North Jersey ACS
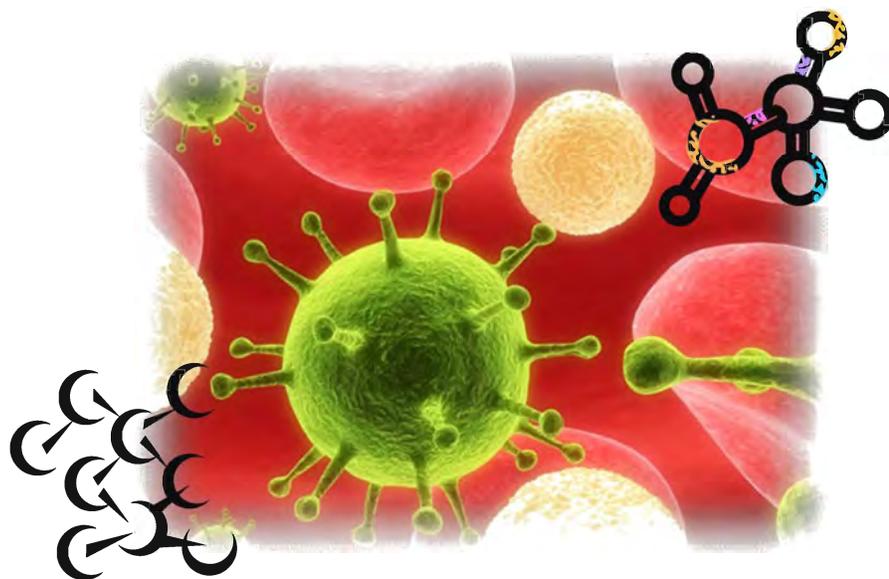# Drug Metabolism Discussion Group

Models, Pharmacogenomics, and Pharmacokinetics

2013 Spring Symposium and Vendor Exhibition
18 April 2013

Hotel Somerset-Bridgewater
Somerset, NJ

2013 Spring Symposium and Vendor Exhibition

Sponsored by the

North Jersey ACS
Drug Metabolism Discussion Group

"Models, Pharmacogenomics, and Pharmacokinetics"

Hotel Somerset-Bridgewater (formerly Somerset Crowne Plaza Hotel)

110 Davidson Avenue
Somerset, New Jersey
18 April 2013
8:00 am – 3:45 pm

Program

"Models, Pharmacogenomics, and Pharmacokinetics"

8:00 a.m. **Registration / Continental Breakfast / Vendor Exhibit**

9:00 a.m. **Introductory Remarks**
   Dr. Allen Jones, Chair, NJDMDG

9:10 a.m. **Novel Hepatic Model Systems for Investigating Mechanisms of Drug-induced Liver Injury (DILI)**
   Edward L. LeCluyse, Ph.D., Associate Investigator, Institute for Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC

10:00 a.m. **Pharmacogenomics in American Indian Populations**
   Erica L. Woodahl, Ph.D. Associate Professor, Department of Biomedical and Pharmaceutical Sciences, University of Montana, Missoula, MT

10:45 a.m. *Vendor Exhibit & Coffee Break*

11:30 p.m. **Glucuronidation, Sulfation, and Pharmacokinetics of Conjugated Metabolites**
Swati Nagar, Ph.D., Associate Professor, Temple University School of Pharmacy, Philadelphia PA

12:15 p.m. *Lunch & Vendor Exhibit*

1:45 p.m. **Pharmacokinetics of Proteins and Peptides**
   Joseph P. Balthasar, Ph.D., Professor of Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY

2:30 p.m. *Vendor Exhibit & Coffee Break*

3:00 p.m. **A Panel of Translational Xenoreceptor, Cytochrome P450, Transporter and Transplanted Liver Humanized Mouse Models for Improved Prediction of Drug Responses in Man**
   Nico Scheer, Ph.D., Head of the tADMET™ portfolio, Taconic Farms, Inc., Cranbury, NJ

3:45 p.m. *Program Closure*

NJDMDG Steering Committee 2012-2013:

Name	Company	E-mail address	Responsibility
Allen Jones	Roche	allen.n.jones@verizon.net	Chair 2012-13
Wing Lam	Janssen R&D	wlam@its.JnJ.com	Chair-elect 2013-14
Philip Krieter	Warner Chilcott	pakrieter@verizon.net	Treasurer
Karl Frank	Roche	karl_b.frank@roche.com	Vice-Treasurer
Karen H. Dingley	Merck Research	karen_dingley@merck.com	Vendor Liaison
Lian Zhou	BMS	Lian.zhou@bms.com	Past Chair, 2011-12
Imad Hanna	Novartis	imad.hanna@novartis.com	Past Chair, 2010-11
Yaofeng Cheng	BMS	Yaofeng.Cheng@bms.com	Member
Matthew Hoffmann	Celgene	mjhoffman@celgene.com	Member
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Maria Markowska	Janssen R&D	MMarkows@its.jnj.com	Member
Roseann Affinito	KCAS Bio	Roseann.Affinito@KCASBIO.com	Member
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Carolina Cabral		cbcabral@gmail.com	Member
Jian-ping Tang		tangjp1@gmail.com	Member

Exhibitors:
- Please contact Karen Dingley (karen_dingley@merck.com) for information concerning exhibits for the Fall 2013 Meeting.

Mark your Calendars for the Fall 2013 Meeting!

The Fall meeting of the North Jersey Drug Metabolism Discussion Group will be held on 17 October 2013 at The Palace At Somerset Park, 333 Davidson Ave, Somerset, NJ (one mile south of our current meeting location). Dr. Wing Lam (wlam@its.JnJ.com) will be the symposium organizer.

Find us on the web at: http://www.njacs.org/topical-groups/drug-metabolism

Novel Hepatic Model Systems for Investigating Mechanisms of Drug-induced Liver Injury (DILI)

Edward L. LeCluyse, Ph.D.

Associate Investigator, Institute for Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC.

Abstract

Idiosyncratic drug-induced liver injury (DILI) remains a great challenge and a major concern in drug development because animal-based preclinical testing does not typically identify this risk. However, the challenge is not only that animals are not good models for human DILI, but that most humans are not good models of human susceptibility. This is because the vast majority of humans do not possess the requisite genotypic and phenotypic risk factors that appear to underlie susceptibility to DILI. Moreover, DILI susceptibility often involves an adaptive immune component and a genetic variation in the function of immune cells as well as hepatocytes. Hence, traditional in vitro hepatic model systems may not provide reliable screens for DILI potential. Induced pluripotent stem cells (iPSC) derived from patients who have experienced DILI and co-cultures of primary hepatocytes and resident macrophages (e.g. Kupffer cells), should be more suitable candidates for *in vitro* models of DILI. The development and validation of *in vitro* cell-based models of DILI using these novel approaches are essential first steps toward more predictive assessment of DILI and has been the focus of our research for the past several years. Results from experiments using prototype DILI compounds, such as isoniazid and trovafloxacin, have shown that both systems are able to reproduce key characteristic metabolic and immune responses attributed to their hepatotoxic effects *in vivo*. Overall, these approaches represent exciting and promising new tools for understanding the underlying mechanisms of idiosyncratic DILI and for screening new compounds for DILI-related liabilities.

Biosketch

Edward LeCluyse, Ph.D., is an Associate Investigator in the Institute for Chemical Safety Sciences at The Hamner Institutes for Health Sciences, and is a participating faculty member of the Curriculum in Toxicology at The University of North Carolina at Chapel Hill (UNC-CH). Dr. LeCluyse has over 25 years of experience in the fields of pharmacology and toxicology, has held industry positions at Merck, CellzDirect, and Invitrogen, and academic positions at UNC's Eshelman School of Pharmacy (1996-2004). More recently, his research has focused on the development and validation of novel in vitro hepatic model systems with which to identify and explore mechanisms of drug- and chemical-induced hepatotoxicity. Dr. LeCluyse is the author of over 100 publications, book chapters, and review articles, and has presented numerous lectures and workshops in topics such as enzyme-induced drug interactions, liver toxicity, and in vitro hepatic culture model systems.

Pharmacogenomics in an American Indian Population

Erica L. Woodahl, Ph.D.

Associate Professor , Department of Biomedical and Pharmaceutical Sciences, University of Montana, Missoula, MT

Abstract

Pharmacogenomics offers the opportunity to identify sources of interindividual variability in drug disposition and response, with the goal of closing the gap in individualizing therapy and improving patient and public health outcomes. However, there is much evidence to show that the incidence and frequency of pharmacogenetic variation is highly diverse across racial and ethnic populations. American Indian and Alaska Native (AI/AN) populations are one group of patients who traditionally have not been included in pharmacogenomics research, and have been overlooked in the advancement of personalized medicine. A key strategy in engaging AI/AN communities in pharmacogenetic research has been implementation of the methodologies of community-based participatory research (CBPR) to identify the priorities of a community and build partnerships to address health disparities. To improve the participation of AI/AN people in pharmacogenetic research, we have developed a partnership with the Confederated Salish and Kootenai Tribes (CSKT) living on the Flathead Indian Reservation in northwestern Montana. Genetic variation in drug-metabolizing enzymes and drug transporters can be a major source of interindividual differences in drug disposition and population-specific variation in dose requirements needed to achieve optimal drug response. To understand interindividual variability in the CSKT population, we have focused our efforts on characterizing variation in the CYP2D6, CYP3A4, CYP3A5, CYP2C9, and ABCB1 genes. Understanding the pharmacogenetic variation in the CSKT population is an important step towards improving dosage regimens and improving treatment outcomes for the CSKT population, which will be essential if pharmacogenetic testing is to reach its optimal clinical utility in AI/AN communities.

Biosketch

Erica L. Woodahl, Ph.D. is an Associate Professor at the University of Montana in the Department of Biomedical and Pharmaceutical Sciences. Erica Woodahl received a B.S. in biochemistry at the University of Notre Dame and a Ph.D. from the Department of Pharmaceutics at the University of Washington. She completed a postdoctoral fellowship in clinical pharmacokinetics at the Fred Hutchinson Cancer Research Center. The research in her lab focuses on pharmacogenomics in drug-metabolizing enzymes and drug transporters to understand interindividual variability in drug response and toxicity. There are two main areas of emphasis in the lab. The first is a project to study pharmacogenomics in American Indian populations. The research includes the identification and characterization of genetic variation in genes that predict drug response and toxicity (particularly cytochrome P450 drug-metabolizing enzymes), as well as a community-based participatory research component to aid in the translation of pharmacogenomic research into the clinic. The second project focuses on pharmacogenomics in genes that encode drug transporters, particularly the drug transporter P-glycoprotein (ABCB1/MDR1). We are using a combination of computational, lipid-based, cell-based, and in vivo models to study pharmacogenomics in the ABCB1 gene with respect to distribution of xenobiotics into target cells and tissues, the development of multidrug resistance in cancer, and the susceptibility to neurodegenerative diseases.

Glucuronidation, Sulfation, and Pharmacokinetics of Conjugated Metabolites

Swati Nagar, Ph.D.,

Associate Professor, Temple University School of Pharmacy, Philadelphia PA

Abstract

For drugs that are significantly converted to conjugated metabolites, several metabolic issues can affect overall drug disposition. These include reversible metabolism and enterohepatic recirculation, kinetics of metabolite formation and elimination, and induction/inhibition and pharmacogenetics of catalytic enzymes. We have used trans-resveratrol, a dietary polyphenol, as a model substrate to study these issues. Resveratrol is known to be highly glucuronidated and sulfated in humans. Specific UGT and SULT isozymes involved in its conjugation have been identified. In vitro, UGT1A1 and 1A9 were found to play a major role in formation of resveratrol-3-glucuronide (R3G), while UGT1A9 was important in the 4'-glucuronide (R4'G) formation. Sulfation occurs via SULT1A1 and SULT1E1. Resveratrol was shown to transcriptionally induce UGT1A1 in human Caco-2 cells, thereby inducing its own glucuronidation. Whether this induction might lead to interactions of resveratrol with other UGT1A1 substrates remains to be evaluated. The pharmacokinetics of resveratrol and its preformed metabolites (sulfates as well as glucuronides) were evaluated in a C57BL mouse model with serial sampling. These studies indicated significant reversible metabolism and enterohepatic recirculation. R3G was the major metabolite. Metabolite kinetics were different when characterizing pre-formed (synthetic metabolite) as compared to metabolite formed in vivo upon parent dosing. Finally, resveratrol was shown to be conjugated in mouse as well as human lung. These results will be discussed, and future directions to evaluate conjugation and transport will be presented.

Biosketch

Swati received her PhD in Pharmaceutics in 2003 from the University of Minnesota. She completed her postdoctoral training in 2005, at the Fox Chase Cancer Center in the department of Pharmacology. She has expertise in pharmacokinetics and drug metabolism, with additional training in pharmacogenetics of drug metabolizing enzymes. She joined Temple University 2007, and teaches Pharm D and graduate pharmacokinetics. Swati's laboratory focuses on the areas of in vitro and in vivo drug metabolism and metabolite pharmacokinetics, xenobiotic glucuronidation and sulfation, and models for drug transport.

Pharmacokinetics of Proteins and Peptides

Joseph P. Balthasar, Ph.D.

Professor of Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY

Abstract

Interest in the development of therapeutic proteins continues to grow, and hundreds of protein drugs are in current clinical development. The pharmacokinetic and pharmacodynamic (PKPD) behavior of macromolecular therapeutics is dramatically different from that of traditional, small-molecule drugs. Due to differences in the mechanisms of drug distribution and elimination, analytical paradigms developed for small molecules are often inappropriate for use in predicting and characterizing protein PKPD. This presentation will review the primary determinants of protein disposition and absorption, with particular focus on the determinants of monoclonal antibody pharmacokinetics. Special attention will be given differences between macromolecules and small molecule drugs with respect to primary transport mechanisms (diffusion vs. convection), sites associated with elimination (liver / kidney v. skin, muscle, GI), drug-specific pathways of elimination (e.g., target-mediated elimination), the influence of anti-drug immune responses on PKPD, and mechanisms associated with drug-drug interactions. Results of recent mechanistic studies will be presented, and the utility of mechanistic, physiologically-based models will be discussed.

Biosketch

Dr. Balthasar is Professor of Pharmaceutical Sciences and Associate Dean for Research in the School of Pharmacy and Pharmaceutical Sciences at the State University of New York at Buffalo. Dr. Balthasar received a B.S. in Pharmacy (1991) and a Ph.D. in Pharmaceutics (1996) from the University at Buffalo. He served as a Clinical Assistant Professor of Pharmaceutics at the University at Buffalo from 1996-1997 and, from 1997-1999, as an Assistant Professor of the Department of Pharmaceutics and Pharmaceutical Chemistry at the University of Utah. Dr. Balthasar rejoined the University at Buffalo as an Assistant Professor in 1999, and was promoted to Associate Professor in 2003 and to Full Professor in 2008. Dr. Balthasar serves as the Director of the Center for Protein Therapeutics. Dr. Balthasar's research utilizes pharmacokinetic and pharmacodynamic analyses to guide the development of new therapies. Current research focuses on physiologically-based modeling of monoclonal antibody disposition, the development of drug targeting strategies to improve the selectivity of cancer chemotherapy, and on the development of new immunotherapies for the treatment of humoral autoimmune diseases.

A Panel of Translational Xenoreceptor, Cytochrome P450, Transporter and Transplanted Liver Humanized Mouse Models for Improved Prediction of Drug Responses in Man

Nico Scheer, Ph.D.

Head of the tADMET™ portfolio, Taconic Farms, Inc., Cranbury, NJ

Abstract

Profound species differences in drug pharmacokinetics, bio-availability, distribution and drug-drug interaction can be caused by differences in the pathways that define drug metabolism and the associated regulatory networks. As a consequence, the toxicity and efficacy of a drug can diverge remarkably between animals and man. In order to address these issues, we have been developing a range of single or multiple genetic humanized mouse models in which we have exchanged different murine xenoreceptor, phase I enzyme and transporter genes for their human counterparts. In this presentation the utility of selected transgenic models in providing human relevant pharmacokinetic and toxicity data will be discussed, focusing primarily on our humanized Cytochrome P450 models. An alternative to transgenic mouse models is the use of tissue humanized mice for predicting human outcomes. In this context, the FRG™ liver humanized model as a promising tool for studying human drug metabolism and pharmacokinetics will be discussed. The approach of transgenic and liver humanized mice will be compared in this presentation and the benefits and limitations of each technology will be discussed.

Biosketch

Nico Scheer, Head of the tADMET™ portfolio at Taconic, received his PhD in Developmental Biology from the University of Cologne. Within Taconic he is responsible for a portfolio of translational mouse models, in vitro tools and services for an improved in vivo analysis of the ADMET characteristics of new compounds. As part of this responsibility he is leading a program to generate new and innovative transgenic mouse lines for the PK, drug-drug interaction and safety profiling of drugs. Nico has published several papers in peer-reviewed scientific journals in the field.

Vendors

Absorption Systems

Alliance Pharma, Inc.
Frank Li

Celsis IVT
Caitlin Brown

Corning Life Sciences
Terri Ruch-Fiero

HepatoChem, Inc.
Ryan Buzdygon

KCAS Bio
Roseann Affinito

Life Technologies
Stephen Harper

Optivia Biotechnology, Inc.
Rachel Whisnant

Qiagen
Adrienne Whitman

QPS
Jerry Gromelski

RMI
Phil Tiller

Triangle Research Labs
Courtney Wells

XenoTech, LLC
Cindy Rewerts