMG-CoA reductase inhibitors. Inhibition of OATP1B1-mediated hepatic uptake may cause clinically significant drug and toxicological interactions. In this presentation, the approach to predict OATP-mediated drug-drug interaction and several industry case examples will be presented.

12:10 PM – 2:00 PM – LUNCH BREAK

**Session III: cont.
Experimental Approaches for Transporter-
related Drug toxicity
Chair: Albert P. Li**

2:00 PM – 2:40 PM

Effects of inflammatory cytokines on transporter gene expression in human hepatocytes: implications in drug-induced liver toxicity (*Albert P. Li, APSciences, Inc and In Vitro ADMET Labs; Columbia, MD*) There is evidence that inflammation may lead to hypersensitivity towards drug-induced liver toxicity. We present here result of our study with primary human hepatocytes, evaluating the effects of inflammatory cytokines on hepatocyte gene expression, including efflux and uptake transporters. The results may also aid the evaluation of the potential cytotoxic potential of biological therapeutics.

2:40 PM – 3:20 PM

Experimental Evaluation of Efflux Transporters-related Hepatotoxicity (*Kenneth Brower, Qualyst; Durham, NC*)

Inhibition of hepatic uptake transporters will often result in increased systemic concentrations and decreased intracellular concentrations. However, inhibition of hepatic efflux transporters can lead to an increase in the intracellular concentration. The relationships between increased intracellular concentration and hepatotoxicity will be discussed.

3:20 PM – 3:50 PM – BREAK

3:50 PM – 4:30 PM

Utilization of Calcein AM as P-gp Probe Substrate in Various In Vitro Assay Systems – A Correlation Study

(*Krisztina Herédi-Szabó, SOLVO Biotechnology; Szeged, Hungary*) There are numerous in vitro test systems to study P-gp so the question arises which gives the most reliable answers and how to choose the best system based on the passive permeability of the test compound. In this presentation the results of three test systems are compared (ATPase assay, vesicular transport assay and cellular dye efflux assay) all utilizing the same probe substrate in order to reveal the characteristics of each test system and the importance of passive permeability in choosing the best one.

4:30 PM – 5:10 PM

Lysosomal Trapping of Lipophilic Amines and its Relationship to Drug Transporters and Phospholipidosis

(*Andrew Parkinson, XenoTech LLC; Lenexa, KS*) A large number of CNS, cardiovascular and antibiotic drugs are lipophilic amines (also known as cationic amphiphilic drugs or CADs), many of which have large volumes of distribution (Vd) and high organ-to-blood levels (such as high liver-to-blood ratios). With chronic dosing, many lipophilic amines can cause phospholipidosis (in a variety of cell types). Lysosomal trapping, rather than transporter-mediated uptake into tissues, is a key process in the disposition and toxicity of lipophilic amines. This presentation will describe: (1) the key physiochemical properties that cause lipophilic amines to undergo lysosomal trapping, namely lipophilicity ($\log P > 1$) and the presence of one or more basic nitrogen atoms with $pK_a > 7$; (2) *in vitro* methods to assess the potential for lysosomal trapping in isolated hepatocytes; (3) the mechanistic relationship between lysosomal trapping and phospholipidosis; (4) the ability of lysosomal trapping – not active transport – to account for high organ-to-blood ratios of cationic drugs.

5:10 PM – 5:50 PM

Recent Regulatory Updates for Transporter Mediated Drug Interaction Assessments to Ensure Patient Safety

(*David Lustig, Optivia Biotechnology; Menlo Park, CA*) Membrane transporter proteins have been well demonstrated to mediate drug-drug interactions (DDIs) in patients. In particular, the FDA is requesting routine transporter DDI assessment for all new drugs for seven transporters: P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3. Each of these 7 FDA transporters serves to protect the body against xenobiotics, including some drugs. Interfering with this protection mechanism can lead to higher drug exposure of substrate drugs by increasing their absorption and/or decreasing elimination. The EMA has issued a draft guidance on the subject as well which includes two additional transporters: OCT1 and BSEP. This presentation will provide an overview of the recent regulatory actions related to transporter mediated drug interaction assessments to ensure patient safety.

5:50 PM – PANEL DISCUSSION – SESSION III

END OF CONFERENCE

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Poster Presentations are always encouraged. Please submit your poster abstract for approval by the organizing board by May 15th. Poster size should be no larger than **3 feet high by 6 feet long**. Abstracts of posters will be included in the conference materials and will be available on the ISC website. The conference materials will be posted on the basis of availability from the author or presenter. There is no formal poster presentation scheduled. All posters will remain displayed throughout the conference. Please be prepared to display your poster during registration on Sunday, June 5th or before the first session begins on Monday, June 6th. Poster presenters will have ample time for discussion during breaks and Panel discussions. Submit posters abstracts for approval to Nola Mahaney, ISC; 8775 Centre Park Drive, #713, MD 21045 or fax at (410) 869-9560 or email files attachment to nola@ifscomm.org. Approved poster applicants are responsible for completing a conference attendance registration form and payment of fee - visit www.ifscomm.org/register - and for the shipping of the poster itself. Please contact Nola Mahaney for any questions or comments. Please refer to "Travel Information" for hotel address and shipping information.



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