Transporters in Drug Discovery and Development: Driving Knowledge from Laboratory to Label

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Yurong Lai, MD, Ph.D., BMS
Manthena Varma, B.Pharm, Ph.D., Pfizer
Ayman El-Kattan, B. Pharm, Ph.D., Pfizer
Guest Lecturer

Dr. Sue-Chih Lee, US Food & Drug Administration

Dr. Lee, a team leader in the FDA’s office of Clinical Pharmacology, will be presenting on the topic of “Introduction to FDA guidance on transporter-mediated DDIs”. Dr. Lee will offer current and first-hand perspective on the regulatory handling of transporter DDIs based on the recent FDA guidance.

Instructors Panel

Angela Slitt, Ph.D.

Dr. Slitt is an Assistant Professor at the Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island. Dr. Slitt received a B.S. in Molecular and Cellular Biology and Ph.D. in Pharmaceutical Sciences from University of Connecticut. From 2000-2004, she finished her postdoctoral fellowship at University of Kansas Medical Center with Dr. Curtis Klaassen, receiving an NIH Postdoctoral Fellowship to study induction of transporter expression in liver and altered acetaminophen excretion. Dr. Slitt research interests focus on how 1) expression of drug transporters affects chemical (i.e. drug and environmental chemical) disposition and toxicity, 2) nutrition and intake of dietary antioxidants affects the expression of drug transporters, 3) liver disease (i.e. diabetes, cholestasis, and alcoholic cirrhosis) affects transporter expression and chemical disposition, and 4) transporter expression affects cholesterol transport and susceptibility to gallstone formation. Dr. Slitt has 48 original publications in peer reviewed journals, 64 published abstracts and over 20 invited presentations at national/international conferences or as a guest speaker. So far, she has graduated 1 Ph.D., 4 Master Students, and trained 1 postdoctoral fellow.

Manthena V. Varma, M.S., Ph.D.

Dr. Manthena Varma, PhD is a Senior Principal Scientist, at Pfizer Inc. Dr. Varma received his B. Pharm. degree from the Kakatiya University, India in 2000, an M.S. degree in Pharmaceutics and PhD in Pharmaceutics in 2001 and 2005, respectively, from the aitional Institute of Pharmaceutical Education and research (NIPER), Punjab, India. From 2006 to 2008 Dr. Varma worked as a Post Doctoral Fellow at the Department of Pharmaceutics, University of Minnesota (Minneapolis). He serves on the committee of the North Jersey ACS Drug Metabolism and Discussion Group and is a member of American Association for Pharmaceutical Scientists and Indian Pharmaceutical Association. His research is focused in the fields of drug transporters in ADME, pharmacokinetics and DDI predictions/evaluation and prodrugs. He has over 50 original publications in the peer-reviewed journals and about 40 presentations in the scientific conferences.

Yurong Lai, M.D., Ph.D.

Dr. Lai is a Sr. Principal Scientist at Pfizer worldwide research and development. He received his M.D from Fujian Medical University in China and his Ph.D. (Toxicology) from Sapporo Medical University in Japan in 1998. From 1998 to 2001, he was a research fellow of Japanese Society for Promotion (JSPS) in Department of Physiopathology, Graduate School of Medicine of Hokkaido University, followed by a position as Research Associate in Department of Pharmaceutics, University of Washington. In 2004, he moved to PDM, PGRD St. Louis and then Groton in 2010,
Pfizer Inc. and has been serving as a PDM representative (PI), postdoc supervisor and lab head for drug transporter research. Research interests of Dr. Lai and his group include: 1) Discovery and development of drug candidates for the treatment of diabetes, inflammation and pain. 2) Drug transporter related ADME/Tox, in particular hepatobiliary transporters. Current research projects involve absolute differences of hepatobiliary transporters across species, structure-activity relationship and the evaluation of in vitro/in vivo models to predict human PK. He is a patent inventor and the author of over 100 original publications in the peer-reviewed journal.

Ayman El-Kattan, B. Pharm., Ph.D. Bio-sketch
Dr. Ayman El-Kattan is Associate Research Fellow at the Pharmacokinetics, Dynamics, and Metabolism Department, Pfizer Inc. Cambridge Laboratories. He led Pfizer efforts in the emerging area of drug transporters with emphasis on developing in vitro and in silico tools to improve ability to predict transporter mediated clearance and DDI in man. Dr. El-Kattan earned his bachelor degree in pharmacy with distinction from University of Jordan and a Ph.D. in Basic Pharmaceutical Sciences at University of South Carolina in the US. His main research interests are focused on understanding the factors that affect drug disposition and oral bioavailability with emphasis on transporters. Also, it involves studying the utility of physiological based pharmacokinetic modeling (PBPK) tools e.g. SimCYP in projecting drug disposition and drug-drug interaction liabilities in man for new molecular entities (NME). Dr. El-Kattan is an Adjunct Professor at College of Pharmacy-University of Rhode Island in Rhode Island, US. He is active member of the American Association of Pharmaceutical Scientists (AAPS) and serves on the executive committee of the physical pharmacy and biopharmaceutics and Northeastern Regional Discussion Group (NERDG) sections of AAPS. He also serves on the editorial board of The International Journal of Pharmacy Education and Practice. He has been invited speaker over 30 times at national and international conferences and meetings and has published over 90 papers in peer-reviewed Journals, book chapters and proceedings.
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Course Scope and Description
Several factors led to the recent re-invigoration in the field of transporters and their impact on drug absorption and disposition. For example, FDA and EMA provided new guidance on approaches to assess the liabilities of transporter-mediated drug-drug interaction (DDI), efficacy and organ toxicity for new chemical entities (NCEs) with special emphasis on certain transporters with considerable knowledge in the clinic. Furthermore, pharmaceutical industry continues to have keen interest in optimizing the physicochemical space of NCEs and minimizing their Cytochrome P-450 (CYP)-mediated metabolic liability. These compounds are identified as Class III and IV according to the Biopharmaceutics Drug Disposition Classification System (BDDCS). Indeed, this led to the increasing selection of compounds that are both hydrophilic and polar in nature. Such chemical space inherits low passive permeability and metabolic clearance characteristics, and more importantly have potential contribution of transporters to their disposition in man. This paradigm shift presents the research community with a more difficult chemical space for addressing drug absorption and predicting pharmacokinetics. Appropriate understanding of transporters and in vitro and in silico tools that characterize their contribution to drug absorption, disposition and toxicity is key for the success of the pharmaceutical industry.

This practical/hands-on course is specifically designed for personnel in the pharmaceutical and biotechnology industries and contract research organizations (CROs), who need to understand:
- Drug transporters as an emerging field of science – why and why now?
- Drug transporters and their roles in maintaining body homeostasis and causing human diseases
- Physicochemical factors that influence cellular permeability
- Transporter organ expression and their impacts on drug absorption and disposition
- Physicochemical factors that determine affinity to renal and hepatic transporters
- Impact of disease states on transporter expression and function.
- Assessment of the impact of disease state, age, and pregnancy on transporter expression and function.
- Transporter and metabolism interplay from extended clearance concept
- The in vitro and in vivo tools to assess transporter contributions to drug disposition.
- Introduction to FDA Transporter DDI regulations and case studies.
- Static models to predict transporter mediated DDI: Emphasis on renal and hepatic DDI prediction
- Dynamic models to predict complex DDI: Introduction to physiologically based pharmacokinetics modeling (PBPK) utility in DDI predictions.
- The workshop will also include a hands-on session that aims at improving your ability to apply these strategies to medicinal chemistry for hit selection, lead optimization, and development candidate selection.

By Dr. Ayman El-Kattan, Associate Research Fellow, Pfizer Inc., Dr. Yurong Lai, Senior Principal Scientist, Bristol Mayer Squip Inc., Dr. Manthena Varma, Senior Principal Scientist, Pfizer Inc., Dr. Angela Slitt, College of Pharmacy, URI
Course Description
Day 1

Continental Breakfast
8:00-10:00 am Introduction
- Why transporters and why now?
  o Review of the factors that contributed to the interest in the field of drug transporters
  o Overview of the role of transporters in ADME
  o Overview of the role of transporters in Tox and drug safety
- Transporter classification based on energy requirement
  o Facilitated diffusion
  o Primary active transporters
  o Secondary active transporters
- Intestinal Transporter
  o Introduction to oral bioavailability
  o Impact of efflux transporters on oral bioavailability and Fa
    ▪ Impact of P-glycoprotein (Pgp) +BCRP + MRP2 on Fa
    ▪ Sensitivity analysis of factors that influence efflux transporter (Pgp) impact on oral drug absorption
  o Impact of influx transporters on oral bioavailability and Fa and case examples
    ▪ Impact of Organic Anion Transporting Polypeptide 2B1 (OATP2B1) and PEPT1 on Fa
    ▪ Impact of transporter kinetics on transporter selection
- Prediction of drug transporter related intestinal absorption: where we are?
- BBB Transporters
  o Impact of efflux transporters on drug brain penetration
  o Impact of influx transporters on drug brain penetration
  o Preclinical tools to assess brain penetration

10:00-10:15 am Coffee Break

10:15-11:00 am Hepatic and renal transporter
- Major renal transporters and their impact on drug disposition
  o Physicochemical factors that affect renal drug elimination
  o Impacts of Organic Cation Transporter 2 (OCT2) on renal elimination
  o Impacts of Organic Anion Transporter 1 and 3 (OAT1 and OAT3) on renal elimination
  o The emerging role of Multidrug and toxin extrusion protein 1 (MATE1) in renal elimination
- Hepato-biliary Transporters
  o NCEs physicochemical properties that affect drug biliary elimination
  o The impacts of Organic Anion Transporting Polypeptide 1B1, 1B3, 2B1, NTCP on drug disposition
    ▪ OATP mediated drug-drug interaction
    ▪ OATP pharmacogenomics impacts on drug disposition
  o The impacts of Organic Cation Transporter 1 (OCT1) on drug disposition: Metformin as a case study

11:00-12:00 pm Hands-on Session 1

Lunch 12:00-12:45 pm

12:45-2:45 pm Impact of metabolic disease and hormones on transporter expression and disposition
• Metabolic stress as a regulator of transporter expression
  o Obesity
  o Diabetes
  o Metabolic syndrome
  o Examples of altered disposition in obesity
• Regulation of transporter expression with nutritional status
  o Impact of insulin and glucagon signaling
  o Fasting and Caloric Restriction, and cachexia
  o Implications for cancer chemotherapy
• Impact of liver disease on transporter expression and drug toxicity
  o NAFLD, NASH
  o Cirrhosis
  o Examples of altered drug disposition or toxicity in NASH
• Impact of metabolic disease on transporter expression in extra-hepatic tissues
  o Kidney
  o Intestine
• Regulation of transporter expression during pregnancy
  o Liver and placental transporter expression

Transporter expression in a model of gestational diabetes

Coffee Break 2:45-3:00 pm
3:00-5:00 pm In vitro and in vivo approaches to assess transporter impact on drug disposition
  • In vitro tools
    o Transfected cell lines
      • Uptake rate and ratio calculations and interpretation
      • Case studies
    o Suspension hepatocytes and cultured human hepatocytes
      • Background and limitations
      • Data analysis and interpretation
    o Caco-2 and MDCK/MDR1 cell lines
      • Background and limitations
      • Data analysis and interpretation
    o Vesicles
      • Background and limitations
      • Data analysis and interpretation
    o Other in vitro approaches

5:00-5:45 pm Hands-on Session 2

5:45 pm End of Day 1
6:30 pm Class dinner/outing downtown
Day 2

Continental breakfast
8:00-8:30 am Reflection and discussion

8:30-9:30 am In vivo approaches to assess transporter impact on drug disposition
- In vivo approaches
  - Renal and biliary recovery and clearance calculation in preclinical species
  - Applications of chemical knockout preclinical models for transporter related drug disposition
  - Gene modified models for the contribution of transporter to drug disposition

9:30-10:30 am Extended clearance concept: Transporter and metabolism interplay
- Theoretical Background and limitation
  - In vitro evidence and sensitivity analysis
  - In vivo evidence: DDIs
  - In vivo evidence: Pharmacogenomics
- Assessing rate-determining step on the hepatic clearance

10:30-10:45 am Coffee Break

10:45-12:00 pm Static and dynamic models to predict human hepatic clearance and DDI
- Static models to project transporter-mediated DDI
  - Background, theory and limitations
- Dynamic models to project transporter mediated DDI
  - Background, theory and limitations
  - Introduction to physiologically-based pharmacokinetic (PBPK) modeling
  - PBPK modeling to assess transporter-enzyme interplay and complex-DDIs

12:00-12:45 pm Lunch

1:45-2:00 pm Introduction to FDA guidance on transporter mediated DDI
- Renal transporter DDI regulation
- Hepatic transporter DDI regulation
- P-gp and BCRP transporter DDI regulation
- Considerations of other emerging transporters: MATE, MRP2 and BSEP

2:00-3:00 pm Hands-on Session 3

3:00-3:15 pm Coffee Break

3:15-4:15 pm Static Models to Predict Human Renal Clearance and DDI
- Static models to project transporter-mediated DDI
  - Background, theory and limitations
- Dynamic models to project transporter mediated DDI
  - Background, theory and limitations
  - Introduction to physiologically-based pharmacokinetic (PBPK) modeling
  - PBPK modeling to assess transporter-enzyme interplay and complex-DDIs

4:15-5:00 pm Hands-on session 4