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

Ayman El-Kattan, B. Pharm, Ph.D.
Yurong Lai, Ph.D.
Manthena Varma, B.Pharm, Ph.D.
Angela Slitt, B.S., Ph.D.

Ayman El-Kattan, B. Pharm., Ph.D.

Dr. Ayman El-Kattan is Associate Research Fellow at the Pharmacokinetics, Dynamics, and Metabolism Department, Pfizer Inc. Cambridge Laboratories. He 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 role of transporters in influencing drug disposition and oral absorption. Also, it involves studying the utility of physiological based pharmacokinetic modeling (PBPK) tools in projecting drug disposition and drug-drug interaction liabilities in man for new molecular entities (NME). He is also an Adjunct Professor at College of Pharmacy-University of Rhode Island in Rhode Island, US where he lectures in the graduate-level pharmacokinetic courses and serves as external advisor on dissertation committees. Dr. El-Kattan is active member of the American Association of Pharmaceutical Scientists (AAPS) and serves on the committee of the Drug Transporter focus group. He has been invited speaker over 50 times at national and international conferences and meetings and has published over 100 papers in peer-reviewed Journals, book chapters and proceedings.

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 ational 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 BMS Pharmaceutical Candidate Optimization Department. His current role in BMS is to lead the transporter labs for the implementation of drug transporter strategies in drug discovery and development and in vitro/in vivo transporter investigations for regulatory filings. Dr Lai holds an Adjunct faculty position in the Department of Pharmacy of the University of Rhode Island. 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 a Research Associate in Department of Pharmaceutics, University of Washington. In 2004, he Joined PDM, PGRD St. Louis and then moved to Groton R&D center in 2010, Pfizer Inc. and has been serving as a PDM representative (PI), postdoc supervisor and lab head for drug transporter research. In 2013, he joined BMS. He has had a significant role in translational researches in transporter associated ADME-PK-Tox and trained 3 postdoc fellows. Current research interests include proteomics analysis for absolute differences of transporters across species, structure-activity relationship and the evaluation of in vitro/in vivo models to predict human PK and toxicity. He is a patent inventor and the author of a book, book chapters and over 120 original publications in peer-reviewed journals.

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.

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

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, the US 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. 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 and tissue distribution. 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?
- Extended clearance classification system [ECCS] and its utility in defining new molecular entity drug transporter-related clearance
- Intestinal transporter organ expression and their impacts on drug absorption and disposition
- Blood brain barrier transporters and their impact on brain delivery
- Renal transporters and their impact on drug renal elimination
- Hepatobiliary transporters and their impact on drug hepatic uptake, liver concentration and biliary elimination
- Impact of disease states on transporter expression and function.
- Assessment of the impact of disease state, age, and pregnancy on transporter expression and function.
- The *in vitro* and *in vivo* tools to assess transporter contributions to drug disposition.
- Introduction to the US FDA and EMA 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, development candidate selection and designing clinical plans for the labels.

By Dr. Ayman El-Kattan, Associate Research Fellow, Pfizer Inc., Dr. Yurong Lai, Senior Principal Scientist, Bristol-Myers Squibb, Dr. Manthena Varma, Senior Principal Scientist, Pfizer Inc., Dr. Angela Slitt, College of Pharmacy, URI

Course Description

Day 1 August 4, 2016

7:00-8:00 Continental Breakfast and Registration

8:00-10:00 Introduction

- Why transporters and why now?
  - Review of the factors that contributed to the interest in the field of drug transporters
  - Overview of the role of transporters in ADME
  - Overview of the role of transporters in Tox and drug safety
- Transporter classification based on energy requirement
  - Facilitated diffusion
  - Primary active transporters
  - Secondary active transporters
- Extended clearance classification system [ECCS] and its utility in predicting drug clearance
  - Theoretical Background and limitation
    - *In vitro* evidence and sensitivity analysis
    - *In vivo* evidence: DDIs
    - *In vivo* evidence: Pharmacogenomics
  - ECCS Frame work Assessing rate-determining step on the hepatic clearance

10:00-10:15 Coffee Break

10:15-11:00 Hands-on Session # 1

11:00-12:00 Intestinal Transporter

- Introduction to oral bioavailability
- Impact of efflux transporters on oral bioavailability and Fa
  - Impact of P-glycoprotein (Pgp) +BCRP on Fa
  - Sensitivity analysis of factors that influence efflux transporter (Pgp) impact on oral drug absorption
- 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

Sponsored Lunch 12:00-1:30

Sponsor Title: TBD

1:30-2:15 BBB Transporters

- Introduction
- Impact of efflux transporters on drug brain penetration
- Impact of influx transporters on drug brain penetration
- Preclinical models to assess brain penetration

2:15-3:00 Renal Transporter

- Introduction
- Physicochemical factors that affect renal drug elimination
- Impacts of Organic Cation Transporter 2 (OCT2) on renal elimination
- Impacts of Organic Anion Transporter 1 and 3 (OAT1 and OAT3) on renal elimination
- The emerging role of Multidrug and toxin extrusion protein 1 (MATE1) and OAT2 in renal elimination

Coffee Break 3:00-3:15

3:00-4:00 Hepato-biliary Transporters

- Introduction
- Physicochemical properties that affect drug biliary elimination
- The impacts of Organic Anion Transporting Polypeptide 1B1, 1B3, 2B1, and NTCP on drug disposition
  - OATP mediated drug-drug interaction

    - OATP pharmacogenomics impacts on drug disposition
- The impacts of Organic Cation Transporter 1 (OCT1) on drug disposition: Metformin as a case study

4:00-5:00 Hands-on Session # 2
6:30-10:00 Dinner

Day 2 August 2, 2015

7:00-8:00 Continental Breakfast

8:00-10:30 *In vitro* Approaches to Assess Transporter Impact on Drug Disposition

- Assays using immortalized human cells
    - introduction to in vitro systems to assess transporter effects on hepatic and renal elimination
    - introduction to in vitro systems to address transporter impacts on drug absorption
- Assays using Recombinant System and Membrane Vesicles for kinetics parameters
- "Bottom up" and "top-down" approaches to assess transporter liabilities

10:30-10:45 Coffee Break

10:45-12:00 *In vivo* Approaches to Assess Transporter Impact on Drug Disposition

- 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
- Cynomolgus Monkey as a Potential Model to Assess Drug Interactions: Application and Limitations
- In vitro/in vivo scalars for human PK prediction
- Biomarkers Informing Transporter DDI

12:00-1:30 Sponsored Lunch

Sponsor Title: TBD

1:30-2:30 Hands-on Session # 3

2:30-3:00 Coffee Break

3:00-5:00 Impact of metabolic disease and hormones on transporter expression and disposition

- Metabolic stress as a regulator of transporter expression
    - Obesity
    - Diabetes
    - Metabolic syndrome
    - Examples of altered disposition in obesity
- Impact of liver disease on transporter expression and drug toxicity
    - NAFLD, NASH
    - Cirrhosis
    - Examples of altered drug disposition or toxicity in NASH
- Impact of metabolic disease on transporter expression in extra-hepatic tissues
    - Kidney
    - Intestine
- Regulation of transporter expression during pregnancy
    - Liver and placental transporter expression
- Transporter expression in a model of gestational diabetes
- Disease impact on drug pharmacokinetics and disposition

6:00-7:00 Cocktail and Dinner, College of Pharmacy URI

7:00-8:30 Sponsor Title: TBD

Day 3 August 3, 2016
Prediction of Drug Interactions Day

7:00-8:00 Continental Breakfast

8:00-10:00 Static Models to Predict Human Hepatic, Renal, and Intestinal Clearance and DDI

- Prediction of hepatic transporter mediated clearance
- Principles of drug-drug interactions

- Extended net effect model to project hepatic transporter-mediated DDI
    - Background, theory and limitations
- Static models to project renal transporter-mediated DDI
    - Background, theory and limitations
- Static models to project intestinal transporter-mediated DDI
    - Background, theory and limitations

10:00-10:15 Coffee Break

10:15-12:00 Introduction to FDA Guidance on Transporter Mediated DDI

- P-gp and BCRP transporter DDI regulation
- Renal transporter DDI regulation
- Hepatic transporter DDI regulation
- Considerations of other emerging transporters: MATE, MRP2, OAT2 and BSEP
- Clinical Trials for transporter-mediated DDIs: The Principals

12:00-1:30 Sponsored Lunch
Sponsor Title: TBD

1:30 – 2:30 Hands-on Session # 4

2:30 - 2:45 Coffee Break

2:45-4:00 Dynamic Models to Predict Human Hepatic and Renal Clearance and DDI (MV)

- Principles of Dynamic models for projecting transporter mediated Drug-Drug Interactions
- 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

4:00 – 5:00 Hands-on Session # 5