ASCPT 2017 ANNUAL MEETING

PROGRAM & PRE-CONFERENCES

ADVANCING PATIENT CARE

THROUGH PRECISION AND TRANSLATIONAL MEDICINE

March 13–14, 2017 ▲ Omni Shoreham Hotel ▲ Washington, DC
March 15–18, 2017 ▲ Washington Marriott Wardman Park ▲ Washington, DC

ASCPT 2018 ANNUAL MEETING

MARCH 20-24, 2018 • HILTON ORLANDO • ORLANDO, FL

CALL FOR PROPOSALS

ASCPT invites members to submit session proposals for the 2018 Annual Meeting in Orlando, Florida.

NEW FOR 2018

The Scientific Program Committee has introduced a new session type, Novel Format, and encourages the inclusion of early career scientists as active Co-Chairs and/or Speakers and proposals that include patients or patient advocates, as well as cross Network/Community proposals. Further, the ASCPT Board has approved increased financial support for all categories of proposals for the 2018 Annual Meeting.

Kellie Schoolar Reynolds, PharmD | **President**
Peter H. O'Donnell, MD | **Scientific Program Committee Chair**

Proposal submission deadline: Friday, June 2, 2017, 4:00 PM ET

CONNECT WITH US

For guidelines and to submit a proposal, visit **www.ascpt.org**

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WELCOME MESSAGE

Dear Colleagues:

Welcome to Washington, DC, and to the 118th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT). We have planned an outstanding scientific program for you with cutting-edge content, engaging speakers, posters, exhibits and many opportunities to network with colleagues from around the world.

The 2017 scientific program includes three outstanding State of the Art lectures by Geraldine Hamilton, PhD, Emulate, Inc.; James J. Collins, PhD, Massachusetts Institute of Technology; and V.A. Shiva Ayyadurai, PhD, CytoSolve, Inc. Featured speakers will include France Mentré, MD, PhD, University Paris Diderot, and J. Steven Leeder, PharmD, PhD, Children's Mercy Hospital.

ASCPT will honor those who have made remarkable contributions in the field of clinical pharmacology and translational medicine. These outstanding scientists will be recognized at the Annual Meeting with awards that acknowledge their contributions to the discipline. This year's award recipients are Kathleen M. Giacomini, PhD; Russ B. Altman, MD, PhD; Richard Lalonde, PharmD; Namandje N. Bumpus, PhD; Michael Pacanowski, PharmD; Donald E. Mager, PharmD, PhD; Patricia W. Slattum, PharmD, PhD; and Carl C. Peck, MD.

Visit the Poster and Exhibit Hall where over 350 scientific posters and 50+ exhibitors will showcase their research, products and services for you. We'll be featuring Poster Walks as well as Exhibit Walks, and unlimited networking opportunities.

Thank you to Susan Abdel-Rahman, PharmD, Chair, and the entire Scientific Program Committee, along with significant contributions from the ASCPT Networks and Communities, for an outstanding scientific meeting that addresses cutting-edge issues in clinical pharmacology, translational and precision medicine, and other important topics in drug discovery, development, regulation, and use.

Finally, I encourage you to make the most of your time here in our nation's capital with the many learning and networking opportunities we have planned. I look forward to our time together spent fostering our discipline and ASCPT, and thank you for your support of the Society. Enjoy the meeting!

Sincerely,

Julie A. Johnson, PharmD
President

SCHEDULE-AT-A-GLANCE

ACKNOWLEDGMENTS

ASCPT BOARD OF DIRECTORS

THANK YOU TO THE ASCPT BOARD OF DIRECTORS FOR THEIR LEADERSHIP AND DEDICATION IN GUIDING THE SOCIETY.

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MONDAY, MARCH 13, 2017

7:00 am – 3:00 pm	ITCW3 Pre-conference Registration	Omni – Blue Room Foyer
8:15 am – 7:00 pm	International Transporter Consortium Workshop 3 (ITCW3): Transporters in Drug Development Pre-conference	Omni – Blue Room

TUESDAY, MARCH 14, 2017

7:00 am – 3:00 pm	ITCW3 Pre-conference Registration	Omni – Blue Room Foyer
7:15 am – 5:15 pm	International Transporter Consortium Workshop 3 (ITCW3): Transporters in Drug Development Pre-conference	Omni – Blue Room

WEDNESDAY, MARCH 15, 2017

6:30 am – 6:30 pm	ASCPT Central and Registration Open	Convention Registration Lobby
7:30 am – 9:30 am	ASCPT Board of Directors Meeting *(By Invitation Only)*	McKinley
7:30 am – 4:30 pm	US FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting	Omni – Blue Room
8:00 am – 4:00 pm	Clinical Pharmacogenetics Implementation Consortium (CPIC) 2017 Conference: Using Pharmacogenetic Tests in Patient Care	Washington
10:00 am – 12:00 pm	Journal EIC/Wiley Meeting *(By Invitation Only)*	McKinley
4:00 pm – 6:30 pm	Opening Reception (Light food and beverages will be served)	Exhibit Hall A/B South
4:00 pm – 6:30 pm	Exhibits, Late-Breaking, Encore Poster Sessions, and Exhibit Walks	Exhibit Hall A/B South
4:30 pm – 5:30 pm	Showcase of Top Trainee Abstracts	Exhibit Hall A/B South
5:15 pm - 6:00 pm	POSTER WALK *Endogenous/Exogenous Predictors of Drug Response Oncology*	Exhibit Hall A/B South
5:15 pm – 5:45 pm	EXHIBIT WALK	Exhibit Hall A/B South

SCHEDULE-AT-A-GLANCE

6:30 pm – 7:30 pm	Capital Campaign Reception *(By Invitation Only)*	Wilson A
6:30 pm – 8:00 pm	PhRMA Reception *(By Invitation Only)*	Wilson C
7:00 pm	University of North Carolina Reception *(By Invitation Only)*	
8:30 pm – 10:30 pm	University of Florida Reception *(By Invitation Only)*	Marriott Foyer/ Mezzanine Level

THURSDAY, MARCH 16, 2017

6:30 am – 5:00 pm	ASCPT Central and Registration Open	Convention Registration Lobby
6:45 am – 8:00 am	Network/Community Leader Meeting *(By Invitation Only)*	McKinley
7:00 am – 8:00 am	Networking Breakfast	Washington
7:00 am – 7:45 am	Awards Breakfast *(By Invitation Only)*	Marriott Balcony B
8:00 am – 9:00 am	Opening Session	Marriott 1/2
9:00 am – 10:00 am	State of the Art Lecture Geraldine A. Hamilton, PhD	Marriott 1/2
9:00 am – 1:30 pm	Exhibit and Poster Hall Open	Exhibit Hall A/B South
9:00 am – 1:30 pm	Headshot Lounge Open	Exhibit Hall A/B South
10:00 am – 10:30 am	Morning Refreshment Break	Exhibit Hall A/B South
10:00 am – 11:00 am	Pharmacometabolomics Community Meeting	Marriott Foyer/ Mezzanine Level
10:15 am – 11:15 am	Rawls-Palmer Progress in Medicine Award Lecture Russ B. Altman, MD, PhD	Maryland
10:30 am – 12:30 pm	SYMPOSIA	
	Using Biomarkers to Predict Registration Endpoints: A Look Inside the Crystal Ball	Marriott 3
	Finding the Right Dose in the Right Patients for Oncology and Immuno-oncology: Are We There Yet and How Have Quantitative Pharmacology, Translational and Precision Medicine Been Utilized?	Marriott 1/2

11:00 am – 12:00 pm	Infectious Diseases Community Meeting	Exhibit Hall Theater
11:45 am – 1:00 pm	Trainee Luncheon *(Pre-registration Required)*	Washington
11:45 am – 1:30 pm	Clinical Pharmacology Program Directors Meeting *(By Invitation Only)*	Congressional Boardroom
12:00 pm – 1:00 pm	Systems Pharmacology Community Meeting	Marriott Foyer/ Mezzanine Level
12:00 pm – 1:30 pm	*CPT* Editorial Team Meeting *(By Invitation Only)*	McKinley
12:00 pm – 1:30 pm	Finance Committee Meeting *(By Invitation Only)*	Capitol Boardroom
12:30 pm – 1:30 pm	Grab & Go Lunch and Dessert Break	Exhibit Hall A/B South
12:30 pm – 1:30 pm	Covance Hosted Event	Marriott Balcony A
12:30 pm – 1:30 pm	Translational Bioinformatics Community Interest Meeting	Exhibit Hall Theater
1:30 pm – 3:00 pm	ROUNDTABLE SESSION	
	Communicating Complex Information to Influence Decisions: What Works and What Doesn't	Washington
1:30 pm – 2:30 pm	FEATURED SPEAKER	
	France Mentré, MD, PhD	Marriott 1/2
1:30 pm – 3:00 pm	WORKSHOP	
	Integrating Big Omics Data: Applications and Challenges	Marriott 3
3:00 pm – 4:30 pm	SPECIAL SESSION	
	Innovation Forum	Marriott 1/2
3:15 pm – 5:15 pm	Quantitative Pharmacology Network Meeting	Marriott 3
4:00 pm – 5:00 pm	International Transporter Consortium Community Meeting	Marriott Foyer/ Mezzanine Level
4:30 pm – 6:30 pm	PRESIDENT'S NETWORKING RECEPTION	Exhibit Hall A/B South
	Exhibits, Late-Breaking and Encore Poster Sessions, Poster and Exhibit Walks	Exhibit Hall A/B South
	Headshot Lounge Open	Exhibit Hall A/B South
4:45 pm – 5:30 pm	POSTER WALK	
	Applications of Novel Technology	Exhibit Hall A/B South

SCHEDULE-AT-A-GLANCE

5:00 pm – 6:00 pm	Biomarkers & Translational Tools Community Meeting	Exhibit Hall Theater
5:15 pm – 5:45 pm	EXHIBIT WALK	Exhibit Hall A/B South
5:30 pm – 6:15 pm	POSTER WALK	
	Endogenous/Exogenous Predictors of Drug Exposure	Exhibit Hall A/B South
5:30 pm – 7:00 pm	UCSF/Stanford/Genentech Reception (*By Invitation Only)*	McKinley
8:00 pm – 10:00 pm	Gavel Club Reception (*By Invitation Only)*	President's Suite

FRIDAY, MARCH 17, 2017

6:30 am – 5:00 pm	ASCPT Central and Registration Open	Convention Registration Lobby
7:00 am – 8:00 am	Global Health Community Meeting	Marriott Foyer/ Mezzanine Level
7:00 am – 8:00 am	Networking Breakfast	Exhibit Hall A/B South
7:00 am – 1:30 pm	Exhibit and Poster Hall Open	Exhibit Hall A/B South
7:00 am – 1:30 pm	Headshot Lounge Open	Exhibit Hall A/B South
7:00 am – 9:00 am	American Board of Clinical Pharmacology (ABCP) Board Meeting *(By Invitation Only)*	Congressional Boardroom
7:00 am – 9:00 am	POSTER SESSION	Exhibit Hall A/B South
7:15 am – 8:00 am	POSTER WALK	
	Endogenous/Exogenous Predictors of Drug Response Cardiac/Metabolic	Exhibit Hall A/B South
7:30 am – 9:00 am	WORKSHOP	
	Biomarkers of CYP3A Activity: What Have We Learned and are We Ready to Utilize Biomarkers to Replace Clinical DDI Studies?	Marriott 1/2
	Joint *CPT*, *PSP*, and *CTS* Journal Editorial Boards Meeting *(By Invitation Only)*	Washington

SCHEDULE-AT-A-GLANCE

	SCIENCE AT SUNRISE	
	How Inert are Excipients? What Clinical Pharmacologists Need to Know	Maryland
	Databases 101 for Clinical Pharmacologists: What You Need to Know	Marriott 3
9:00 am – 10:00 am	Pharmacogenomics Community Meeting	Marriott Foyer/ Mezzanine Level
9:00 am – 10:00 am	PRA Product Theater	Exhibit Hall Theater
9:15 am – 10:15 am	STATE OF THE ART LECTURE	
	James J. Collins, PhD	Marriott 1/2
10:00 am – 10:30 am	Morning Refreshment Break	Exhibit Hall A/B South
10:30 am – 12:30 pm	SYMPOSIA	
	Clinical Practice, Hurdles and Expectations in the Individualized Treatment Route to Optimizing Therapy for Biologics	Marriott 3
	Integration of Genomics and Translational Clinical Pharmacology to Guide Development of Precision Medicines	Marriott 1/2
11:00 am – 12:00 pm	Drug Utilization & Outcomes Community Meeting	Marriott Foyer/ Mezzanine Level
11:45 am – 1:00 pm	Speed Mentoring	Washington
12:00 pm – 1:00 pm	PAREXEL Product Theater	Exhibit Hall Theater
12:00 pm – 1:30 pm	*CTS* Editorial Team Meeting *(By Invitation Only)*	Congressional Boardroom
12:30 pm – 1:30 pm	Grab & Go Lunch and Dessert Break	Exhibit Hall A/B South
1:00 pm – 2:00 pm	Oncology Community Meeting	Marriott Foyer/ Mezzanine Level
1:15 pm – 2:15 pm	FEATURED SPEAKER	
	J. Steven Leeder, PharmD, PhD	Virginia
1:15 pm – 2:45 pm	WORKSHOPS	
	Physiologically Based Pharmacokinetics (PBPK) Modeling to Support Dosing Recommendations for Patients with Renal Impairment: Are We There Yet?	Marriott 1/2
	Tumor Cell Drug Penetration for Individualized Cancer Treatment	Marriott 3

SCHEDULE-AT-A-GLANCE

1:30 pm – 2:30 pm	ORAL ABSTRACT SESSION	
	Drug Development	Maryland
2:00 pm – 3:00 pm	Journal Club *(By Invitation Only)*	McKinley
3:00 pm – 4:00 pm	SHEINER-BEAL AWARD LECTURE	
	Carl C. Peck, MD	Marriott 1/2
3:00 pm – 4:00 pm	Biologics Community Meeting	Marriott Foyer/ Mezzanine Level
3:00 pm – 4:30 pm	WORKSHOP	
	Leveraging Limited Data for Innovative Drug Development and Utilization Analyses	Virginia
3:00 pm – 5:00 pm	Translational & Precision Medicine Network Meeting	Marriott 3
	Development, Regulatory & Outcomes Network Meeting	Maryland
4:15 pm – 5:15 pm	LEON I. GOLDBERG EARLY INVESTIGATOR AWARD LECTURE	
	Namandje N. Bumpus, PhD Michael Pacanowski, PharmD, MPH	Marriott 1/2
4:30 pm – 6:00 pm	*CTS* Reception *(By Invitation Only)*	McKinley
4:30 pm – 6:00 pm	Early Career Speed Networking *(Pre-registration Required)*	Washington
5:00 pm – 6:30 pm	Pharmacometrics & Pharmacokinetics & Regulatory Science Community Meeting	Marriott Foyer/ Mezzanine Level
6:00 pm – 7:30 pm	Donor Reception *(By Invitation Only)*	Omni – Birdcage Walk

SATURDAY, MARCH 18, 2017

7:00 am – 10:00 am	ASCPT Central and Registration Open	Convention Registration Lobby
7:30 am – 9:00 am	SPECIAL EDUCATION SESSION	
	Publish or Perish: Getting in the Game, and Getting the Most Out of Your Published Works	Virginia

SCHEDULE-AT-A-GLANCE

7:30 am – 9:00 am	SPECIAL SESSION	
	Subject Safety in First-in-Human (FIH) Studies: Perspectives, Pragmatism, and Practice	Marriott 1/2
9:45 am – 10:45 am	STATE OF THE ART LECTURE	
	V. A. Shiva Ayyadurai, PhD	Marriott 1/2
11:00 am – 12:00 pm	ORAL ABSTRACT SESSIONS	
	Drug Metabolizing Enzymes, Neonatal and Pediatric Pharmacology	Maryland
	Regulators of Drug Transporters	Virginia
11:00 am – 1:00 pm	ASCPT Board of Directors Meeting *(By Invitation Only)*	Capitol Boardroom
11:00 am – 1:00 pm	SYMPOSIUM	
	Innovation at the Intersection of Clinical Trials and Real-World Data to Advance Patient Care	Marriott 3
1:15 pm – 2:45 pm	WORKSHOP	
	Epigenetics in Drug Response	Virginia
1:15 pm – 3:15 pm	SYMPOSIA	
	Reverse Translation Fueled by Quantitative Pharmacology: Informing Biology, Drug Development Decision-Making, and Therapeutic Optimization	Marriott 3
	Gut Microbiome and Drug Response Phenotype	Maryland

SPECIAL EVENTS & HIGHLIGHTS

To achieve the goal of attaining a diverse, well-rounded, educational program, the Scientific Program Committee (SPC) has developed an overall Annual Meeting theme of **"Advancing Patient Care Through Precision and Translational Medicine."** This theme is incorporated in Symposia, Workshops, Roundtables, and Science at Sunrise sessions and throughout the entire program.

Additionally, the SPC has resumed the identification and branding of sessions according to the drug discovery, development, regulation, and utilization (DDRU) continuum to be consistent with ASCPT's Strategic Plan and the ongoing work of its members.

Component(s) of the DDRU continuum that apply to the particular Symposium, Workshop, Roundtables, and Science at Sunrise session have been identified and branded accordingly.

D Discovery
R Regulation
D Development
U Utilization

For example, this image indicates that the corresponding session includes the Discovery and Development components of the DDRU continuum.

PRE-CONFERENCE PROGRAMS

ASCPT offers three scientific Pre-conference programs designed for scientists and health professionals engaged in all aspects of clinical pharmacology, including educators, regulatory officials, consultants, industry professionals, and students and fellows. Please see pages 23–44 for details on these sessions.

MONDAY, MARCH 12 – TUESDAY, MARCH 13

International Transporter Consortium Workshop 3 (ITCW3): Transporters in Drug Development

MONDAY, MARCH 13 – TUESDAY, MARCH 14
OMNI - BLUE ROOM

WEDNESDAY, MARCH 15

Clinical Pharmacogenetics Implementation Consortium (CPIC) 2017 Conference: Using Pharmacogenetic Tests in Patient Care

SPECIAL SESSION

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

Organized by the US Food and Drug Administration
7:30 AM – 4:30 PM
OMNI – BLUE ROOM

The use of model-informed drug development (MIDD) for new and generic drugs has significantly increased over the past several years. The Advisory Committee will discuss strategies, approaches, and challenges in MIDD with specific focus on two areas: approaches and evidentiary information needed for applying physiologically-based pharmacokinetic modeling and simulation throughout a drug's lifecycle and mechanistic model-informed safety evaluation with a focus on drug potential for causing arrhythmias. The Comprehensive *in vitro* proarrhythmia assay will be discussed as an exemplar.

The Advisory Committee meeting is open to all interested individuals. Registration for the ASCPT Annual Meeting is not required to attend the Advisory Committee meeting.

OPENING RECEPTION AND EXHIBITS
4:00 PM – 6:30 PM
EXHIBIT HALL A/B SOUTH

ASCPT invites you to join your colleagues on Wednesday evening for the first networking event of the meeting. Interact with fellow experts in clinical pharmacology and translational science from all over the globe and exhibitors representing a wide range of services and products. Light food and beverages will be served.

ENCORE AND LATE-BREAKING POSTER SESSIONS
4:00 PM – 6:30 PM
EXHIBIT HALL A/B SOUTH

View the Encore and Late-breaking abstracts selected by the ASCPT Scientific Program Committee.

SHOWCASE OF TOP TRAINEE ABSTRACTS
4:30 PM – 5:30 PM
EXHIBIT HALL A/B SOUTH

View the top trainee abstracts submitted by the 2017 Presidential Trainee Award recipients, while supporting your peers and networking with colleagues. Posters will be on display during the Opening Reception and poster session hours Thursday and Friday.

EXHIBIT WALK
5:15 PM – 5:45 PM
EXHIBIT HALL A/B SOUTH

Join us on a guided tour of select exhibitors in the Exhibit Hall. Led by Walter Kraft, MD, you'll gain some new knowledge on offerings for clinical pharmacologists and translational scientists.

POSTER WALK
Endogenous/Exogenous Predictors of Drug Response Oncology
5:15 PM – 6:00 PM
EXHIBIT HALL A/B SOUTH

Led by Mark Dresser, PhD and Kari Morrissey, PhD.

THURSDAY, MARCH 16

OPENING SESSION
8:00 AM – 9:00 AM
MARRIOTT 1/2

Join us as ASCPT President, Julie A. Johnson, PharmD, presents the State of the Society Address and recognizes the 2017 ASCPT Award recipients.

EXHIBITS
9:00 AM – 1:30 PM
EXHIBIT HALL A/B SOUTH

Visit the Exhibit Hall to view all of the latest products and services. Join exhibitors and colleagues for a morning refreshment break at 10:00 am and a special dessert break starting at 12:30 pm.

TRAINEE LUNCHEON
11:45 AM – 1:00 PM
WASHINGTON

The Trainee Luncheon will have a focus on informational interviewing, which should be an integral part of your networking, career exploration, and job-hunting plan. The event will allow trainees, young scientists or those exploring a career change to meet with established clinical pharmacologists and translational scientists. Facilitators include top leaders from industry, academia, government, and consulting sectors of clinical pharmacology and translational medicine.

Registration is required.

INNOVATION FORUM
3:00 PM – 4:30 PM
MARRIOTT 1/2

Chaired by Susan Abdel-Rahman, PharmD, the 2017 Innovation Forum will include innovative thinking in bioscience and pharmacology. These compelling talks bring together elements from therapeutics, translational science, consumer, patient care and global healthcare concerns in an entertaining and dynamic format. Interact with speakers to create an energetic thought-provoking environment.

PRESIDENT'S NETWORKING RECEPTION AND EXHIBITS
4:30 PM – 6:30 PM
EXHIBIT HALL A/B SOUTH

Join us for the President's Networking Reception, offering further opportunities to network and interact with your colleagues and the exhibitors.

POSTER WALKS
Applications of Novel Technology
4:45 PM – 5:30 PM
EXHIBIT HALL A/B SOUTH

Led by Richard Peck, MD, PhD, and Mohamed Shahin, PhD.

Endogenous/Exogenous Predictors of Drug Exposure
5:30 PM – 6:15 PM
EXHIBIT HALL A/B SOUTH

Led by Stacey Shord, PharmD, and Larrissa Wenning, PhD.

SPECIAL EVENTS & HIGHLIGHTS

EXHIBIT WALKS
5:15 PM – 5:45 PM
EXHIBIT HALL A/B SOUTH
Join us on a guided tour of select exhibitors in the Exhibit Hall. Led by a Aubrey Stoch, MD, you'll gain some new knowledge on offerings for clinical pharmacologists and translational scientists.

FRIDAY, MARCH 17

EXHIBITS
7:00 AM - 1:30 PM
EXHIBIT HALL A/B SOUTH

Head to the last day of the exhibit hall and take advantage of the many things it has to offer including a Networking Breakfast at 7:00 am, a Morning Refreshment Break at 10:00 am and a Dessert Break at 12:30 pm.

POSTER WALK
Endogenous/Exogenous Predictors of Drug Response Cardiac/Metabolic
7:15 AM – 8:00 AM
EXHIBIT HALL A/B SOUTH
Led by Larissa Cavallari, PharmD, and Sony Tuteja, PharmD.

SPEED MENTORING
11:45 AM – 1:00 PM
WASHINGTON

The Career Development Committee is pleased to offer the Speed Mentoring event. Participants from all career levels (mentees) are matched with established clinical pharmacologists and translational scientists (mentors) for a series of 15 minute one-on-one discussions that may ultimately result in mentoring partnerships that are valuable to both parties. Matches are made prior to the Annual Meeting based on profiles provided by the mentees and mentors.

Registration is required.

EARLY CAREER SPEED NETWORKING
4:30 PM – 6:00 PM
WASHINGTON

Are you looking to have some fun while making new connections? Join us for a super fun, informal evening of networking with early career members. Event Requirement: Your attendance and readiness to have fun!! This social event is meant for early career members to build connections with peers in industry, regulatory, academia, consulting and nonprofit. The speed networking event is an opportunity to expand your network. Each attendee will have 3 minutes to connect with a member, with the intent to meet as many members as possible. Did you connect with someone and would like the conversation to continue? You will have an additional 15 minutes after the speed networking event to do so. Come join us for this great opportunity to exchange experiences, ideas and above all to meet new people!

*Light refreshments will be provided during the event.

Registration is required.

SATURDAY, MARCH 18

SPECIAL EDUCATION SESSION
Publish or Perish: Getting in the Game, and Getting the Most Out of Your Published Works
7:30 AM – 9:00 AM
VIRGINIA

The overall goal of this session is to provide guidance to our ASCPT members on ways to optimize their publications. There is a need for guidance at all points of a clinical pharmacologist's career on how to get the most out of his or her published work. The speakers will provide advice on requirements and expectations for publishing. They will also discuss skills, experiences, and preparation needed to find the right journal, and how to measure impact.

SPECIAL SESSION
Subject Safety in First-in-Human (FIH) Studies: Perspectives, Pragmatism, and Practice
7:30 AM – 9:30 AM
MARRIOTT 1/2

This special education session will provide a forum for open and interactive discussion around current best practices to ensure the safety of healthy volunteers participating in first-in-human (FIH) studies for novel therapeutic compounds. The session will include presentations from an international CRO scientist, the CEO of Biotrial, a legal expert, and regulatory and industry representatives, providing a broad range of

experiences from those involved in ensuring a safe and efficient FIH study experience. The speakers will bring their perspectives to current FIH practices, recent changes to regulatory guidance, and pragmatic approaches to maximizing subject safety while preserving innovation. The speakers and panelists will engage the audience in a productive discussion about the current state and future direction of FIH studies.

NETWORK & COMMUNITY MEETINGS

THURSDAY, MARCH 16

PHARMACOMETABOLOMICS (PM) COMMUNITY MEETING
10:00 AM – 11:00 AM
MARRIOTT FOYER/MEZZANINE LEVEL

Led by PM Leadership.

INFECTIOUS DISEASES (INF) COMMUNITY MEETING
11:00 AM – 12:00 PM
EXHIBIT HALL THEATER

Please join the Infectious Diseases (INF) Community at our meeting featuring highlights such as: discussion of INF Community's role in advancing PK-PD science in the antimicrobial world (dialogue with regulators, industry, academia); development of INF Steering Committee to direct the next year's activities (nominations for members welcome!); brainstorming for INF webinars for 2017; single slide abstracts by new and senior INF investigators; solicitation of ideas for recruiting/outreach. Come join us!

SYSTEMS PHARMACOLOGY (SP) COMMUNITY MEETING
12:00 PM – 1:00 PM
MARRIOTT FOYER/MEZZANINE LEVEL

Collective Progression, a 5-Year Plan for the Systems Pharmacology Community.

We stand at an exciting time to define, form and focus our Systems Pharmacology discipline. Attentive and efficient development of the models that we use to illustrate, estimate, evaluate, simulate and disseminate our understandings of the systems we study requires consistencies in methods and tools that don't currently exist. We'll discuss a 5-year vision for our discipline's progression. Areas identified for collective development will feed our Community's future goals and member offerings. Please join us to contribute your experiences and thoughts.

TRANSLATIONAL BIOINFORMATICS COMMUNITY INTEREST MEETING
12:30 PM – 1:30 PM
EXHIBIT HALL THEATER

Calling all members interested in bioinformatics, medical informatics, molecular epidemiology or data sciences as related to translational medicine or clinical pharmacology. We need 30 members to help form a Translational Bioinformatics (TBI) Community. Come help kick off this grass-roots effort in the exploratory meeting.

The proposed focus of the TBI Community will be to spur the development, benchmarking, standardization, and application of quantitative methodologies to advance translational medicine in clinical pharmacology. However, the direction, goals and target membership is up to you. We are looking for a few good folks to help lead this effort.

SPECIAL EVENTS & HIGHLIGHTS

QUANTITATIVE PHARMACOLOGY (QP) NETWORK MEETING
3:15 PM – 5:15 PM
MARRIOTT 3

The Quantitative Pharmacology Network has over 800 members from across all sectors of ASCPT. However, we are all passionate about the application of quantitative pharmacology principles to drug/biologic/target discovery, development and clinical practice. Come join us at our Network meeting where we will be:

- Hosting "flash presentations" highlighting examples of the impact of QP within our discipline. Presenters will be selected from accepted abstracts, as well as from submissions to our "Influence and Impact" Initiative.
- Highlighting contributions from our early career members.
- Providing updates from across our Network, which includes the following Communities: Biologics, Pharmacometrics & Pharmacokinetics (PMK) and Systems Pharmacology (SP).

This meeting will be a great opportunity to network with other members and find out how you can get more involved.

INTERNATIONAL TRANSPORTER CONSORTIUM (ITC) COMMUNITY MEETING
4:00 PM – 5:00 PM
MARRIOTT FOYER/MEZZANINE LEVEL

Following a short business meeting focused on activities for 2016/2017, the ITC will host a series of "Transporter Lightning Talks," which provide the audience with highlights of exciting research relevant to transporters in a short and pithy format. Speakers for the lightning talks will be selected from ASCPT and ITCW3 abstract presenters.

BIOMARKER & TRANSLATIONAL TOOLS (BTT) COMMUNITY MEETING
5:00 PM – 6:00 PM
EXHIBIT HALL THEATER

The BTT Community Meeting will cover the 2017 leadership transition and introduction of the incoming Chair and Vice-Chair. Discussion on 2017 objectives and methods of communication. Presentation on translational biomarker topic (speaker TBD).

FRIDAY, MARCH 17

GLOBAL HEALTH (GH) COMMUNITY LAUNCH MEETING
7:00 AM – 8:00 AM
MARRIOTT FOYER/MEZZANINE LEVEL

Led by Global Health Leadership.

PHARMACOGENOMICS (PMG) COMMUNITY MEETING
9:00 AM – 10:00 AM
MARRIOTT FOYER/MEZZANINE LEVEL

Led by PMG Leadership.

DRUG UTILIZATION & OUTCOMES (DUO) COMMUNITY MEETING
11:00 AM – 12:00 PM
MARRIOTT FOYER/MEZZANINE LEVEL

Led by DUO Leadership.

ONCOLOGY (ONC) COMMUNITY MEETING
1:00 PM – 2:00 PM
MARRIOTT FOYER/MEZZANINE LEVEL

The Oncology Community will host a business meeting followed by two student or trainee oral abstract presentations. The title and presenter for the student/trainee oral abstract presentations will be provided in the updated program found on the ASCPT Annual Meeting mobile app.

BIOLOGICS COMMUNITY MEETING
3:00 PM – 4:00 PM
MARRIOTT FOYER/MEZZANINE LEVEL

Biologics continue to represent the fastest growing area of drug development. However, there remains much to learn and new frontiers to discover for this exciting class of drugs. Please join the Biologics Community Meeting to learn about our planned activities for 2017, find out about leadership opportunities and tell us how you would like the Community to grow to better meet your needs.

DEVELOPMENT, REGULATORY & OUTCOMES (DRO) NETWORK MEETING
3:00 PM – 5:00 PM
MARYLAND

- 3:00 PM–3:30 PM DRO Updates
- 3:30 PM–3:45 PM Introduction of the Global Health Community
- 3:45 PM–5:00 PM Scientific Topics

TRANSLATIONAL & PRECISION MEDICINE (TPM) NETWORK MEETING
3:00 PM – 5:00 PM
MARRIOTT 3

The TPM Network will host 3 talks followed by TPM General Business and Networking.

"*Results of the Implementation of Pharmacogenomics into Primary Care Project*", Paul C. Bank, Leiden University Medical Center.

"*Pharmacometrics as a Tool for Therapeutic Solutions via Precision Dosing*", Vijay Ivaturi, MS, PhD, Center for Translational Medicine, University of Maryland Baltimore.

"*Biomarkers as Translational Tools; Current State of the Art*", Richard. A. Graham, PhD, Theravance Biopharma, Inc.

PHARMACOMETRICS & PHARMACOKINETICS (PMK) AND REGULATORY SCIENCE (RS) JOINT COMMUNITY MEETING
5:00 PM – 6:30 PM
MARRIOTT FOYER/MEZZANINE LEVEL

Please join us for the following topics:

- Introductions & Community Updates
  - Meet & greet with the Steering Committee Members from PMK and RS
  - 2016 goals & accomplishments
  - Acknowledgement/Award for the members who submitted program ideas
- Presentation: Recent trends for Regulatory Initiatives
- Brain Storming for 2018 Annual Meeting Program and Webinar Ideas

This meeting will be a great opportunity to network with members cross PMK and RS Communities and volunteer yourself for future ASCPT activities!

SCHEDULE-AT-A-GLANCE

STATE OF THE ART LECTURES

DON'T MISS OUT! PLAN TO ATTEND THE STATE OF THE ART LECTURES FROM THESE RENOWNED PROFESSIONALS IN THEIR FIELDS.

THURSDAY, MARCH 16

9:00 AM – 10:00 AM
MARRIOTT 1/2

Geraldine A. Hamilton, PhD, Emulate, Inc., Boston, MA
Organs-on-Chips: A Technology Platform for Translational and Precision Medicine

FRIDAY, MARCH 17

9:15 AM – 10:15 AM
MARRIOTT 1/2

James J. Collins, PhD, Massachusetts Institute of Technology, Cambridge, MA
Radical Approaches to Antibiotics and Antibiotic Resistance

SATURDAY, MARCH 18

9:45 AM – 10:45 AM
MARRIOTT 1/2

V. A. Shiva Ayyadurai, PhD, The Inventor of Email & Chairman/CEO, CytoSolve, Inc., Cambridge, MA
In Silico Mechanistic Modeling: The Future of Precision Medicine

FEATURED SPEAKERS

JOIN US FOR THE TWO ASCPT 2017 ANNUAL MEETING FEATURED SPEAKER SESSIONS AND HEAR PRESENTATIONS FROM YOUR FELLOW ASCPT MEMBERS.

THURSDAY, MARCH 16

1:30 PM – 2:30 PM
MARRIOTT 1/2

France Mentré, MD, PhD, University of Paris Diderot
Bridging the Gap Between Pharmacometricians and Statisticians in Clinical Pharmacology and Therapeutics

FRIDAY, MARCH 17

1:15 PM – 2:15 PM
VIRGINIA

J. Steven Leeder, PharmD, PhD, Children's Mercy Hospital
Precision Therapeutics for Children

STUDENT AND TRAINEE INFORMATION

The ASCPT 2017 Annual Meeting features several education sessions and networking events designed specifically for trainees and young scientists to guide them in their personal and professional development.

TRAINEE LUNCHEON

THURSDAY, MARCH 16, 2017

11:45 AM – 1:00 PM

This is a ticketed event; you must have registered and received a ticket with your registration materials to attend this luncheon.

In support of ASCPT's strategic initiative to build capacity through the development and support of career development and leadership programs for junior scientists and investigators, ASCPT is pleased to bring back the highly successful Trainee Luncheon to the 2017 Annual Meeting. This luncheon – open only to trainees and students – is a roundtable discussion for trainees and young scientists to meet with established clinical pharmacologists and translational medicine scientists to discuss potential career paths and other topics driven by trainees' questions.

Participants will rotate between tables to allow for multiple facilitator discussions. Facilitators include top leaders from the academia, consulting, government, and industry sectors of clinical pharmacology and translational medicine scientists. Facilitators will be seated at tables bearing their names and the employment sector that they represent. A short summary of each facilitator's background and current position is available on the ASCPT website at www.ascpt.org.

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Bertino Consulting

SPEED MENTORING

FRIDAY, MARCH 17, 2017
11:45 AM – 1:00 PM

The Career Development Committee is pleased to offer the Speed Mentoring event. Participants from all career levels (mentees) are matched with established clinical pharmacologists and translational scientists (mentors) for a series of 15 minute one-on-one discussions that may ultimately result in mentoring partnerships that are valuable to both parties. Matches are made prior to the Annual Meeting based on profiles provided by the mentees and mentors.

Registration required.

PUBLISH OR PERISH: GETTING IN THE GAME AND GETTING THE MOST OUT OF YOUR PUBLISHED WORKS

SATURDAY, MARCH 18, 2017
7:30 AM – 9:00 AM

The overall goal of this session is to provide guidance to our ASCPT members on ways to optimize their publications. There is a need for guidance at all points of a clinical pharmacologist's career on how to get the most out of his or her published work. The speakers will provide advice on requirements and expectations for publishing. They will also discuss skills, experiences, and preparation needed to find the right journal, and how to measure impact.

PRE-CONFERENCE

INTERNATIONAL TRANSPORTER CONSORTIUM WORKSHOP 3 (ITCW3): TRANSPORTERS IN DRUG DEVELOPMENT

ACKNOWLEDGMENTS

ASCPT WISHES TO ACKNOWLEDGE THE OUTSTANDING EFFORTS OF THE SCIENTIFIC PROGRAM COMMITTEE IN DEVELOPING AN EXCEPTIONAL EDUCATIONAL OFFERING.

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Susan I. Vear, MD
Larissa A. Wenning, PhD
Honghui Zhou, PhD

MONDAY, MARCH 13

8:15 AM – 8:30 AM
WELCOME AND OPENING REMARKS
Kathleen M. Giacomini, PhD
University of California, San Francisco, San Francisco, CA

SESSION 1: MEMBRANE TRANSPORTERS IN HUMAN HEALTH AND PATHOBIOLOGY: FROM BIOMARKERS TO THERAPY

MODERATORS
Kim L. R. Brouwer, PharmD, PhD
University of North Carolina at Chapel Hill, Chapel Hill, NC

Joseph W. Polli, PhD
GlaxoSmithKline, King of Prussia, PA

8:30 AM – 9:00 AM
Renal Transporters, Kidney Disease and Toxicity
Jonathan Himmelfarb, MD
University of Washington, Seattle, WA

9:00 AM – 9:30 AM
Hepatic Phospholipid and Bile Acid Transport Deficiencies: Therapeutic/ Clinical Implications
Ronald Oude Elferink, PhD
Academic Medical Center, Amsterdam, Netherlands

9:30 AM – 10:00 AM
Gout and Uric Acid: From Disease to Transporters to Therapy
Jeffrey N. Miner, PhD
Ardea Biosciences, San Diego, CA

10:00 AM – 10:30 AM
BREAK

SESSION 2: IMAGING AND PHARMACOKINETICS OF INTRACELLULAR DISTRIBUTION

MODERATORS
Shiew-Mei Huang, PhD
US Food and Drug Administration, Silver Spring, MD

Ken Korzekwa, PhD
Temple University School of Pharmacy, Philadelpia, PA

10:30 AM – 11:00 AM
Modeling Intracellular Concentrations with In Vitro Imaging and Liver Perfusion Studies
Ken Korzekwa, PhD
Temple University School of Pharmacy, Philadelphia, PA

11:00 AM – 11:30 AM
Imaging Studies with the Transporter Probe ^{99m}Tc-Mebrofenin Reveal Altered Hepatic Exposure in Patients with Non-Alcoholic Steatohepatitis (NASH)
Kim L. R. Brouwer, PharmD, PhD
University of North Carolina, Chapel Hill, NC

11:30 AM – 12:00 PM
Is Prediction of Tissue Exposure from In Vitro Data Using PBPK Modeling Possible? Confirmation by PET Imaging to Study the Clinical Disposition of Membrane Transporter Substrates
Yuichi Sugiyama, PhD
RIKEN, Yokohama, Japan

12:00 PM – 1:00 PM
LUNCH AND POSTER SESSION

SESSION 3: RECENT AND EMERGING TRANSPORTERS

MODERATORS
Maciej Zamek-Gliszczynski, PhD
GlaxoSmithKline, King of Prussia, PA

Richard B. Kim, MD
University of Western Ontario, London, ON, Canada

1:00 PM – 1:30 PM
New Developments in Renal Drug Transport
Adrian S. Ray, PhD
Gilead Sciences, Foster City, CA

1:30 PM – 2:00 PM
OATP2B1: In Vitro, Proteomic, and Clinical PK Relevance in GI and Liver
Jashvant D. Unadkat, PhD
University of Washington, Seattle, WA

2:00 PM – 2:30 PM
Emerging Importance of Nutrient Transporter-Mediated DDIs
Yan Zhang, PhD
Incyte Corporation, Wilmington, DE

2:30 PM – 3:00 PM
BREAK

SESSION 4: MODELING OF TRANSPORTERS FROM MOLECULAR MECHANISMS TO PBPK

MODERATORS

Aleksandra Galetin, PhD
University of Manchester, Manchester, UK

Pär Matsson, PhD
Uppsala University, Uppsala, Sweden

3:00 PM – 3:30 PM
Inhibitor Discovery for the Human GLUT1 from Homology Modeling and Virtual Screening
Avner Schlessinger, PhD
Icahn School of Medicine at Mount Sinai, New York, NY

3:30 PM – 4:00 PM
Computational Modeling to Predict the Functions and Impact of Drug Transporters
Pär Matsson, PhD
Uppsala University, Uppsala, Sweden

4:00 PM – 4:30 PM
PBPK Modeling of Renal Impairment: What is Missing?
Aleksandra Galetin, PhD
University of Manchester, Manchester, United Kingdom

4:30 PM – 5:30 PM
BREAKOUT SESSIONS FOR WHITEPAPERS

4:30 PM – 7:00 PM
POSTER SESSION AND RECEPTION

TUESDAY, MARCH 14

7:15 AM – 8:15 AM
BREAKOUT SESSIONS FOR WHITEPAPERS

SESSION 5: TRANSPORTER GENOMICS: GENOMEWIDE AND MASSIVELY PARALLEL SEQUENCING STUDIES

MODERATORS

Kathleen M. Giacomini, PhD
University of California, San Francisco, San Francisco, CA

Mikko Niemi, MD, PhD
University of Helsinki, Helsinki, Finland

8:30 AM – 9:00 AM
Massively Parallel Sequencing of Drug Transporters: SLCO1B1 and Beyond
Mikko Niemi, MD, PhD
University of Helsinki, Helsinki, Finland

9:00 AM – 9:30 AM
Genomewide Studies Reveal Transporters as Determinants of Drug Response
Kathleen M. Giacomini, PhD
University of California, San Francisco, San Francisco, CA

9:30 AM – 10:00 AM
Na+/Citrate Transporter [SLC13A5] Variants in Epilepsy and Developmental Delay
Ana M. Pajor, PhD
University of California, San Diego, La Jolla, CA

10:00 AM – 10:30 AM
BREAK

SESSION 6: BIOMARKERS AND PROBES FOR CLINICAL STUDIES

MODERATORS

Lei Zhang, PhD
US Food and Drug Administration, Silver Spring, MD

Xiaoyan Chu, PhD
Merck, Rahway, NJ

10:30 AM – 11:00 AM

Endogenous Biomarkers for Renal Transporters
Hiroyuki Kusuhara, PhD
University of Tokyo, Tokyo, Japan

11:00 AM – 11:30 AM

Endogenous Biomarkers for OATP1B: Preclinical to Clinical Translation
Yurong Lai, MD, PhD
Gilead Sciences, Foster City, CA

11:30 AM – 12:00 PM

Pharmacokinetic Evaluation of a Drug Transporter Cocktail Consisting of Digoxin, Furosemide, Metformin, and Rosuvastatin
Mitchell Taub, PhD
Boehringer Ingelheim, Ridgefield, CT

12:00 AM – 1:00 PM

LUNCH AND POSTER SESSION

SESSION 7: REGULATORY ISSUES IN TRANSPORTER MEDIATED DRUG-DRUG INTERACTIONS

MODERATORS:
Donald Tweedie, PhD
Merck, West Point, PA

Yurong Lai, MD, PhD
Gilead Sciences, Foster City, CA

1:00 PM – 1:30 PM

FDA Perspective
Lei Zhang, PhD
US Food and Drug Administration, Silver Spring, MD

1:30 PM – 2:00 PM

A European Perspective
Eva Gil Berglund, PhD
Medical Products Agency, Uppsala, Sweden

2:00 PM – 2:15 PM

Case Study 1: Industry/Academia

2:15 PM – 2:30 PM

Case Study 2: Industry/Academia

2:30 PM – 2:45 PM

Case Study 3: Industry/Academia

2:45 PM – 3:00 PM

Presentation from IQ Drug Metabolism Transporter Subgroup
Speakers TBD

3:00 PM – 4:00 PM

Panel Discussion with Academic, Industry and Regulatory Scientists
Kathleen M. Giacomini, PhD
University of California, San Francisco, San Francisco, CA

Joseph W. Polli, PhD
GlaxoSmithKline, King of Prussia, PA

Kathleen Hillgren, PhD
Eli Lilly, Indianapolis, IN

Shiew-Mei Huang, PhD
US Food and Drug Administration, Silver Spring, MD

Eva Gil Berglund, PhD
Medical Products Agency, Uppsala, Sweden

4:00 PM – 4:15 PM

CLOSING REMARKS AND END OF WORKSHOP

4:15 PM – 5:15 PM

OPEN FORUM TO PROVIDE FEEDBACK TO ITC

INTERNATIONAL TRANSPORTER CONSORTIUM WORKSHOP 3 (ITCW3): TRANSPORTERS IN DRUG DEVELOPMENT

ITC-001

CHARACTERIZATION AND VALIDATION OF MAMMALIAN CELLS DERIVED P-GP, BCRP, MRP2 AND BSEP MEMBRANE VESICLES.

N. Li, J. Wang, J. Bourgea, K. Cooper; Corning Life Sciences, Bedford, MA, USA.

BACKGROUND: ATP-binding cassette (ABC) transporters translocate numerous endogenous substrates and xenobiotics across cell membranes, thereby significantly contributing to drug bioavailability, disposition and elimination. For compounds with low passive permeability, inside-out vesicles are the gold standard to study drug interactions with ABC transporters. Compared to *in vivo*, the commonly used vesicle model, based on insect cell expression system, contains different membrane composition and post-translational modifications. In this study, a new ABC transporter vesicle model was developed using a mammalian expression system.
METHODS: HEK293 cells were used to overexpress the human efflux transporters P-gp, BCRP, MRP2 and BSEP. After transient transfection, the cells were harvested and membrane vesicles were prepared based on the method described by Keppler *et al.* (1998). The vesicular transport activity was measured using a rapid filtration technique on 96-well microplates.
RESULTS: The vesicles prepared from mammalian cells demonstrate superior transport properties over those made from insect cells, and especially with significantly lower background. For all four transporters, the transport activity is protein-dependent and osmolarity dependent. The kinetic profiles of selective probe substrates and IC50s of multiple inhibitors recommended by the regulatory guidance or ITC white papers are comparable to the published data.
CONCLUSION: Mammalian cells derived ABC transporter vesicles are validated for *in vitro* evaluation of drug interaction with ABC transporter. This model with more human-like recombinant ABC transporter proteins and membrane composition could potentially improve the accuracy of *in vitro* to *in vivo* correlation.

ITC-002

NICOTINE METABOLISM AND RENAL TRANSPORT AS PREDICTORS OF ABSTINENCE IN TREATMENT-SEEKING SMOKERS RECEIVING VARENICLINE.

A.R. Peng[1], C. Lerman[2], A.Z. Zhu[1], R.F. Tyndale[1], PGRN-PNAT Research Group; [1]University of Toronto, Toronto, ON, Canada, [2]University of Pennsylvania, Philadelphia, PA, USA.

BACKGROUND: Hepatic enzyme CYP2A6 inactivates nicotine; its phenotypic marker, the nicotine metabolite ratio (NMR), predicts smoking cessation. Varenicline, a smoking cessation drug, is eliminated through glomerular filtration and active tubular secretion (i.e.OCT2). The aims were to examine whether genetic variation in OCT2 influences varenicline levels and to assess the impact of variation in NMR and OCT2 on end-of-treatment abstinence in smokers taking varenicline.
METHODS: Week 1 salivary varenicline levels and biochemically-verified abstinence (exhaled CO≤8 ppm) were assessed in treatment-seeking smokers (NCT01314001). Baseline blood NMR was measured and OCT2 variants were genotyped. Regression analyses were used to assess impact of predictors on varenicline levels and abstinence.
RESULTS: Among those with detectable week 1 varenicline, OCT2 rs595374 (CCvsCT+TT) predicted varenicline levels (beta=-.140,p=.047); CC genotype was associated with decrease in varenicline levels. NMR and OCT2 rs595374 were unique predictors of abstinence, even after controlling for varenicline level. Specifically, normal compared to slow metabolizers (OR=2.63,95%CI=1.49,4.65;p=.001) and CC participants compared to CT+TT (OR=2.07,95%CI=1.10,3.87;p=.02) were more likely to achieve end-of-treatment abstinence. Normal metabolizers with the CC genotype, compared to all others, (OR=3.87,95 %CI=1.93,7.79;p=.001) were most likely to be abstinent.
CONCLUSION: Variation in OCT2 alters varenicline levels. Further, variation in OCT2 and NMR is associated with abstinence, which may involve mechanisms beyond varenicline levels. In this first study on abstinence following varenicline treatment, these novel findings suggest a complex role for variation in OCT2 and NMR in cessation.

ITC-003

COMPARISON OF THE EFFECT OF CHRONIC KIDNEY DISEASE (CKD) ON PHARMACOKINETICS OF CYP1A2, CYP2C8, CYP2C9, CYP2C19 AND OATP SUBSTRATES.

M.-L. Tan[1], K. Yoshida[1], P. Zhao[1], L. Zhang[1], A. Galetin[2], S.-M. Huang[1]; [1]US Food and Drug Administration, Silver Spring, MD, USA, [2]University of Manchester, Manchester, UK.

BACKGROUND: Recent studies have shown elimination-pathway dependent effect of chronic kidney disease (CKD) on pharmacokinetics of nonrenally eliminated drugs. In this study, we compared effects of CKD on clearance of drugs mediated by CYP1A2, CYP2C8, CYP2C9, CYP2C19 and OATP that are not significantly eliminated renally.
METHODS: The University of Washington Metabolism and Transport Drug Interaction Database and New Drug Application reviews were searched in order to identify model substrate drugs. The model drugs were defined based on clinical drug-drug interaction and pharmacogenetics studies for the metabolized drugs and the contribution of nonrenal clearance for the transported drugs. Clinical CKD study data were collected for the selected model drugs. The ratios of clearance between CKD groups and the healthy controls were calculated.
RESULTS: **Figure 1**
CONCLUSION: OATP mediated clearance is generally decreased in parallel with the severity of CKD. CYP2C8 model drugs also showed reduction in the clearance with CKD, however, many of these drugs are CYP2C8/OATP dual substrates and interplay of these pathways needs to be investigated further. In contrast, CKD has no large effect on metabolic enzymes CYP1A2, CYP2C9 and CYP2C19. The observed pathway dependency in CKD effects may inform the need to conduct clinical CKD studies.

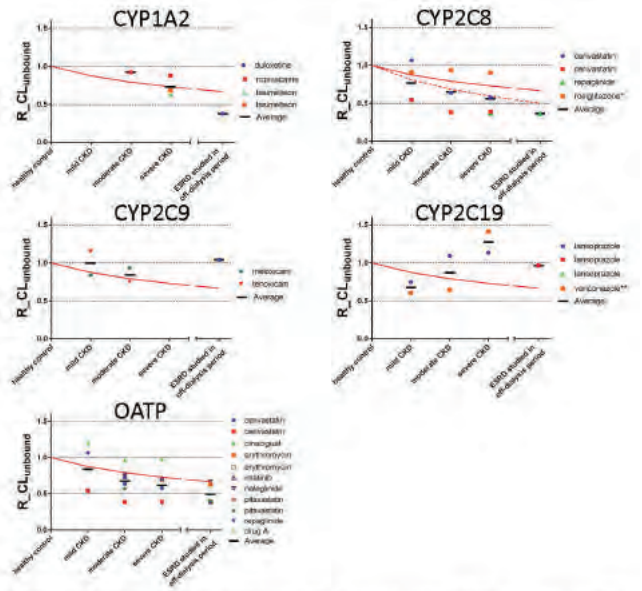

Figure 1. Comparison of observed R_CL unbound and theoretical lowest R_CL assuming no change in nonrenal clearance in CKD (red solid line: 0.667 + 0.333xR_GFR for AUCR=3 and dashed red line: 0.5 + 0.5xGFR for AUCR=2, where R_GFR represents ratio of average GFR in CKD subjects compared to that in normal subjects) for CYP1A2, CYP2C8, CYP2C9, CYP2C19 and OATP model drugs. General decrease in clearance for OATP model drugs with the CKD severity was observed and the observed R_CL was lower than the theoretical lowest R_CL indicating that nonrenal clearance may be affected by CKD. CYP2C8 model drugs also showed reduction in the clearance with CKD. In contrast, the observed R_CL for CYP1A2 and CYP2C9 model drugs were comparable to the theoretical lowest R_CL and the observed R_CL for CYP2C19 model drugs were slightly larger than the theoretical lowest R_CL indicating that CKD had no additional effect on nonrenal pathways for these enzymes. *Drug with 2 ≤ AUCR < 3.

ITC-004

PHYSIOLOGYICALLY BASED PHARMACOKINETIC MODEL OF ACYCLOVIR TO PREDICT CONCENTRATION OF ACYCLOVIR IN RENAL TUBULES AND ASSOCIATED RISK OF ACUTE KIDNEY INJURY.

F. Hagos, H. Kalluri, R. Joshi, S. Adams, P. Empey, R. Venkataramanan; University of Pittsburgh, Pittsburgh, PA, USA.

BACKGROUND: Despite its effectiveness at lowering mortality and morbidity in HSV-encephalitis, IV acyclovir (ACY), is associated with supersaturation in renal tubules leading to acute kidney injury (AKI). The relation between ACY doses, ACY levels in renal tubules and AKI risk is not established due to impracticality of measuring ACY in renal tubules in humans. This study aims to use PBPK modeling to estimate ACY concentration in renal tubules and assess AKI risk.
METHODS: A full BPK model of ACY was built in Simcyp Simulator. Parameters were obtained from published literature. The permeability-limited mechanistic kidney model was used to account for renal clearance processes including secretion of ACY to urine mediated by uptake and efflux transporters. Model verification and validation were performed by comparing the simulated ACY PK values to two separate published clinical data sets. The PBPK model was used to perform clinical studies in virtual populations at varying ACY doses.
RESULTS: Model verification and validation showed that the model simulated conc-time profiles of ACY were consistent with observed data across three doses (2.5, 5, 10mg/kg). Model predicted PK parameters (CL, AUC, C_{max}, CL-R and amount excreted in urine) were within 25% of published values. Estimated C_{max} of ACY in renal tubules exceeded ACY solubility in urine in none of the patients at 2.5 or 5mg/kg doses and in 17% of patients at 10mg/kg exposing them to AKI.
CONCLUSION: A validated full PBPK model of IV ACY was built and used to estimate the concentration of ACY in renal tubules and the associated risk of AKI. Future studies will investigate how different dosing strategies such as adjustments based on plasma C_{max} could be used to avoid AKI risk.

ITC-005

TOP-DOWN PROTEOMIC ANALYSIS OF THE APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER.

L.C. Czuba, C.L. Carter, M.A. Kane, P.W. Swaan; University of Maryland, Baltimore, MD, USA.

BACKGROUND: The human apical sodium-dependent bile acid transporter (hASBT) is integral in maintaining bile acid and cholesterol homeostasis. Post-translational modifications (PTMs) have been shown to mediate the functional expression of hASBT. yfAsbt is a bacterial transporter with similar properties to hASBT that can be purified for use as a standard to develop a pipeline for PTM analysis by mass spectrometry (MS). We use both proteins to develop complimentary MS approaches that will be integral for mapping hASBT PTMs.
METHODS: Cos-1 cells transiently expressing hASBT were immunopurified (IP) using Anti-HA Agarose. Protein profiling was carried out by bottom-up MS. To reduce protein contaminatio, transfected cells were ultracentrifuged to isolate detergent soluble and insoluble membranes prior to IP. Samples were pooled to ensure concentration was high enough for MS. Purified yfAsbt in detergent was used as a standard in place of hASBT to optimize protein precipitation and resolubilization solutions, and LC-MS/MS conditions. Detection of yfAsbt was carried out by MALDI-MS after each step. LC-MS/MS was carried out on a Thermo Orbitrap Fusion mass spectrometer.
RESULTS: Membrane isolates and pre-clearing prior to IPs reduced protein contamination and improved sensitivity. Purified yfAsbt was essential for the optimization and characterization of protein precipitations, resolubilization, and LC-MS/MS conditions. MALDI-MS detection at each step proved minimal protein loss occurred.
CONCLUSION: Sample preparation must be optimal for the detection of membrane transporters by MS. yfAsbt played a vital role in determining the workflow procedures and LC-MS/MS conditions. This workflow will provide novel insight to the molecular mechanisms governing functional expression of hASBT.

ITC-006

IDENTIFICATION OF FIMH ANTAGONIST INTERACTIONS WITH OATP2B1 TRANSPORTER.

J. Bezençon[1], C. Ferreira[2], J. Hussner[2], H. Meyer zu Schwabedissen[2], B. Ernst[1]; [1]Institute of Molecular Pharmacy, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, [2]Group of Biopharmacy, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland.

BACKGROUND: Urinary tract infections (UTIs) belong to the most prevalent infectious diseases and are mainly caused by uropathogenic *Escherichia coli* (UPEC). The adhesion of UPEC to the mannosylated glycoprotein uroplakin Ia (UPIa) on urothelial cells is mediated by the lectin FimH, which is located at the tip of bacterial type 1 pili. Its interaction can be prevented by FimH antagonists, which inhibit the adhesion step and therefore provide a novel therapeutic opportunity for prevention and treatment of UTIs. To ensure drug delivery of an orally administrated standard therapy to the bladder, oral absorption at the enterocytes, metabolic stability, and slow and prolonged renal excretion is required. To evaluate possible contributions by active uptake, the interaction of FimH antagonists with the ubiquitously expressed uptake transporter OATP2B1, which is highly expressed in enterocytes, was studied.
METHODS: Interaction of FimH antagonists was analyzed in a cellular system (MDCKII-cells) over-expressing OATP2B1. The impact of several classes of FimH antagonists on OATP2B1-mediated uptake of tritium labeled estrone-3 sulfate (E_1S^+, natural substrate) was determined by inhibition and competitive counterflow studies.
RESULTS: Eight FimH antagonists were identified as inhibitors of the OATP2B1-mediated E_1S^+ uptake and showed IC_{50} values (0.19 - 4.72 µM) comparable to the known inhibitor atorvastatin (0.15 µM). Subsequent some of the inhibitory FimH antagonists showed significantly reduced E_1S^+ (< 70% of control) in MDCKII-OATP2B1 cells in the competitive counterflow studies, comparable to known substrates.
CONCLUSION: FimH antagonists were identified to interact with the OATP2B1 transporter. Furthermore, OATP2B1 may contribute to intestinal uptake of these compounds.

ITC-007

ABCG2 C.421C>A IS ASSOCIATED WITH CLINICAL OUTCOMES FOLLOWING TRAUMATIC BRAIN INJURY.

S.M. Adams[1], Y.P. Conley[2], D. Ren[2], D.O. Okonkwo[3], A.M. Puccio[3], C. Dixon[3], R.S. Clark[3], P.M. Kochanek[3], P.E. Empey[1]; [1]University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA, [2]University of Pittsburgh School of Nursing, Pittsburgh, PA, USA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

BACKGROUND: Traumatic brain injury (TBI) is a leading cause of death and lacks pharmacologic treatments. Transporters may participate in CNS recovery after TBI, and genetic variations that impact transporter function are associated with TBI outcomes. *ABCG2* is a transporter in the CNS with a common variation, c.421C>A, which decreases expression. We evaluated the association of *ABCG2* c.421C>A with TBI outcomes and hypothesized that subjects with variant alleles would have improved outcomes.
METHODS: In a retrospective cohort study, subjects with severe TBI were identified for discovery (N=297) and validation (N=188) cohorts, then genotyped for *ABCG2* c.421C>A. Glasgow Outcome Scale (GOS) scores at 3, 6, 12, and 24 m. post-TBI were compared with mixed effects ordinal regression with covariates time post-TBI, age, sex, race, and Glasgow Coma Scale score with an additive and/or dominant variant allele models.
RESULTS: A dominant variant allele model was used for the discovery cohort and an additive model was used for the validation due to presence of homozygote variant subjects. The A (variant) allele at *ABCG2* c.421C>A was associated with favorable GOS scores, [p = 0.009 (discovery) and p = 0.042 (validation)], and the interaction between the A allele with age was associated with worse GOS scores [p = 0.019 (discovery) and p = 0.024 (validation)].

CONCLUSION: The A allele at *ABCG2* c.421C>A was associated with favorable outcomes following TBI, but the association was mitigated with advancing subject age. Findings were replicated in two cohorts. The age effect provides further insight into the TBI recovery trajectory in younger versus older subjects. Future studies will seek to identify the mechanism associated with this finding, which may lead to novel treatment/prognostication modalities.

ITC-008

RAPID AND LOW-COST ASSESSMENT OF COMPOUND DDI POTENTIALS USING MDCK-II CELLS CO-EXPRESSING REGULATORY TRANSPORTERS OATP1B1, OATP1B3, OAT1, OAT3, OCT2, P-GP, BCRP AND MATE1.

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BACKGROUND: Transporter substrate test has become a common practice in drug development to inform potential drug-drug interactions (DDI). Applying such test to early stage compounds can minimize expensive clinical DDI liabilities, which however is hindered by high costs of assessing many DDI transporters. This work presents a novel assay method for accurate and low-cost substrate assessment for eight regulatory transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT2, P-gp, BCRP and MATE1.
METHODS: Polarized MDCK-II cells were transfected to express GFP (control), uptake transporters OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 (uptake model), the uptake transporters plus three efflux transporters P-gp, BCRP and MATE1 (uptake+efflux model). Apparent B>A permeability ($P_{app,B>A}$), cellular concentration (C_{cell}) of 20+ compounds were measured with these models. A new parameter, apparent apical efflux permeability ($P_{eff,ap}$) defined as B>A transport rate divided by C_{cell}, was introduced to assess apical efflux activity. Differences in $P_{app,B>A}$, C_{cell} or $P_{app,B>A}$ among the three models were used to determine whether a compound is transported by one or more uptake and/or efflux transporters.
RESULTS: Compared to GFP control, the uptake+efflux model exhibited >2x increases in $P_{app,B>A,}$ C_{cell} or $P_{eff,ap}$ for all reported substrates of the eight transporters. Uptake and efflux substrate activities were further delineated by comparing the parameters among control, uptake, and uptake+efflux models. Compared with $P_{app,B>A}$, $P_{eff,ap}$ is more accurate in assessing apical efflux activities, especially for highly permeable compounds.
CONCLUSION: The presented assay method using multi-transporter models can be used for accurate and low-cost substrate assessment for the eight common DDI transporters.

ITC-009

INVESTIGATION OF BEAGLE DOGS FOR THE PREDICTION OF HEPATIC TRANSPORTER-MEDIATED CLEARANCE.

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BACKGROUND: There is minimal information on hepatic transporter-mediated clearance in beagle dogs. The aim of the present study was to evaluate beagle dogs as an alternative preclinical animal to study hepatic uptake.
METHODS: Nine known OATP substrates (atorvastatin, cerivastatin, fexofenadine, pitavastatin, pravastatin, repaglinide, rosuvastatin, telmisartan, and valsartan) were used. *In vitro* uptake experiments were performed in plated male beagle dog hepatocytes in the absence and presence of OATP inhibitors to obtain total uptake clearance (CL_{uptake}), passive diffusion clearance ($CL_{passive}$), and total and unbound cell-to-medium concentration ratio (Kp and Kp_{uu}). *In vitro-in vivo* extrapolation (IVIVE) of dog uptake data was performed; *in vivo* intrinsic hepatic clearance ($CL_{int,H}$) values were determined following intravenous administration (0.1 mg/kg) in male beagle dogs.
RESULTS: A 15-fold range in CL_{uptake} was observed, with fexofenadine and telmisartan

showing the lowest and highest CL_{uptake}, respectively. For 5/9 drugs investigated, active uptake contributed >75% to CL_{uptake}. A 35-fold range in $CL_{passive}$ was observed; this parameter was correlated with the $logD_{7.4}$ of the drugs investigated. Rosuvastatin and valsartan showed high *in vitro* Kp_{uu} (>10), whereas cerivastatin, pitavastatin, repaglinide and telmisartan had Kp_{uu}<5. IVIVE resulted in a good agreement between predicted and observed intrinsic uptake clearance (3-fold bias).
CONCLUSION: In the present study, transporter-mediated uptake was confirmed in plated dog hepatocytes for all nine OATP substrates. The extrapolation of *in vitro* dog uptake data resulted in a good agreement with *in vivo* $CL_{int,H}$ for most drugs, highlighting its suitability as a preclinical model for the investigation of hepatic uptake.

ITC-010

DETERMINATION OF INTRACELLULAR UNBOUND DRUG CONCENTRATION IN PRESENCE OF TRANSPORTERS - STUDIES WITH BOSENTAN.

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BACKGROUND: Accurate prediction of target activity of drug requires knowledge of drug concentration at the target. Poor permeability and transporter activity could result in unequal unbound concentrations in plasma and cell. The present study aims to predict intracellular unbound drug concentration with a 5 compartment membrane model.
METHODS: Single pass liver perfusion was conducted in male Sprague Dawley rats using bosentan (BOS 1μM) alone and with rifampin (RIF 20μM), 1-aminobenzotriazole (ABT 1mM) and ABT+RIF. Perfusate into the liver (C_{in}), out of the liver (C_{out}) over time, liver homogenate and bile samples were analyzed with LC-MS/MS.
RESULTS: The C_{out} for BOS after a 50 min perfusion (0.099 μM) was 3.4 fold higher in presence of RIF (0.34 μM). Total dose recovered in bile was 2-2.5% in absence of RIF and 1.1-1.25% in presence of RIF in all groups. The mean liver concentrations of BOS in presence of RIF were 1.48 fold higher than without RIF for all groups. Liver concentrations of hydroxy-BOS and hydroxy desmethyl-BOS were not significantly different across groups. Dose recovered as metabolites in bile was 0.46%, 0.065%, 0.049% and 0.009% in BOS, BOS+RIF, BOS+ABT and BOS+ABT+RIF groups, respectively.
CONCLUSION: We have previously utilized compartmental modeling to predict atorvastatin intracellular concentrations in the presence of active uptake transport. Studies for modeling these BOS data are ongoing. Together, these results support the use of compartmental modeling to predict intracellular concentrations in dynamic organ-based systems. These predictions can provide insight into the role of uptake transporters and metabolizing enzymes in determining drug tissue concentrations. This work was funded by NIH grants R01GM104178 and R01GM114369.

INTERNATIONAL TRANSPORTER CONSORTIUM WORKSHOP 3 (ITCW3): TRANSPORTERS IN DRUG DEVELOPMENT

ITC-011

MATURATION OF HUMAN HEPATIC MEMBRANE TRANSPORTER PROTEINS IN THE FIRST FOUR MONTHS OF LIFE.

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BACKGROUND: Hepatic membrane-embedded proteins are involved in trafficking endogenous and exogenous compounds and may influence the pharmacokinetics of drugs. Transporter-specific age-related changes in protein abundance were found in a pilot study (n=24), but now we aimed to elucidate the exact developmental pattern of clinically relevant hepatic transporters in a larger cohort of 63 fetuses, preterm and term neonates and infants and compare it with adults.
METHODS: Protein expression of BCRP, BSEP, GLUT1, MCT1, MDR1, MRP1-3, NTCP, OCT1, OATP1B1, OATP1B3, and OATP2B1 was quantified using UPLC-MS/MS, on snap-frozen post mortem fetal and infant liver samples and adult surgical liver samples. Protein expression was quantified in isolated crude membrane fractions. Pairwise comparison Kruskal-Wallis test was used to analyze a possible age-related difference.
RESULTS: Thirty-six fetal [median GA 23.4 weeks (range 15.3-41.3), no PNA], 12 premature neonatal [GA 30.2 weeks (24.9-36.7), PNA 1.0 weeks (0.14-11.4)], 11 term neonatal [GA 40.0 weeks (39.7-41.3), PNA 4.14 weeks (0.29-18.1)], 4 pediatric [PNA 4.13 years (1.08-7.44)] and 8 adult liver samples were studied. Expressions of BCRP, MCT1, OATP1B3, and OATP2B1 were similar in all age groups. MDR1, MRP1, MRP2, MRP3 and OCT1 expressions were low in fetus and high in adults (all $p<0.05$). Expression of BSEP increased from fetal to term newborn and to adult age (both $p<0.01$) and of NCTP increased over the whole age range (all $p<0.05$). GLUT1 and OATP1B1 expressions were high in fetuses and decreased towards newborns age (both $p<0.01$). GLUT1 expression decreased further in children's and adult age (both $p<0.05$).
CONCLUSION: These data further delineate transporter specific changes in protein abundance across the first months of age.

ITC-012

PHARMACOKINETIC MODELING OF ^{99M}TC-MEBROFENIN BLOOD AND LIVER SCINTIGRAPHY DATA IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS (NASH) AND HEALTHY SUBJECTS.

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BACKGROUND: ^{99m}Tc-mebrofenin (MEB), a radiodiagnostic agent used clinically to image the liver and gallbladder, is a substrate of the hepatic uptake transporters OATP1B1 and OATP1B3, biliary efflux transporter MRP2, and the basolateral efflux transporter MRP3. MEB has been used as an *in vivo* probe to assess transporter function. The objective of this study was to evaluate changes in hepatic transporter function in NASH patients using compartmental modeling.
METHODS: MEB disposition (blood concentrations and mass in liver obtained by gamma scintigraphy) in 13 healthy subjects and 7 NASH patients[1] was used to develop a compartmental model (Phoenix WinNonlin, version 7). The final structural model that best described the data included one central blood compartment and two liver compartments with clearance from the second liver compartment into bile. The model was parameterized using rate constants that represented hepatic uptake, biliary efflux, basolateral efflux, renal excretion, and partitioning into and out of the liver subcellular compartment. Data from the two groups were modeled separately using the same structural and error model.
RESULTS: Two parameters were significantly different between the groups. The mean rate

constant (± SD) for biliary excretion of MEB was decreased in patients with NASH compared to healthy subjects (0.025 ± 0.006 vs. 0.094 ± 0.101 min^{-1}; p = 0.031). The volume of distribution of the central compartment in patients with NASH was 5.81 ± 2.00 L and 11.61 ± 2.51 L (p<0.001) in healthy subjects.
CONCLUSION: Compartmental modeling of MEB in patients with NASH demonstrated decreased function of MRP2, which may have important clinical consequences for drugs that are substrates of this transporter. *Funded by NIH R01GM041935* Reference:J. Slizgi, et al. ASCPT 2017 Abstract.

ITC-013

CHARACTERIZATION OF ORGANIC SOLUTE TRANSPORTER (OST) ALPHA/BETA FUNCTION AND IDENTIFICATION OF DRUG TRANSPORT INTERACTIONS.

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BACKGROUND: OSTα/β is a bidirectional bile acid transport protein expressed in hepatic basolateral membranes. Characterization of OSTα/β function and identification of inhibitors would be beneficial for accurate drug safety prediction.
METHODS: A human OSTα/β overexpressing cell line (OSTab) was established by transfecting Flp-In-HEK293 cells with pcDNA5/FRT/OSTα/β and pOG44 vectors. Expression of OSTα/β was detected by qRT-PCR and immunofluorescence (IF). OSTab cells were cultured in 24-well plates; transport kinetics of taurocholate (TCA), estrone 3-sulfate (E3S), dehydroepiandrosterone sulfate (DHEAS) and digoxin (DIG) were determined. Further, 26 structurally diverse compounds were explored as human OSTα/β inhibitors: known OSTα/β inhibitors, known bile acid transport inhibitors, and compounds associated with cholestatic liver injury.
RESULTS: OSTα/β mRNA levels were ≥20,000-fold higher in OSTab than in mock cells; membrane localization was confirmed by IF. Uptake of TCA, E3S, DHEAS and DIG by OSTab cells (0.01-1000 uM; 0.01-100 uM for DIG) was linear and did not follow Michaelis-Menten kinetics at 0.5 and 2 min; the velocity of TCA and E3S uptake at 5 s and 1 min decreased rapidly from 126.1±10.7 to 43.1±6.6 (TCA) and 92.6±28.6 to 22.5±1.9 (E3S) pmol/min/mg protein. Fidaxomicin was identified as a novel inhibitor of OSTα/β-mediated TCA transport (41±7% of control); inhibition of OSTα/β by taurolithocholic acid sulfate, E3S, spironolactone and indomethacin was confirmed. Interestingly, some compounds consistently stimulated TCA uptake in OSTab cells.
CONCLUSION: This is the first drug interaction study with the human OSTα/β transporter in a stably expressing transfected cell line. This OSTα/β inhibition assay may be useful in identifying hepatotoxic compounds.

ITC-014

VALIDATION OF A MICRODOSE PROBE DRUG COCKTAIL FOR CLINICAL DRUG INTERACTION ASSESSMENTS FOR DRUG TRANSPORTERS AND CYP3A.

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BACKGROUND: Simultaneous assessment of the impact of drug perpetrators on common enzyme and transporter pathways in the clinic presents an opportunity to improve cycle time and better understanding of complex transporter/enzyme interactions. To test this concept, a microdose cocktail containing midazolam, dabigatran etexilate (DABE), pitavastatin, rosuvastatin, and atorvastatin as probes for cytochrome P450 (CYP) 3A, organic anion-transporting polypeptides (OATP) 1B, breast cancer resistance protein (BCRP), and MDR1 P-glycoprotein (P-gp) was established.
METHODS: Twelve healthy subjects were enrolled in a three-period, randomized, incomplete block, fixed-sequence clinical study. In period 1, all 12 subjects received a single dose of the microdose cocktail (containing 10 µg midazolam, 375 µg DABE, 10 µg of pitavastatin, 50 µg rosuvastatin, and 100 µg atorvastatin). The cocktail was co-administered in periods 2 and 3 either with a single dose of 600 mg rifampin, or on Day 4 of 5 days multiple dosing with 200 mg itraconazole once daily or 500 mg clarithromycin twice daily.
RESULTS: Generally, the pharmacokinetic profiles of the probe substrates were comparable to data for corresponding pharmacological doses with or without inhibitors. DABE as a microdose had an approximately two-fold higher P-gp drug-drug interaction than at the clinical dose (at which P-gp likely is saturated), suggesting this cocktail approach can identify a worst-case scenario.
CONCLUSION: This study demonstrated the utility of a microdose cocktail approach as a means to efficiently assess DDIs across multiple pathways in the clinic. Broader application of this microdose cocktail will facilitate a more comprehensive understanding of the roles of drug transporters in drug disposition and drug interactions.

ITC-015

A PHASE I, OPEN-LABEL STUDY TO EVALUATE THE EFFECT OF GDC-0810 ON THE PHARMACOKINETICS OF PRAVASTATIN IN HEALTHY FEMALE SUBJECTS OF NON-CHILDBEARING POTENTIAL.

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BACKGROUND: GDC-0810 is being developed as an oral anti-cancer drug for use as a single agent, or in combination, as treatment for estrogen receptor-positive (ER+) breast cancer. Based on an *in vitro* transporter assay, GDC-0810 has been shown to be a potent inhibitor of OATP1B1/1B3. Therefore, a study was conducted to explore the potential for drug-drug interaction (DDI) between GDC-0810 and pravastatin, a relatively selective and sensitive OATP1B1/1B3 substrate.
METHODS: Fifteen healthy female subjects of non-childbearing potential were enrolled in the study. On Day 1 in Period 1, a single 10 mg dose of pravastatin was administered to all subjects; this was followed by a washout period of 4 days before GDC 0810 administration. In Period 2, 600 mg GDC-0810 was administered once daily on Days 5 through 8 to achieve steady state concentrations. On Day 7, a single dose of 10 mg pravastatin was co-administered with the 600 mg GDC-0810 dose. Concentrations of pravastatin (Periods 1 and 2) and GDC-0810 (Period 2 only) were quantified in blood samples and subsequently used to calculate the PK parameters according to the model independent approach.
RESULTS: The pravastatin mean C_{max} and AUC values were approximately 20% higher

(90% CI for C_{max} of 97.8% to 146.8%) and approximately 41% higher (90% CI for AUC_{0-t} of 120.6% to 164.1% and 90% CI for AUC_{0-inf} of 119.8% to 165.3%), respectively, following pravastatin coadministered with GDC-0810 compared to pravastatin alone.
CONCLUSION: GDC-0810 was shown to modestly impact the PK of pravastatin which is unlikely to be of clinical significance based on the available drug interaction profile of pravastatin in the literature. Based on these results, dose adjustments for pravastatin and other OATP1B1/1B3 substrates are not necessary when administered with GDC-0810.

ITC-016

IMPROVING OATP1B1 AND OATP1B3 EXPRESSION IN HUMAN EMBRYONIC KIDNEY (HEK) CELLS USING VIRAL TRANSDUCTION TECHNIQUE.

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BACKGROUND: Evaluating Organic anion transporting polypetide (OATP) 1B1 and 1B3 mediated drug-drug interaction potential for a new molecular entities is essential in drug development. Our group previously generated plasmid transfected cell lines to evaluate OATP liability. However, OATP expression levels were low resulting in narrow dynamic range. Thus, we transduced OATP1B1 and 1B3 using lentiviral vector in HEK-293 cells to improve OATP1B1 and 1B3 expression.
METHODS: OATP1B1, OATP1B3, and vector Lenti6.3 were constructed and transfected into a lentiviral package cell line, Lenti-X-293T. The cells were selected by blasticidin (5 µg/mL) to generate stable cell lines. We confirmed OATP1B1 and 1B3 expression by flow cytometry and enriched OATP1B1 or OATP1B3 positive cells by Fluorescent-Activated Cell Sorting (FACS) technique. The uptake ratios and/or kinetic parameters of several known OATP1B1 and 1B3 substrates were compared in viral versus plasmid system.
RESULTS: Flow cytometry confirmed cell surface expression of OATP1B1 and OATP1B3. The uptake ratios in viral transduced cells increased up to four fold over plasmid transfected cells. We also compared Cholecystokinin-8 (CCK-8) in the viral transduced and plasmid transfected OATP1B3 cells and showed a similar K_m values with 10 fold higher V_{max} value in viral transduced cells indicating higher expression of OATP1B3 in viral system. The K_m value for rosuvastatin was measured and was similar to literature value (K_m =3.29±0.50 µM in viral OATP1B1 cell versus K_m= 0.8 to 7.3 µM in literature and K_m=6.40±1.16µM in viral OATP1B3 cell versus K_m= 14.2 µM in literature).
CONCLUSION: We developed and validated a robust OATP1B1 and OATP1B3 expression system using a viral transduction to support discovery and development programs at Lilly.

ITC-017

FUNCTIONAL INCREASE IN BILE ACID EFFLUX AFTER TREATMENT OF SANDWICH-CULTURED HUMAN HEPATOCYTES WITH THE FXR AGONISTS CHENODEOXYCHOLIC ACID AND OBETICHOLIC ACID.

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BACKGROUND: Farnesoid X Receptor (FXR) is a nuclear receptor that regulates genes involved in bile acid homeostasis. Chenodeoxycholic acid (CDCA) and obeticholic acid (OCA), two FXR agonists, significantly increased mRNA expression of basolateral efflux transporters in sandwich-cultured human hepatocytes (SCHH) [1]. This study evaluated functional changes in the uptake, basolateral efflux, and biliary excretion of a model bile acid, taurocholate (TCA), in SCHH after CDCA and OCA treatment.
METHODS: SCHH were treated with 100 µM CDCA, 1 µM OCA, or vehicle control for 72 hr followed by measurement of deuterated TCA (d_8-TCA) uptake and efflux in Ca^{2+}-containing and Ca^{2+}-free conditions (n=3 donors). The amount of TCA in cell lysate and medium was measured

at designated times. A mechanistic pharmacokinetic model was modified and fit to the TCA mass-time data to obtain unbound clearance (CL_u) estimates: uptake ($CL_{u,Uptake}$), basolateral efflux ($CL_{u,BL}$), and biliary ($CL_{u,Bile}$).
RESULTS: In the control group, the mean (±SD) area under the curve (AUC) of TCA in Cell+Bile and Cell was 1308 (412) and 433 (94) pmol*min/mg protein, respectively. AUC in Cell+Bile was decreased to 62% and 29% in OCA- and CDCA-treated SCHH, respectively. Control recovery of TCA in Ca^{2+}-containing medium after 2-min efflux was 14%, which was increased by >4-fold in treated SCHH, indicating increased basolateral efflux. Modeling results revealed that $CL_{u,BL}$ was increased by >10-fold in treated SCHH while changes in $CL_{u,Uptake}$ and $CL_{u,Bile}$ were modest.
CONCLUSION: CDCA and OCA significantly increased basolateral efflux of TCA, which contributed to the decrease in TCA intracellular accumulation.
Funded by Intercept Pharmaceuticals and NIH R01GM041935
Reference: 1. J.P. Jackson, et al. Appl In Vitro Tox. 2016.

ITC-018

SUBSTANTIAL ENHANCER ACTIVITY OF NON-CODING REGIONS IN ABCG2 (BREAST CANCER RESISTANCE PROTEIN, BCRP).

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BACKGROUND: Genetic variants in *ABCG2*, which encodes the breast cancer resistance protein (BCRP), have been associated at genomewide levels with variation in response to several clinically used therapeutics including statins, the anti-gout medication, allopurinol (ALLO) and the anticancer drug, methotrexate. The functional variants of *ABCG2*, such as the non-synonymous SNP 421C>A, have been well studied; yet the effect of non-coding variants on BCRP expression and activity is largely unknown. Using top hits from a GWAS that our lab performed which showed that *ABCG2* is a major determinant of ALLO response, we aimed to characterize the intronic variants for their enhancer activity *in vitro*.
METHODS: SNPs associated with ALLO response, or SNPs in high linkage disequilibrium (h^2>0.8) were gathered for analysis. Using HaploReg, RegulomeDB, and TRANSFAC, we identified 5 regions predicted to affect transcriptional activity. Enhancer activity of these regions, both reference and variant alleles, was investigated using a dual-luciferase reporter system in Huh-7 hepatic cells.
RESULTS: All tested regions significantly increased promoter activity. Three of these regions, 4:88144201, 4:88159564,and 4:88122482, increased the activity by as much as 340-, 1000- and 180-fold over empty vector, respectively ($p<1x10^{-6}$). Further, the variant allele of region 4:88148254 (rs2622624) was found to increase the promoter by 20-fold over the reference allele ($p = 0.01$).
CONCLUSION: Non-coding regions of *ABCG2* associated with ALLO response have a significant enhancer effect on promoter activity *in vitro*. Further studies are being done to characterize the relationship between these regions and BCRP activity and expression.

ITC-019

ORGANIC CATION TRANSPORTER 1 (OCT1; SLC22A1) MODULATES HEPATIC ENERGY METABOLISM.

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BACKGROUND: The organic cation transporter, OCT1, a well-established drug transporter, plays a key role in the hepatic uptake of many drugs including the opiate analgesic, morphine, and the anti-diabetic drug, metformin. In sharp contrast, little is known about its endogenous function. Previously, our laboratory identified thiamine, Vitamin B1, as a major endogenous substrate for OCT1. Unexpectedly, *Oct1*$^{-/-}$ mice were protected from hepatic steatosis. Here, we tested the hypothesis that OCT1, through regulation of hepatic thiamine levels plays a key role in hepatic energy metabolism in humans and in mice.

METHODS: Using publicly available datasets and extensive literature searching, data from human genetic studies were mined. An *Oct1* knockout mouse model was used to test specific hypotheses. RESULTS: OCT1 reduced function variants were associated at genomewide level significance ($p < 5x10^{-8}$) with increased plasma LDL-cholesterol and triglyceride levels, and in some studies, with increased plasma glucose. *Oct1*$^{-/-}$ mice had 3.3-fold ($p < 0.0001$) higher hepatic glycogen levels, and 5.9-fold higher ($p = 0.0006$) hepatic glucose level. Lower activity of thiamine-associated enzyme, pyruvate dehydrogenase (PDH), was shown in *Oct1*$^{-/-}$ mouse liver. *Oct1*$^{-/-}$ mice had higher plasma LDL-cholesterol ($p < 0.0001$), total cholesterol ($p < 0.0001$), and fasting insulin ($p = 0.02$). CONCLUSION: Collectively our data suggest that OCT1 plays a critical role in modulating glucose and lipid metabolism in mice and humans. These results suggest that drug interactions mediated by OCT1 may result in deleterious effects on plasma lipids and glucose levels. Further studies are ongoing in *Oct1*$^{-/-}$ mice and in patients with reduced function variants of OCT1.

ITC-020

DISCORDANCE BETWEEN DRUG TRANSPORTERS AND P450 INDUCTION: DETERMINATION OF THE EFFECT OF MULTIPLE ASCENDING DOSES OF RIFAMPIN ON P-GP, OATP, BCRP, CYP3A, CYP2C9 AND CYP1A2.

J.D. Lutz, B.J. Kirby, J. Ling, J. Weston, B.P. Kearney, A. Mathias; Gilead Sciences, Foster City, CA, USA.

BACKGROUND: Drug transporter and cytochrome P450 expression is regulated by shared nuclear receptors and hence, an inducer should induce both, though magnitude may differ. The objective of this study was to identify and characterize correlations between induction of transporters and P450s using ascending doses of rifampin (RIF) to elicit weak, moderate and strong induction. METHODS: Twenty healthy volunteers received dabigatran etexilate, pravastatin, rosuvastatin and a midazolam/tolbutamide/caffeine cocktail in the morning; separated by 48 hr. Probes were administered before and after 2, 10, 75 or 600 mg daily RIF. RIF was administered in the evenings for 10 days prior to and continuing through probe evaluation. RESULTS: Results for after 10 and 75 mg RIF are depicted below. The results for after 2 and 600 mg RIF will be included upon final presentation. CONCLUSION: Preliminary data indicates that P-gp and OATP are less inducible than CYP3A but similar in magnitude to CYP2C9, even after accounting for differences in probe sensitivity. Additional pending RIF data will provide mechanistic insight to into whether this phenomenon is due to differences in maximum induction capability (E_{max}) or affinity (ED_{50}). Data from this study will help to establish if P450 induction data can be leveraged to inform on the effect on transporters.

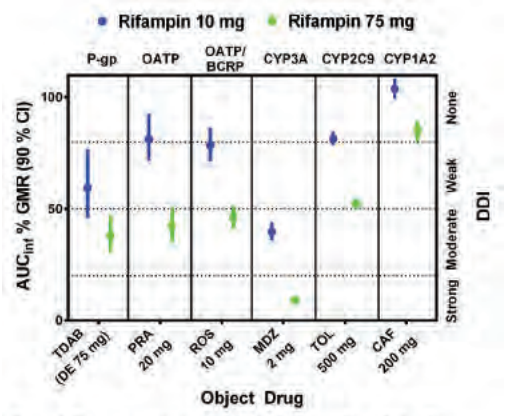

Figure 1. The treatment/control AUC_{inf} % Geometric Mean Ratios (% GMRs) for total dabigatran (TDAB, the active and monitorable metabolite of the prodrug, dabigatran etexilate), pravastatin (PRA), rosuvastatin (ROS), midazolam (MDZ), tolbutamide (TOL) and caffeine (CAF) after 10 and 75 mg multiple dose RIF. TDAB, PRA, ROS, MDZ, TOL and CAF are probes for the activity of P-gp, OATP, OATP/BCRP, CYP3A, CYP2C9 and CYP1A2, respectively.

INTERNATIONAL TRANSPORTER CONSORTIUM WORKSHOP 3 (ITCW3): TRANSPORTERS IN DRUG DEVELOPMENT

ITC-021

EVALUATION OF DRUG-DRUG INTERACTION POTENTIAL BETWEEN SACUBITRIL/VALSARTAN (LCZ696) AND STATINS USING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL.

I. Hanna, H. He, W. Lin; Novartis, East Hanover, NJ, USA.

BACKGROUND: Sacubitril/valsartan (LCZ696) has been approved for the treatment of heart failure. Sacubitril is an *in vitro* inhibitor of OATPs. In clinical studies, LCZ696 increased atorvastatin C_{max} by 1.7-fold and AUC by 1.3-fold, but had little or no effect on simvastatin or simvastatin acid exposure. A PBPK modelling approach was applied to explore the underlying mechanisms behind the statin-specific LCZ696 drug interaction observations.
METHODS: The model incorporated OATP-mediated clearance (CLint,T) for simvastatin and simvastatin acid to successfully describe the PK profiles of either analyte in the absence or presence of LCZ696.
RESULTS: The PBPK model successfully described the clinically observed drug effect with atorvastatin. The simulations clarified the critical parameters responsible for the observation of a low, yet clinically relevant, DDI between sacubitril and atorvastatin and the lack of effect with simvastatin acid. Similar models were used to evaluate the DDI risk for additional OATP-transported statins which predicted to maximally result in a 1.5-fold exposure increase.
CONCLUSION: Atorvastatin is administered in its active form and rapidly achieves C_{max} that coincide with the low C_{max} of sacubitril. In contrast, simvastatin requires a hydrolysis step to the acid form and therefore is not present at the site of interactions at sacubitril concentrations that are inhibitory.

ITC-022

EVALUATION OF DABIGATRAN ETEXILATE AS A CLINICAL PROBE FOR P-GP INHIBITION: COMPARISON WITH DIGOXIN.

X. Chu; Merck & Co., Inc, Rahway, NJ, USA.

BACKGROUND: Digoxin is a probe substrate broadly accepted by regulatory agencies and used by pharmaceutical companies to evaluate P-gp inhibition. However, it lacks sensitivity and selectivity to P-gp both *in vitro* and *in vivo*, according to many emerging studies. As digoxin has a narrow therapeutic index, the evaluation of digoxin DDIs is largely driven by its safety concerns. In recently released EMA DDI guideline, dabigatran etexilate (DABE), an anticoagulant prodrug, has been proposed as a clinical probe to evaluate intestinal P-gp inhibition. DABE is rapidly absorbed and converted into the active parent drug, dabigatran, by esterases. As DABE, but not dabigatran, is a substrate of P-gp, P-gp-mediated DDIs are restricted to intestinal absorption of DABE.
METHODS: In this presentation, the suitability of DABE as a clinical P-gp probe has been evaluated based on *in vitro* and clinical DDI data.
RESULTS: Generally, the magnitude of DDIs using DABE as the probe is comparable to those of using digoxin as probe. However, our recent clinical microdosing study demonstrated that DABE showed more profound DDIs with P-gp inhibitors itraconazole and clarithromycin. This difference is likely caused by the saturation of P-gp at DABE therapeutic dose.
CONCLUSION: Our studies suggest that DABE clinical microdosing studies may be a useful approach to assess P-gp related DDIs as worst case scenario. The recommendations on the selection of P-gp probe substrates to obtain more clinically and mechanistically relevant DDI results will be discussed.

PRODUCT THEATER & EXHIBITOR HOSTED EVENTS

Join our exhibitors as they host the following special events at this year's Annual Meeting. Space is limited so arrive early!

COVANCE
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COVANCE HOSTED EVENT

THURSDAY, MARCH 16, 2017

12:30 PM – 1:30 PM

MARRIOTT BALCONY A

Join Covance as they present a free, exclusive luncheon seminar, **"Phase I cGMP Drug Manufacturing at the CRU: 3 Key Benefits"** presented by Marcus Stavchansky, PharmD. Drug manufacturing can make up to 40% of the total cost to develop a new chemical entity and can be an inflexible, time consuming and frustrating experience during your first-in-human clinical trial. But it doesn't have to when you use a cGMP pharmacy at your clinical research unit (CRU) for Phase I drug manufacturing. Our approach yields benefits in quality and safety, timeline reduction and cost efficiency. Complimentary lunch will be provided and space is limited!

PRAHEALTHSCIENCES

PRA HEALTH SCIENCES PRODUCT THEATER

FRIDAY, MARCH 17, 2017

9:00 AM – 10:00 AM

EXHIBIT HALL THEATER

Enjoy complimentary morning snacks while attending, **"Expediting Value Inflection by Early Clinical Learning"** presented by Ewoud-Jan Hoogdalem. In this special sponsored event, PRA Health Sciences addresses the importance of development program design with the end-goal in mind, i.e. a target label claim that underscores the medical relevance of the novel product. More in particular, the presentation will address how an ambitiously tailored and feasible early clinical development plan expedites value building by early clinical learning. The message of the session will be reinforced with real-life case examples in different therapeutic areas, with one common theme: only a tailored early clinical development plan with studies that go beyond the standard package in the 'usual healthy suspects' maximizes informative value for the owner of the asset. Space in this session is limited to 50 attendees.

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PAREXEL PRODUCT THEATER

FRIDAY, MARCH 17, 2017

12:00 PM – 1:00 PM

EXHIBIT HALL THEATER

Join PAREXEL Early Phase Services and enjoy complimentary afternoon refreshments as they present a free, exclusive luncheon seminar, **Current Best Practices for Safety in First-in Human Clinical Trials**. In this seminar Edward Bernton, MD will discuss the systematic approach to evaluating nonclinical data and protocol designs to mitigate risk in FIH will be described. The motivation and the impact of changes in EMEA guidances for FIH risk mitigation, expected in 2017, will also be discussed. PAREXEL's experience evaluating over 500 proposed FIH studies will provide illustrations. With just 50 seats at this sponsored event, be sure to arrive early to save your spot!

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THURSDAY, JUNE 1, 2017, 4:00 PM ET

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CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (CPIC) 2017: USING PHARMACOGENETIC TESTS IN PATIENT CARE

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WEDNESDAY, MARCH 15

INTRODUCTORY SESSION

Registration is required to attend this Pre-conference. On-site registration is $150.

REGISTRATION

6:30 AM – 8:00 AM
CONVENTION REGISTRATION LOBBY

7:30 AM – 8:00 AM
COFFEE SERVICE

8:00 AM – 8:15 AM
WELCOME AND INTRODUCTION
Kelly Caudle, PharmD, PhD
St. Jude Children's Research Hospital

SESSION 1: STRATEGIES FOR IMPLEMENTING PHARMACOGENETICS

8:15 AM – 8:50 AM
Outcomes with CYP2C19 Genotyping for Clopidogrel Response: An Update from the IGNITE Network
Larisa Cavallari, PharmD
University of Florida

8:50 AM – 9:25 AM
Economic Considerations for Implementation
Josh Peterson, MD, MPH
Vanderbilt University Medical Center

9:25 AM – 10:00 AM
Using EHR for Implementation/PharmCAT
Marylyn Ritchie, PhD
Geisinger Health System

10:00 AM – 10:35 AM
CPIC Tables for EHR Implementation
Mary Relling, PharmD
St. Jude Children's Research Hospital

10:35 AM – 10:50 AM
BREAK

SESSION 2: CHALLENGING CASES FOR PHARMACOGENETICS IMPLEMENTATION

10:50 AM – 11:25 AM
Implementation of Warfarin Pharmacogenetics by Race Groups
Stuart Scott, PhD
Icahn School of Medicine at Mount Sinai

11:25 AM – 12:00 PM
CYP2D6 Genotype and the Use of Tamoxifen in Breast Cancer
Matthew Goetz, MD
Mayo Clinic

12:00 PM – 12:30 PM
PANEL DISCUSSION

12:30 PM – 1:00 PM
LUNCH
(included with registration)

SESSION 3: GLOBAL PERSPECTIVES FOR PHARMACOGENETICS IMPLEMENTATION

1:00 PM – 1:35 PM
Global Implementation of Genomic Medicine
Howard McLeod, PharmD
Moffitt Cancer Center

1:35 PM – 2:10 PM
Pharmacogenetics Implementation: European Perspectives
Munir Pirmohamed, PhD
University of Liverpool

2:10 PM – 2:40 PM
Pharmacogenetics Implementation: Asian Perspectives
Ming Ta Michael Lee, PhD
Geisinger Health System

2:40 PM – 2:55 PM
BREAK

2:55 PM – 3:25 PM
Pharmacogenetics Implementation: African Perspectives
Collen Masimirembwa, PhD
African Institute of Biomedical Science and Technology

3:25 PM – 3:50 PM
PANEL DISCUSSION

3:50 PM – 4:00 PM
WRAP UP

GENERAL INFORMATION

ACKNOWLEDGMENTS

ASCPT WOULD LIKE TO GIVE SPECIAL THANKS TO THE LEADERSHIP OF THE NETWORKS & COMMUNITIES AND RECOGNIZE THE CHAIRS AND VICE CHAIRS FOR THEIR DEDICATED LEADERSHIP OF IMPORTANT SOCIETY ENDEAVORS.

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CONVENTION REGISTRATION LOBBY

WEDNESDAY, MARCH 15
6:30 AM – 6:30 PM

THURSDAY, MARCH 16
6:30 AM – 5:00 PM

FRIDAY, MARCH 17
6:30 AM – 5:00 PM

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7:00 AM – 10:00 AM

TARGET AUDIENCE

Clinical pharmacologists and translational scientists, including physicians, pharmacists, scientists, and others interested in learning about the most current advances in drug discovery, translational medicine, development, regulation and safe utilization of drugs in humans.

BADGES

For security reasons, all attendees MUST wear their badge at all times for admission to sessions, the poster and exhibit hall, and social events.

To provide a safe and secure meeting experience for all attendees, badge policies are in effect for the ASCPT Annual Meeting. Please have your picture ID ready to present when you pick up your badge materials. Once issued, badges are non-transferable.

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GENERAL INFORMATION

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ASCPT Central will be open during the following hours:

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7:00 AM – 10:00 AM

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The Poster and Exhibit Hall will be open during the following hours:

WEDNESDAY, MARCH 15
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9:00 AM – 1:30 PM and 4:30 PM – 6:30 PM

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7:00 AM – 1:30 PM

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Meal vouchers valued up to $20 for Thursday, Friday, and Saturday will be provided to all registered attendees. Meal vouchers may be used between 11:30 am and 1:30 pm for Grab & Go Lunch in the Exhibit Hall or at the following food vendors inside the hotel: Harry's Pub, Stone's Throw, and Woodley Pantry.

GENERAL INFORMATION

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Communities are categorized into three main Networks: Quantitative Pharmacology (QP), Translational & Precision Medicine (TPM), and Development, Regulatory & Outcomes (DRO). Each Symposia, Workshop, Roundtable and Science at Sunrise session is correlated with or reflective of a Community. See the Scientific Agenda for the sessions representing your field of interest.

QUANTITATIVE PHARMACOLOGY (QP)

	Biologics
PMK	Pharmacometrics & Pharmacokinetics
SP	Systems Pharmacology

TRANSLATIONAL & PRECISION MEDICINE (TPM)

BTT	Biomarker & Translational Tools
INF	Infectious Diseases
ITC	International Transporter Consortium
ONC	Oncology
PMG	Pharmacogenomics
PM	Pharmacometabolomics
SPO	Special Populations

DEVELOPMENT, REGULATORY & OUTCOMES (DRO)

DUO	Drug Utilization & Outcomes
EDDS	Early Development & Drug Safety
RS	Regulatory Science
GB	Global Health

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SHEINER-BEAL PHARMACOMETRICS AWARD
Terrence F. Blaschke, MD
Jeannette Blaschke, MDA
Richard C. Brundage, PharmD, PhD
Lei Zhang, PhD
John T. Callaghan, MD, PhD
Yuichiro Takeda

MALLE JURIMA-ROMET AWARD
Shiew-Mei Huang, PhD
Kim L. R. Brouwer, PharmD, PhD
J. Frederick Pritchard, PhD

OSCAR B. HUNTER AWARD
Issam Samir Hamadeh, PharmD

RAWLS-PALMER AWARD
Russ B. Altman, MD, PhD

SCIENTIFIC AWARDS
Gregory L. Kearns, PharmD, PhD
Kathleen Neville, MD, MS

STUDENT/TRAINEE AWARDS & TRAVEL
Raymond J. Hohl, MD, PhD
Nina Gannon, DVM
Gregory L. Kearns, PharmD
Kathleen Neville, MD, MS
Anne C. Heatherington, PhD
Kellie Schoolar Reynolds, PharmD
Shiew-Mei Huang, PhD
Susan M. Abdel-Rahman, PharmD
Kim L. R. Brouwer, PharmD, PhD
Patricia W. Slattum, PharmD, PhD, CGP
Joann L. Data, MD, PhD
Richard C. Brundage, PharmD, PhD
Lei Zhang, PhD
Anuradha Ramamoorthy, PhD
Otito Frances Iwuchukwu, RPh, PhD
Saskia N. de Wildt, MD, PhD
Kathleen M. Tornatore, PharmD
J. Greg Slatter, PhD

ASCPT/FDA ABRAMS LECTURE
Lei Zhang, PhD

GENERAL INFORMATION

CAPITAL CAMPAIGN DONATION

Richard M. Weinshilboum, MD
Mario L. Rocci, Jr, PhD
Andre Terzic, MD, PhD, FAHA
Carmen Terzic, MD, PhD
Gregory L. Kearns, PharmD, PhD
Kathleen Neville, MD, MS
Julie A, Johnson, PharmD
Walter Kraft, MD, FACP
Sharon J. Swan, FASAE, CAE
Scott A. Waldman, MD, PhD, FCP
Sean Hennessy, PharmD, PhD
Shiew-Mei Huang, PhD
Shinya Ito, MD, FRCPC
Alexander A. Vinks, PharmD, PhD, FCP
Virginia (Ginny) D. Schmith, PhD, FCP
Kim L. R. Brouwer, PharmD, PhD
Judith K. Jones, MD, PhD
Donald E. Mager, PharmD, PhD
Susan E. Shoaf, PhD
Jean D. Gray, MD, FRCPC
David W. Nierenberg, MD & Joan Nierenberg
Jae-Gook Shin, MD, PhD
John T. Sullivan, MD, ChB, FRACP
Addison A. Taylor, MD, PhD
Kathleen Uhl, MD
Leslie Z. Benet, PhD

UNRESTRICTED GIFT

Mark J. Dresser, PhD
D. Craig Brater, MD
Walter Kraft, MD, FACP
David Y. Mitchell, PhD
Steve Ryder, MD
Andre Terzic, MD, PhD, FAHA
Carmen Terzic, MD, PhD
Scott A. Waldman, MD, PhD, FCP
Kellie Schoolar Reynolds, PharmD
Raymond L. Woosley, MD, PhD
Kathleen Uhl, MD
Piet H. van der Graaf, PharmD, PhD
John Vincent, MD, PhD
Lei Zhang, PhD
David W. Nierenberg, MD
Patrick K. Noonan, PhD
Michelle A. Rudek, PharmD, PhD
Morna Conway, PhD
Michael J. Avram, PhD
Donald R. Bennett, MD, PhD, MPH
Anne C. Heatherington, PhD
Pavur R. Sundaresan, MD, PhD
Leslie Z. Benet, PhD
Pavur R. Sundaresan, MD, PhD
Marcus M. Reidenberg, MD
Shinya Ito, MD, FRCPC
Rosina B. Dixon, MD
Jae-Gook Shin, MD, PhD
Michael H. Skinner, MD, PharmD
Wayne R. Snodgrass, MD, PhD
Robert E. Vestal, MD
Yasutsuna Sasaki, MD, PhD
Arnold G. Vulto, PhD, PharmD
Russ B. Altman, MD, PhD
Peter R. Bieck, MD, PhD
Neeraj Gupta, PhD
Robert L. Roe, MD
Addison A. Taylor, MD, PhD
Kathleen M. Tornatore, PharmD

MATCHING GIFTS

AMGEN*
Ayco Charitable Foundation*

OPENING SESSION

8:00 AM – 9:00 AM
MARRIOTT 1/2

STATE OF THE SOCIETY ADDRESS

Julie A. Johnson, PharmD
University of Florida

RECOGNITION OF THE SCIENTIFIC PROGRAM COMMITTEE

Susan Abdel-Rahman, PharmD
Children's Mercy Hospital

AWARD PRESENTATIONS

HENRY W. ELLIOTT DISTINGUISHED SERVICE AWARD

PRESENTER
Micheline Piquette, PhD
University of Toronto

RECIPIENT
Kathleen M. Giacomini, PhD
University of California, San Francisco

GARY NEIL PRIZE FOR INNOVATION IN DRUG DEVELOPMENT

PRESENTER
Brian Corrigan, PhD
Pfizer, Inc.

RECIPIENT
Richard L. Lalonde, PharmD
Pfizer, Inc.

MALLE JURIMA-ROMET MID-CAREER LEADERSHIP AWARD

PRESENTER
Darrell Abernethy, MD, PhD
US Food and Drug Administration

RECIPIENT
Donald E. Mager, PharmD, PhD
University at Buffalo, SUNY

TOP MEMBERSHIP RECRUITER

PRESENTER
Jin Yan Jin, PhD
Genentech

RECIPIENT
In-Jin Jang, MD, PhD
Seoul National University College of Medicine and Hospital

2017 DAVID J. GOLDSTEIN TRAINEE AWARD

PRESENTER
Julie A. Johnson, PharmD
University of Florida

RECIPIENT
Sarah Kim, PhD
University of Florida

2017 JASON MORROW TRAINEE AWARD

PRESENTER
Julie A. Johnson, PharmD
University of Florida

RECIPIENTS
Arjun Athreya
University of Illinois at Urbana-Champaign

Mariam Ahmed
University of Minnesota/AbbVie

2017 ASCPT MENTOR AWARD

PRESENTER
Catherine M. T. Sherwin, PhD
University of Utah School of Medicine

RECIPIENT
Patricia W. Slattum, PharmD, PhD
Virginia Commonwealth University

CPT: PHARMACOMETRICS & SYSTEMS PHARMACOLOGY AWARD

PRESENTER
Piet H. van der Graaf, PhD, PharmD
Leiden University/Certara

RECIPIENT
Matthew Hutmacher, MS
Ann Arbor Pharmacometrics Group, Inc.

GENERAL INFORMATION

CLINICAL AND TRANSLATIONAL SCIENCE AWARD

PRESENTER
John A. Wagner, MD, PhD
Takeda Pharmaceuticals International Co.

RECIPIENT
Sharyn D. Baker, PharmD, PhD
The Ohio State University College of Pharmacy

PHRMA FOUNDATION AWARDS

2016 Research Starter Grants in Translational Medicine

PRESENTER
Michael Liebman, PhD
Strategic Medicine, Inc.

RECIPIENTS
Emanuela Ricciotti, PhD
University of Pennsylvania

Mehdi Javanmard, PhD
Rutgers University

Nariman Balenga, PhD
University of Maryland School of Medicine

2016 Paul Calabresi Medical Student Fellowship

PRESENTER:
Darrell Abernethy, MD, PhD
US Food and Drug Administration

RECIPIENT
Krystian A. Kozek
Vanderbilt University

2017 Award in Excellence in Clinical Pharmacology

PRESENTER
Darrell Abernethy, MD, PhD
US Food and Drug Administration

RECIPIENT
Craig W. Hendrix, MD
Johns Hopkins University School of Medicine

TRANSITION TO THE FUTURE

Kellie Schoolar Reynolds, PharmD

CEO REMARKS

Sharon J. Swan, FASAE, CAE

PROGRAM & SCIENTIFIC AGENDA

ACKNOWLEDGMENTS

AWARD NOMINATIONS TASK FORCE AND SCIENTIFIC AWARDS SELECTION TASK FORCE

ASCPT WOULD LIKE TO RECOGNIZE THE SCIENTIFIC AWARDS NOMINATIONS TASK FORCE FOR SECURING NOMINATIONS FOR THE 2017 SCIENTIFIC AWARDS.

Virginia (Ginny) Schmith, PhD, FCP

Chair

Hartmut Derendorf, PhD

Hendrik Jan Guchelaar, PharmD, PhD

Masako Nakano, MD, PhD

Kenneth Thummel, PhD

ASCPT WOULD LIKE TO ACKNOWLEDGE THE SCIENTIFIC AWARDS SELECTION TASK FORCE FOR SELECTING THE 2017 SCIENTIFIC AWARD RECIPIENTS FROM A ROBUST AND HIGHLY COMPETITIVE ROSTER OF EXCEPTIONAL NOMINEES.

Peter Honig, MD, MPH

Chair

Richard F. Bergstrom, PhD

Matthew K. Breitenstein, PhD

Richard A. Graham, PhD

Mary Jayne Kennedy, PharmD

Teddy Kosoglou, PharmD

Michael L. Maitland, MD, PhD

Vijay A. Ramchandani, PhD

Mary V. Relling, PharmD

Donald R. Stanski, MD

Yusuke Tanigawara, PhD

Issam Zineh, PharmD, MPH

Maurice G. Emery, PharmD, PhD

WEDNESDAY, MARCH 15, 2017

6:30 AM – 6:30 PM
ASCPT CENTRAL AND REGISTRATION
CONVENTION REGISTRATION LOBBY

7:30 AM – 9:30 AM
ASCPT BOARD OF DIRECTORS MEETING
(By invitation only)
MCKINLEY

7:30 AM – 4:30 PM
US FDA PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE MEETING
OMNI - BLUE ROOM

8:00 AM – 4:00 PM
CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (CPIC) 2017 CONFERENCE: USING PHARMACOGENETIC TESTS IN PATIENT CARE
WASHINGTON

10:00 AM – 12:00 PM
JOURNAL EIC/WILEY MEETING
(By invitation only)
MCKINLEY

4:00 PM – 6:30 PM
OPENING RECEPTION
EXHIBIT HALL A/B SOUTH

4:30 PM – 5:30 PM
SHOWCASE OF TOP TRAINEE ABSTRACTS
EXHIBIT HALL A/B SOUTH

For complete abstract content download the ASCPT Annual Meeting Mobile App.

PT-001
COMPARISON OF NON-COMPARTMENTAL ANALYSIS (NCA) ESTIMATION AND POPULATION PHARMACOKINETIC (PPK) PREDICTIONS OF EXPOSURE CHANGES AS A FUNCTION OF RENAL IMPAIRMENT.
Presenter: Mariam Ahmed, PhD, University of Minnesota

PT-002
CLINICAL IMPLEMENTATION OF WARFARIN PHARMACOGENETICS IN A REAL-WORLD SETTING: A PROPOSAL FOR A NEW PHARMACOGENETIC DOSING APPROACH FOR DIVERSE PATIENT POPULATIONS.
Presenter: Meghan Arwood, PharmD, University of Florida

PT-003
DATA-DRIVEN LEARNING ANALYSIS IDENTIFIES GENDER DIFFERENCES IN METABOLIC TREATMENT RESPONSE OF CITALOPRAM/ESCITALOPRAM IN MAJOR DEPRESSIVE DISORDER.
Presenter: Arjun Athreya, University of Illinois at Urbana-Champaign

PT-004
RESULTS OF THE IMPLEMENTATION OF PHARMACOGENOMICS INTO PRIMARY CARE PROJECT.
Presenter: Paul Bank, PharmD, Leiden University Medical Center

PT-005
A GENETIC VARIANT OF ABCG2 CONFERS RISK FOR POOR RESPONSE TO ALLOPURINOL INDEPENDENT OF ITS EFFECT ON GOUT SEVERITY.
Presenter: Deanna Brackman, University of California, San Francisco

PT-006
MAN1A2 IS A NOVEL PREDICTIVE MARKER OF REFRACTORY RESPONSE TO R-CHOP THERAPY IN DIFFUSE LARGE B-CELL LYMPHOMA.
Presenter: Matthew Breitenstein, PhD, Mayo Clinic

PT-007
IN VITRO AND IN VIVO FUNCTIONAL TESTING OF SNPS IN THE 3'UTR OF CYP2B6.
Presenter: Kimberly Burgess, Indiana University School of Medicine

WEDNESDAY, MARCH 15, 2017

PT-008
TACROLIMUS POPULATION PHARMACOKINETICS AND CYP3A5 GENOTYPES IN AFRICAN AMERICAN AND CAUCASIAN RENAL TRANSPLANT RECIPIENTS.
Presenter: Olivia Campagne, PharmD, University at Buffalo, SUNY

PT-009
AGGREGATE BOTTOM-UP PBPK MODELS FOR DRUG EXPOSURE INDIVIDUALIZATION.
Presenter: Jean Dinh, PharmD, PhD, Children's Mercy Hospital

PT-010
DISCOVERY OF SUBSTRATES FOR GLUT2, A TRANSPORTER IMPLICATED IN METFORMIN RESPONSE.
Presenter: Osatohanmen Enogieru, University of California, San Francisco

PT-011
AGE-DEPENDENT DEVELOPMENTAL CHANGES IN HEPATIC ORGANIC CATION TRANSPORTER 1 (OCT1) PROTEIN EXPRESSION IN NEONATES AND SMALL INFANTS.
Presenter: David Hahn, PhD, Cincinnati Childrens Hospital Medical Center

PT-012
AN EXEMPLAR OF A SYSTEMS PHARMACOLOGY APPROACH FOR A DETAILED INVESTIGATION OF AN ADVERSE DRUG EVENT AS A RESULT OF DRUG-DRUG INTERACTIONS.
Presenter: Sarah Kim, PhD, University of Florida

PT-013
ORGANIC CATION TRANSPORTER 1 (OCT1; SLC22A1) MODULATES HEPATIC ENERGY METABOLISM.
Presenter: Xiaomin Liang, University of California, San Francisco

PT-014
UGT1A9 RS3832043 INFLUENCES ACETAMINOPHEN GLUCURONIDATION IN NEONATES.
Presenter: Matthew Linakis, University of Utah

PT-015
MATERNAL AND FETAL METHADONE EXPOSURE: ASSOCIATIONS WITH NEONATAL ABSTINENCE SYNDROME.
Presenter: Ingrid Metzger, PhD, Indiana University School of Medicine

PT-016
HUMAN MICRODOSING AND MICE XENOGRAFT DATA OF AGM-130 APPLIED TO SIMULATE EFFICACIOUS DOSES IN PATIENTS.
Presenter: Wan-Su Park, The Catholic University of Korea

PT-017
COMMON GENETIC VARIANTS IN NEUROBEACHIN (NBEA) ARE ASSOCIATED WITH METFORMIN DRUG RESPONSE IN INDIVIDUALS WITH TYPE 2 DIABETES IN THE ACCORD CLINICAL TRIAL.
Presenter: Daniel Rotroff, PhD, North Carolina State University

PT-018
DEVELOPMENT OF A PHARMACOKINETIC (PK)/ PHARMACODYNAMIC (PD) MODEL TO EVALUATE THE IMPACT OF PK VARIATION ON PD FOR EXTENDED RELEASE METOPROLOL FORMULATIONS.
Presenter: Vishnu Sharma, PhD, University of Florida

D Discovery
R Regulation
D Development
U Utilization

WEDNESDAY, MARCH 15, 2017

PT-019
A GENOME WIDE ASSOCIATION STUDY IDENTIFIES PHARMACOGENOMIC VARIANTS ASSOCIATED WITH CHLORTHALIDONE INDUCED GLUCOSE CHANGE IN AFRICAN AMERICANS.
Presenter: Sonal Singh, PhD, University of Florida

PT-020
COMPARISON OF THE EFFECT OF CHRONIC KIDNEY DISEASE (CKD) ON PHARMACOKINETICS OF CYP1A2, CYP2C8, CYP2C9 AND CYP2C19 SUBSTRATES.
Presenter: Ming-Liang Tan, PhD, US Food and Drug Administration

PT-021
IMAGING ANTIRETROVIRAL DISTRIBUTION WITHIN GASTROINTESTINAL TISSUES ACROSS PRE-CLINICAL SPECIES: IMPLICATIONS FOR HIV ERADICATION.
Presenter: Corbin Thompson, PharmD, University of North Carolina at Chapel Hill

PT-022
FEASIBILITY OF A PEDIATRIC MICRODOSE STUDY OF [^{14}C] MIDAZOLAM TO STUDY THE ONTOGENY OF CYP3A-MEDIATED DRUG METABOLISM.
Presenter: Bianca van Groen, Erasmus MC - Sophia Children's Hospital

PT-023
MATURATION OF HUMAN HEPATIC MEMBRANE TRANSPORTER PROTEINS IN THE FIRST FOUR MONTHS OF LIFE.
Presenter: Bianca van Groen, Erasmus MC - Sophia Children's Hospital

PT-024
EXCIPIENTS INHIBIT HUMAN ORGANIC ANION TRANSPORTING PEPTIDE 2B1 (OATP2B1)-MEDIATED INTESTINAL UPTAKE OF LEVOTHYROXINE.
Presenter: Ling Zou, PhD, University of California, San Francisco

PT-025
RNA-SEQ ANALYSES IDENTIFY MOLECULAR MARKERS OF BLOOD PRESSURE (BP) RESPONSE TO THIAZIDE DIURETICS (TD).
Presenter: Ana Caroline Costa Sa, University of Florida

PT-026
TCL1A IDENTIFICATION AS A NOVEL TRANSCRIPTION FACTOR AND A PHARMACOGENOMIC LINK TO AROMATASE INHIBITOR-INDUCED MUSCULOSKELETAL ADVERSE EVENTS.
Presenter: Ming-Fen Ho, Ph.D, Mayo Clinic

PT-027
INTACT NEPHRON THEORY MAY NOT FULLY EXPLAIN THE EFFECT OF SEVERE RENAL IMPAIRMENT FOR DRUGS ACTIVELY SECRETED VIA RENAL ORGANIC ANION TRANSPORTERS.
Presenter: Chia-Hsiang Hsueh, PhD, US Food and Drug Administration, University of California, San Francisco

PT-028
THIAZIDE INDUCED HYPERURICEMIA: NOVEL INSIGHTS FROM METABOLOMICS AND GENOMICS INTEGRATION IN THE PHARMACOGENOMIC EVALUATION OF ANTIHYPERTENSIVE RESPONSES 2 (PEAR 2) STUDY.
Presenter: Mohamed Shahin, PhD, University of Florida

WEDNESDAY, MARCH 15, 2017

5:15 PM – 5:45 PM
EXHIBIT WALKS
EXHIBIT HALL A/B SOUTH

CHAIR
Walter Kraft, MD, PhD
Thomas Jefferson University
Philadelphia, PA

5:15 PM – 6:00 PM
POSTER WALK
Endogenous/Exogenous Predictors of Drug Response Oncology
CO-CHAIRS
Mark Dresser, PhD, and Kari Morrissey, PhD
EXHIBIT HALL A/B SOUTH

For complete abstract content download the ASCPT Annual Meeting Mobile App.

PWI-001
TCL1A IDENTIFICATION AS A NOVEL TRANSCRIPTION FACTOR AND A PHARMACOGENOMIC LINK TO AROMATASE INHIBITOR-INDUCED MUSCULOSKELETAL ADVERSE EVENTS.
Presenter: Ming-Fen Ho, PhD, Mayo Clinic

PWI-002
MAN1A2 IS A NOVEL PREDICTIVE MARKER OF REFRACTORY RESPONSE TO R-CHOP THERAPY IN DIFFUSE LARGE B-CELL LYMPHOMA.
Presenter: Matthew Breitenstein, PhD, Mayo Clinic

PWI-003
PHARMACOGENETICS OF CHEMOTHERAPY RESPONSE IN OSTEOSARCOMA: A GENETIC VARIANT IN SLC7A8 IS ASSOCIATED WITH PROGRESSIVE DISEASE.
Presenter: Marieke Coenen, PhD, Radboud UMC

PWI-004
PRECISION MEDICINE BY MODELING PHARMACOKINETIC AND BIOMARKER DRIVERS OF TUMOR KINETICS: ASSESSING EFFECTS OF ALISERTIB EXPOSURE AND TARGET SNP STATUS ON ANTITUMOR ACTIVITY.
Presenter: Dean Bottino, PhD, Takeda Pharmaceuticals International Co.

PWI-005
TSPYL GENE FAMILY REGULATES CYP17A1 AND CYP3A4 EXPRESSION: POTENTIAL MECHANISM CONTRIBUTING TO ABIRATERONE RESPONSE IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS.
Presenter: Sisi Qin, PhD, Mayo Clinic

D Discovery
R Regulation
D Development
U Utilization

THURSDAY, MARCH 16, 2017

6:45 AM – 8:00 AM
NETWORK/COMMUNITY LEADER MEETING
MCKINLEY

7:00 AM – 7:45 AM
AWARDS BREAKFAST
(By invitation only)
MARRIOTT BALCONY B

8:00 AM – 9:00 AM
OPENING SESSION
MARRIOTT 1/2

STATE OF THE SOCIETY ADDRESS
Julie A. Johnson, PharmD, University of Florida

RECOGNITION OF THE SCIENTIFIC PROGRAM COMMITTEE
Susan Abdel-Rahman, PharmD, Chair

HENRY W. ELLIOTT DISTINGUISHED SERVICE AWARD
PRESENTER
Micheline Piquette, PhD, University of Toronto, Toronto, ON, Canada

RECIPIENT
Kathleen M. Giacomini, PhD, University of California, San Francisco, San Francisco, CA

GARY NEIL PRIZE FOR INNOVATION IN DRUG DEVELOPMENT
PRESENTER
Brian W. Corrigan, PhD, Pfizer Global Research and Development, New London, CT

RECIPIENT
Richard L. Lalonde, PharmD, Pfizer, Groton, CT

MALLE JURIMA-ROMET MID-CAREER LEADERSHIP AWARD
PRESENTER
Darrell Abernethy, MD, PhD, US Food and Drug Administration, Silver Spring, MD

RECIPIENT
Donald E. Mager, PharmD, PhD, University at Buffalo, SUNY, Buffalo, NY

2016 TOP MEMBERSHIP RECRUITER
PRESENTER
Jin Yan Jin, PhD, Genentech

RECIPIENT
In-Jin Jang, MD, PhD, Seoul National University College of Medicine and Hospital

2017 DAVID J. GOLDSTEIN TRAINEE AWARD
PRESENTER
Julie A. Johnson, PharmD, University of Florida

RECIPIENT
Sarah Kim, PhD, University of Florida

2017 JASON MORROW TRAINEE AWARD
PRESENTER
Julie A. Johnson, PharmD, University of Florida

RECIPIENTS
Arjun Athreya, University of Illinois at Urbana-Champaign

Mariam Ahmed, University of Minnesota/AbbVie

ASCPT MENTOR AWARD
PRESENTER
Catherine M. T. Sherwin, PhD, University of Utah School of Medicine

RECIPIENT
Patricia W. Slattum, PharmD, PhD, Virginia Commonwealth University, Richmond, VA

CPT: PHARMACOMETRICS & SYSTEMS PHARMACOLOGY AWARD
PRESENTER
Piet H. van der Graaf, PhD, PharmD
Leiden University/Certara

RECIPIENT
Matthew Hutmacher, MS
Ann Arbor Pharmacometrics Group, Inc.

THURSDAY, MARCH 16, 2017

CLINICAL AND TRANSLATIONAL SCIENCE AWARD
PRESENTER
John A. Wagner, MD, PhD, Takeda Pharmaceuticals International Co.

RECIPIENT
Sharyn D. Baker, PharmD, PhD, The Ohio State University College of Pharmacy

PHRMA FOUNDATION AWARDS

2016 RESEARCH STARTER GRANTS IN TRANSLATIONAL MEDICINE
PRESENTER
Michael Liebman, PhD, Strategic Medicine, Inc.

RECIPIENTS
Emanuela Ricciotti, PhD, University of Pennsylvania

Mehdi Javanmard, PhD, Rutgers University

Nariman Balenga, PhD, University of Maryland School of Medicine

2016 PAUL CALABRESI MEDICAL STUDENT FELLOWSHIP
PRESENTER
Darrell Abernethy, MD, PhD, US Food and Drug Administration

RECIPIENT
Krystian A. Kozek, Vanderbilt University

2017 AWARD IN EXCELLENCE IN CLINICAL PHARMACOLOGY
PRESENTER
Darrell Abernethy, MD, PhD, US Food and Drug Administration

RECIPIENT
Craig W. Hendrix, PhD, Johns Hopkins University School of Medicine

9:00 AM – 10:00 AM
STATE OF THE ART LECTURE
MARRIOTT 1/2

CHAIR
Julie A. Johnson, PharmD
University of Florida

SPEAKER

Organs-on-Chips: A Technology Platform for Translational and Precision Medicine
Geraldine A. Hamilton, PhD, Emulate, Inc., Boston, MA

10:15 AM – 11:15 AM
AWARD LECTURE
Rawls-Palmer Progress in Medicine Award Lecture
MARYLAND

AWARD PRESENTER
Kathleen M. Giacomini, PhD, University of California, San Francisco, San Francisco, CA

SPEAKER

Analyzing text to extract information about gene-drug-disease interactions
Russ B. Altman, MD, PhD, Stanford University, Stanford, CA

D Discovery R Regulation
D Development U Utilization

THURSDAY, MARCH 16, 2017

10:30 AM – 12:30 PM

SYMPOSIUM

Finding the Right Dose in the Right Patients for Oncology and Immuno-oncology: Are We There Yet and How Have Quantitative Pharmacology, Translational and Precision Medicine Been Utilized?

MARRIOTT 1/2

COMMUNITIES

Oncology (ONC), Pharmacometrics & Pharmacokinetics (PMK)

CHAIRS

Yan Ji, PhD, Novartis Pharmaceuticals, Ease Hanover, NJ

Ajit Suri, PhD, Takeda Pharmaceuticals, Cambridge, MA

SPEAKERS

Dose Selection in Translational Clinical Oncology and Immuno-oncology: An Industry Perspective
Charles Davis, PhD, Novartis Institutes for Biomedical Research, East Hanover, NJ

Challenges and Opportunities for Modeling and simulation in Late Phase Oncology Development: Combinations, Cancer Immunotherapy, and More
Jin Jin, PhD, Genentech, Inc., South San Franscisco, CA

Precision and Translational Medicine in Dose and Patient Selection in Oncology
David Hyman, MD, Memorial Sloan Kettering Cancer Center, New York, NY

Oncology Dose Finding for Small Molecules and Biologics: Perspective of the FDA-AACR Oncology Dose Finding Workshops
Geoffrey Kim, MD, US Food and Drug Administration, Silver Spring, MD

Upon completion of this Symposium, the attendee should be able to

- Discuss recent advances and share new learnings of dose optimization in Oncology and Immuno-oncology from early to late phase drug development, including both mono- and combination therapies of small molecules and biologics.
- Describe novel strategies, showcase their applications, and illustrate the impact of a multi-disciplinary approach integrating quantitative pharmacology, pharmacometrics, translational and Precision medicine in oncology dose and patient selection.

10:30 AM – 12:30 PM

Using Biomarkers to Predict Registration Endpoints: A Look Inside the Crystal Ball

MARRIOTT 3

COMMUNITIES

Pharmacometrics & Pharmacokinetics (PMK)

CHAIRS

Cecilia Fosser, PhD, Cytel, Inc., Cambridge, MA

Scott Hynes, PharmD, PhD, Eli Lilly, Indianapolis, IN

SPEAKERS

An Overview of Current Progress towards an Evidentiary Framework for Biomarker Qualification
John A. Wagner, MD, PhD, Takeda Pharmaceuticals International Co. Cambridge, MA

Role of Biomarkers and Quantitative Models in Drug Development
Yaning Wang, PhD, CDER, US Food and Drug Adminstration, Silver Spring, MD

Early Clinical Development Planning via Biomarkers, Clinical Endpoints, and Simulation: A Case Study to Optimize for Phase 3 Dose Selection
Bret Musser, PhD, Merck, Kenilworth, NJ

THURSDAY, MARCH 16, 2017

Linking Exploratory Clinical Development Endpoints to Phase 3 Endpoints: A Quantitative Basis for Decision-making
Richard Lalonde, PharmD, Pfizer, Groton, CT

Upon completion of this Symposium, the attendee should be able to:

Become acquainted with the new developments regarding the creation of evidentiary criteria for biomarker qualification;

- Understand the FDA's perspective regarding biomarkers and quantitative models and the role they play in drug development;
- Understand how quantitative pharmacology and pharmacometric approaches linking biomarkers to registration endpoints can be leveraged to support drug development decisions via case studies that exemplify situations in which a link was and was not found;
- Understand how planning in early clinical development via biomarkers, clinical endpoints, and trial simulations can optimize Phase 3 dose selection.

1:30 PM – 2:30 PM
FEATURED SPEAKER
MARRIOTT 1/2

CHAIR
Donald Stanski, MD, AstraZeneca, LP, Gaithersburg, MD

SPEAKER

Bridging the Gap Between Pharmacometricians and Statisticians in Clinical Pharmacology and Therapeutics
France Mentré, MD, PhD, University of Paris Diderot, Paris, France

1:30 PM – 3:00 PM
WORKSHOP
Integrating Big Omics Data: Applications and Challenges
MARRIOTT 3

COMMUNITIES
Pharmacometabolomics (PM)

D D R U

CHAIRS
Daniel Rotroff, PhD, North Carolina State University, Raleigh, NC

Mohamed Shahin, PhD, University of Florida, Gainesville, FL

SPEAKERS
Opportunities and Challenges of Big Data Integration: An Overview with Examples
Sudeepa Bhattacharyya, PhD, UAMS College of Medicine, Little Rock, AR

Antihypertensive Response and Precision Medicine: Novel Insights from Genomics and Metabolomics Integration
Mohamed Shahin, PhD, University of Florida, Gainesville, FL

Computational Approaches for Omics Data Integration
Jianguo Xia, PhD, McGill University (Macdonald Campus), Quebec, Canada

Upon completion of this Workshop, the attendee should be able to:

- Understand the scope of integrated omics in precision medicine, its applications in uncovering personalized information and the key challenges that scientists face in data integration;
- Present the most widely used cutting-edge tools and algorithms for integrating multiple omics data; and
- Discuss different recently developed bioinformatics tools that would enable the audience to analyze and visualize their own omics data.

D Discovery
R Regulation
D Development
U Utilization

THURSDAY, MARCH 16, 2017

1:30 PM – 3:00 PM

ROUNDTABLE

Communicating Complex Information to Influence Decisions: What Works and What Doesn't

WASHINGTON

COMMUNITIES

Pharmacometrics & Pharmacokinetics (PMK), Regulatory Science (RS)

CHAIRS

Virginia (Ginny) Schmith, PhD, FCP, Nuventra Pharma Sciences, Durham, NC

Noelia Nebot, PhD, Novartis, East Hanover, NJ

SPEAKERS

Communication of Complex Information: Stakeholder Feedback

Norman Stockbridge, MD, PhD, US Food and Drug Administration, Silver Spring, MD

Communicating Complex Information in the Journal Anesthesiology

Michael Avram, PhD, Northwestern University Feinberg School of Medicine, Chicago, IL

Practical Tips for Communicating Complex Information and Analyses in Drug Development

Danny Howard, PhD, Novartis, East Hanover, NJ

Preparing our Future Leaders to be Effective Communicators

Kim L. R. Brouwer, PharmD, PhD, University of North Carolina at Chapel Hill, Chapel Hill, NC

Upon completion of this Roundtable, the attendee should be able to:

- Acquire information that will improve their ability to communicate complex information to clinicians and stakeholders and to influence decisions;
- List key training program objectives regarding communication and "soft skills"
- Describe various approaches currently being used to prepare trainees to be effective communicators; and
- Understand how rapid changes in technology require us to constantly adapt our approaches in order to teach scientists and our trainees how to be effective communicators.

3:00 PM – 4:30 PM

SPECIAL SESSION

Innovation Forum

MARRIOTT 1/2

Explore how patients are driving therapeutic innovation... how therapeutic innovation is advancing precision medicine... how precision medicine is directly impacting the lives of patients... and how partnerships that fuel this cycle of innovation are forged. You won't want to miss this dynamic, fast moving and engaging Session, sure to be a highlight of ASCPT 2017!

CHAIR

Susan Abdel-Rahman, PharmD
Children's Mercy, Kansas City, MO

SPEAKERS

Martín J. Sepúlveda, MD, MPH, Retired, VP IBM Health Systems and Policy Research, IBM Research, Southbury, CT

Ron Winslow, Former Wall Street Journal Reporter, New York, NY

Erin Moore, Eli Lilly and Company, Cincinnati, OH

Nick Dougherty, MassChallenge, Boston, MA

THURSDAY, MARCH 16, 2017

4:45 PM – 5:30 PM

POSTER WALK

Applications of Novel Technology

EXHIBIT HALL A/B SOUTH

CHAIRS

Richard Wilson Peck, MD, FRCP
F. Hoffmann La Roche Ltd., Basel, Switzerland

Mohamed H. Shahin, BPharm, PhD
University of Florida, Gainesville, FL

For complete abstract content download the ASCPT Annual Meeting Mobile App.

PWII-001
A NOVEL HIGH-THROUGHPUT BIOASSAY TO FUNCTIONALLY TEST GENETIC VARIANTS IN MICRO-RNA BINDING SITES.
Presenter: Joseph Ipe, PhD, Indiana University School of Medicine

PWII-002
IMAGING ANTIRETROVIRAL DISTRIBUTION WITHIN GASTROINTESTINAL TISSUES ACROSS PRE-CLINICAL SPECIES: IMPLICATIONS FOR HIV ERADICATION.
Presenter: Corbin Thompson, PharmD, University of North Carolina at Chapel Hill

PWII-003
ZEBRAFISH: A NEW SCREENING TOOL TO EVALUATE ORGANIC CATION TRANSPORTERS.
Presenter: Alix Leblanc, PhD, The Ohio State University

PWII-004
MICRODOSING PREVENTS THE KNOWN PHARMACOKINETIC DRUG INTERACTION BETWEEN CHLORZOXAZONE AND MIDAZOLAM.
Presenter: Nicolas Hohmann, MD, University Hospital Heidelberg

PWII-005
DATA-DRIVEN LEARNING ANALYSIS IDENTIFIES GENDER DIFFERENCES IN METABOLIC TREATMENT RESPONSE OF CITALOPRAM/ESCITALOPRAM IN MAJOR DEPRESSIVE DISORDER.
Presenter: Arjun Athreya, University of Illinois at Urbana-Champaign

5:15 PM – 5:45 PM

EXHIBIT WALK

EXHIBIT HALL A/B SOUTH

CHAIR

Aubrey Stoch, MD
Merck, Rahway, NJ

D Discovery
R Regulation
D Development
U Utilization

THURSDAY, MARCH 16, 2017

5:30 PM – 6:15 PM

Endogenous/Exogenous Predictors of Drug Exposure
POSTER WALK
EXHIBIT HALL A/B SOUTH

CHAIRS
Stacy S. Shord, PharmD, US Food and Drug Administration, Silver Spring, MD

Larissa A. Wenning, PhD, Merck & Co., Inc., North Wales, PA

For complete abstract content download the ASCPT Annual Meeting Mobile App.

PWIII-001
CLINICAL APPLICATION OF PBPK MODELING: MECHANISTIC INSIGHTS INTO VARIABILITY IN MORPHINE CLEARANCE AMONG PEDIATRIC AND ADULT PATIENTS.
Presenter: Chie Emoto, PhD, Cincinnati Children's Hospital Medical Center

PWIII-002
TACROLIMUS POPULATION PHARMACOKINETICS AND CYP3A5 GENOTYPES IN AFRICAN AMERICAN AND CAUCASIAN RENAL TRANSPLANT RECIPIENTS.
Presenter: Olivia Campagne, PharmD, University at Buffalo, SUNY

PWIII-003
INTACT NEPHRON THEORY MAY NOT FULLY EXPLAIN THE EFFECT OF SEVERE RENAL IMPAIRMENT FOR DRUGS ACTIVELY SECRETED VIA RENAL ORGANIC ANION TRANSPORTERS.
Presenter: Chia-Hsiang Hsueh, PhD, US Food and Drug Administration, University of California, San Francisco

PWIII-004
UGT1A9 RS3832043 INFLUENCES ACETAMINOPHEN GLUCURONIDATION IN NEONATES.
Presenter: Matthew Linakis, University of Utah

PWIII-005
APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING FOR PREDICTION OF BUPRENORPHINE EXPOSURE IN SUBJECTS WITH HEPATIC IMPAIRMENT (HI).
Presenter: Karen Rowland-Yeo, PhD, Simcyp (part of Certara)

FRIDAY, MARCH 17, 2017

7:15 AM – 8:00 AM

POSTER WALK

Endogenous/Exogenous Predictors of Drug Response Cardiac/Metabolic

EXHIBIT HALL A/B SOUTH

CHAIRS

Larisa H. Cavallari, PharmD, BCPS, FCCP, University of Florida, Gainesville, FL

Sony Tuteja, PharmD, University of Pennsylvania School of Medicine, Philadelphia, PA

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PWIV-001

RNA-SEQ ANALYSES IDENTIFY MOLECULAR MARKERS OF BLOOD PRESSURE (BP) RESPONSE TO THIAZIDE DIURETICS (TD).

Presenter: Ana Caroline Costa Sa, University of Florida

PWIV-002

DISCOVERY OF SUBSTRATES FOR GLUT2, A TRANSPORTER IMPLICATED IN METFORMIN RESPONSE.

Presenter: Osatohanmen Enogieru, PharmD, University of California, San Francisco

PWIV-003

COMMON GENETIC VARIANTS IN NEUROBEACHIN (NBEA) ARE ASSOCIATED WITH METFORMIN DRUG RESPONSE IN INDIVIDUALS WITH TYPE 2 DIABETES IN THE ACCORD CLINICAL TRIAL.

Presenter: Daniel Rotroff, PhD, North Carolina State University

PWIV-004

A GENETIC VARIANT OF ABCG2 CONFERS RISK FOR POOR RESPONSE TO ALLOPURINOL INDEPENDENT OF ITS EFFECT ON GOUT SEVERITY.

Presenter: Deanna Brackman, University of California, San Francisco

PWIV-005

GENOME-WIDE COPY NUMBER VARIATION AND WARFARIN DOSE RESPONSE IN AFRICAN AMERICANS.

Presenter: Wenndy Hernandez, PhD, The University of Chicago

SCIENCE AT SUNRISE SESSIONS

7:30 AM – 9:00 AM

Databases 101 for Clinical Pharmacologists: What You Need to Know

MARRIOTT 3

COMMUNITIES

International Transporter Consortium (ITC), Pharmacogenomics (PMG)

CHAIRS

Kari M. Morrissey, PhD, Genentech, South San Francisco, CA

Russ B. Altman, MD, PhD, Stanford University, Stanford, CA

SPEAKERS

Tools and Resources for Genomewide Studies

Sook Wah Yee, PhD, University of California San Francisco, San Francisco, CA

Pharmacogenomics Knowledgebase

Michelle Whirl-Carrillo, PhD, Stanford University, Department of Genetics, CA

FDA Pharmacogenomics and Biomarker Databases

Anuradha Ramamoorthy, PhD, US Food and Drug Administration, Silver Spring, MD

Upon completion of this Science at Sunrise Session, the attendee should be able to:

- Describe how PharmGKB and the NHGRI/EBI GWAS Catalog can be used to obtain information on the genes involved in the pharmacokinetics and pharmacodynamics of drugs, as well as treatment decisions for researchers, clinicians, patients and public health agencies; and
- Describe how you can use FDA databases to extract information on response and toxicity of currently approved prescription drugs.

D Discovery
R Regulation
D Development
U Utilization

FRIDAY, MARCH 17, 2017

7:30 AM – 9:00 AM

How Inert are Excipients? What Clinical Pharmacologists Need to Know
MARYLAND

COMMUNITIES
International Transporter Consortium (ITC), Regulatory Science (RS)

CHAIRS
Xinyuan Zhang, PhD, US Food and Drug Administration, Silver Spring, MD

Arik Zur, PhD, TEVA Pharmaceutical Industries, Holon, Israel

SPEAKERS
Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)
Robert Lionberger, PhD, US Food and Drug Administration, Silver Spring, MD

What We Do Not Know About Drug Excipients
Brian Shoichet, PhD, University of California, San Francisco, San Francisco, CA

Transporter-Mediated Interactions of Drugs with Excipients
Kathleen M. Giacomini, PhD, University of California, San Francisco, San Francisco, CA

Upon completion of this Science at Sunrise Session, the attendee should be able to:

- List at least three excipients and their role in drug product formulations and describe two situations that biowaivers may be granted for generic drug products under the revised FDA Guidance 'Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS); and
- Will be able to use the excipient browser (http://excipients.ucsf.bkslab.org/), which allows exploration of the physical chemical properties of approved FDA excipients.

7:30 AM – 9:00 AM

WORKSHOP
Biomarkers of CYP3A Activity: What Have We Learned and are We Ready to Utilize Biomarkers to Replace Clinical DDI Studies?
MARRIOTT 1/2

COMMUNITIES
Biomarker & Translational Tools (BTT), Regulatory Science (RS)

CHAIRS
Sam Rebello, PhD, Novartis, East Hanover, NJ

Lei Zhang, PhD, US Food and Drug Administration, Silver Spring, MD

SPEAKERS
Review of the Biology of Emerging Endogenous Biomarkers of CYP3A
Yvonne Lin, PhD, University of Washington, Seattle, WA

Perspectives and Case Examples from Industry
Helen Gu, DMPK - Novartis Institute for Biomedical Research, East Hanover, NJ

Regulatory Perspectives on the Use of CYP3A Biomarkers for Assessing DDI
Lei Zhang, PhD, US Food and Drug Administration, Silver Spring, MD

PANELISTS
Jialin Mao, PhD, Genentech, South San Francisco, CA

Karthick Vishwanathan, PhD, AstraZeneca, Waltham, MA

Bindu Murthy, PharmD, Bristol-Myers Squibb, Lawrenceville, NJ

FRIDAY, MARCH 17, 2017

Upon completion of this Workshop, the attendee should be able to:

- Review the biology of endogenous CYP3A biomarkers and understand the Industry and Regulatory perspective on the topic; and
- Through case examples from industry, learn how study design aspects (treatment duration of NCE, dose, sample size, etc.) influence biomarker selection and data interpretation while assessing CYP3A inhibition and/or induction. Learn how companies have used the biomarker information to influence drug development decisions.

9:15 AM – 10:15 AM

STATE OF THE ART LECTURE
MARRIOTT 1/2

CHAIR
Kellie Schoolar Reynolds, Gaithersburg, MD

SPEAKER

Radical Approaches to Antibiotics and Antibiotic Resistance
James J. Collins, PhD, Massachusetts Institute of Technology, Cambridge, MA

10:30 AM – 12:30 PM

SYMPOSIUM
Integration of Genomics and Translational Clinical Pharmacology to Guide Development of Precision Medicines
MARRIOTT 1/2

COMMUNITIES
Pharmacogenomics (PMG), Pharmacometrics & Pharmacokinetics (PMK)

D D R U

CHAIRS
Anuradha Ramamoorthy, PhD, US Food and Drug Administration, Silver Spring, MD
Rebecca Blanchard, PhD, Merck & Co Inc., North Wales, PA

SPEAKERS

A Patient's Perspective on Developing Precision Medicines
Katherine Wilemon, The FH Foundation, Pasadena, CA

Bridging the Gap Between the Laboratory and Clinic in Precision Medicine
Sara Van Driest, MD, PhD, Vanderbilt University, Nashville, TN

Translational Opportunities to Utilize Precision Medicine in Drug Development
Megan Gibbs, PhD, AbbVie, Inc., North Chicago, Chicago, IL

Opportunities and Challenges in the Development and Regulatory Evaluation of Precision Medicines
Issam Zineh, PharmD, MPH, US Food and Drug Administration, Silver Spring, MD

Upon completion of this Symposium, the attendee should be able to:

- Provide an overview of the current trends and the future role of genomics-guided clinical pharmacology strategy in developing precision medicines; and
- Describe the ongoing efforts to bring precision medicine into main stream from the perspective of the patient, academia, industry, and regulatory speakers.

D Discovery
R Regulation
D Development
U Utilization

FRIDAY, MARCH 17, 2017

10:30 AM – 12:30 PM

Clinical Practice, Hurdles and Expectations in the Individualized Treatment Route to Optimizing Therapy for Biologics

MARRIOTT 3

COMMUNITIES

Biologics

D D R U

CHAIRS

Indranil Bhattacharya, PhD, Pfizer, Cambridge, MA

Rong Deng, PhD, Genentech, San Francisco, CA

SPEAKERS

Clinician's Guide to Optimizing Therapy in Inflammatory Bowel Disease

Brian Feagan, MD, FRCPC, Robarts Clinical Trials, Inc., Western University, London, ON, Canada

Individualized Dosing Sequences in Dynamic Precision Medicine

Robert Beckman, MD, Georgetown University, Washington, DC

Therapeutic Drug Monitoring: Overcoming the Hurdles

Diane Mould, PhD, Projections Research Inc., Phoenixville, PA

Regulatory Perspectives of Implementing TDM: Challenges and Opportunities

Yow-Ming Wang, PhD, US Food and Drug Administration, Silver Spring, MD

Upon completion of this Symposium, the attendee should be able to:

- Learn from a clinical perspective using examples from two different therapeutic areas as to why there is a need for optimizing therapy, what information drives the decision making and what is used including tools to guide how much change is needed; and
- Learn about need for effective integration of drug concentrations and biomarkers and decision support tools such as dashboards to allow physicians to integrate patient data and generate treatment recommendations. Learn how given the unique properties of biologics, early interaction with different centers in health authorities and understanding the current regulatory hurdles are crucial for a successful implementation of TDM for biologics.

1:15 PM – 2:15 PM

FEATURED SPEAKER

VIRGINIA

CHAIR

Stephen P. Spielberg, MD, PhD, Lansdale, PA

SPEAKER

Precision Therapeutics for Children

J. Steven Leeder, PharmD, PhD, Children's Mercy Hospital, Kansas City, MO

FRIDAY, MARCH 17, 2017

WORKSHOPS

1:15 PM – 2:45 PM

Physiologically Based Pharmacokinetics (PBPK) Modeling to Support Dosing Recommendations for Patients with Renal Impairment: Are We There Yet?

MARRIOTT 1/2

COMMUNITIES

Regulatory Science (RS), Pharmacometrics & Pharmacokinetics (PMK)

CHAIRS

Ying Ou, PhD, Amgen, South San Francisco, CA

Robin L. O'Connor-Semmes, PhD, PAREXEL International, Research Triangle Park, NC

SPEAKERS

Physiologically Based Pharmacokinetics (PBPK) Modeling to Support Dosing Recommendations for Patients with Renal Impairment: An Industry Perspective
Steve Hall, PhD, Eli Lilly, Indianapolis, IN

The Readiness and Specific Paths of Using PBPK to Support Dosing Recommendation in Patients with Renal Impairment
Ping Zhao, PhD, US Food and Drug Administration, Silver Spring, MD

Towards Quantitative Prediction of the Effect of Renal Impairment: Filling the Gap for Drug Transporters
Kathleen M. Giacomini, PhD, University of California, San Francisco, San Francisco, CA

Upon completion of this Workshop, the attendee should be able to:

- Discuss the current status and knowledge gaps regarding physiological changes of renal impairment (eg., protein binding, metabolism and transporter) and applying PBPK modeling for predicting pharmacokinetics of drugs in patients with renal impairment. The session will cover drugs that are mainly renally cleared and drugs that are non-renally cleared;
- Describe the strategy and utility of PBPK modeling to gather information to support dosing recommendation in patients with renal impairment;
- Discuss when PBPK may be used to support the labeling language; and
- Describe how the PBPK modeling be used in conjunction with dedicated renal impairment studies and population PK analysis during drug development.

FRIDAY, MARCH 17, 2017

1:15 PM – 2:45 PM

Tumor Cell Drug Penetration for Individualized Cancer Treatment
MARRIOTT 3

COMMUNITIES
Oncology (ONC), Drug Utilization & Outcomes (DUO)

CHAIRS
Imke Bartelink, PharmD, PhD, University of California, San Francisco, San Francisco, CA

Sheerin Shahidi-Latham, PhD, Genentech, South San Francisco, CA

SPEAKERS
Molecular Imaging to Support Insight in Drug Effects at the Level of the Tumor Lesions in Patients
Elisabeth de Vries, MD, PhD, University Medical Center Groningen, Groningen, Netherlands

MALDI-MS Imaging of Targeted Therapies in Cellular and Necrotic Tissues
Brendan Prideaux, PhD, Rutgers New Jersey Medical School, Newark, NJ

Measuring Single-Cell Uptake of Antibody Drug Conjugates In Vivo: Using Imaging and Drug Transport Analysis to Understand Payload Delivery in Tumors
Greg Thurber, PhD, University of Michigan, Michigan, MI

Upon completion of this Workshop, the attendee should be able to:

- Describe techniques such as MALDI MS-imaging, radiolabeled drug-imaging, fluorescence and biochemical imaging of targeted therapeutics which can be applied to measure drug penetration in tumor cells; and
- Describe the main determinants of variability of drug uptake in solid tumors, discuss methods to individualize therapies based on measurements of drug uptake in solid tumors and define which methods are most suitable for tumor site measurements in translational research and clinical care.

1:30 PM – 2:30 PM

ORAL ABSTRACT SESSION
Drug Development
MARYLAND

CHAIRS
Daria Stypinski, BSc(Pharm), PhD, Pfizer, Inc., New York, NY

Geert Jan Groeneveld, MD, PhD, Centre for Human Drug Research, Leiden, Netherlands

For complete abstract content download the ASCPT Annual Meeting Mobile App.

OI-001
METABOLOMIC AND GENOME-WIDE ASSOCIATION STUDIES REVEAL POTENTIAL ENDOGENOUS BIOMARKERS FOR OATP1B1.
Presenter: Sook Wah Yee, PhD, University of California, San Francisco

OI-002
COMPARISON OF NON-COMPARTMENTAL ANALYSIS (NCA) ESTIMATION AND POPULATION PHARMACOKINETIC (PPK) PREDICTIONS OF EXPOSURE CHANGES AS A FUNCTION OF RENAL IMPAIRMENT.
Presenter: Mariam Ahmed, PhD, University of Minnesota

OI-003
AN EXEMPLAR OF A SYSTEMS PHARMACOLOGY APPROACH FOR A DETAILED INVESTIGATION OF AN ADVERSE DRUG EVENT AS A RESULT OF DRUG-DRUG INTERACTIONS.
Presenter: Sarah Kim, PhD, University of Florida

OI-004
REPORTS OF TORSADES DE POINTES (TDP) ASSOCIATED WITH INTRAVENOUS (IV) DRUG FORMULATIONS THAT CONTAIN THE PRESERVATIVE CHLOROBUTANOL (CB).
Presenter: Raymond D. Woosley, MD, PhD, AZCERT, Oro Valley, AZ

FRIDAY, MARCH 17, 2017

3:00 PM – 4:00 PM

AWARD LECTURE

Sheiner-Beal Pharmacometrics Award Lecture

MARRIOTT 1/2

AWARD PRESENTER

Terrence F. Blaschke, MD, Global Health Discovery & Translational Sciences, Bill & Melinda Gates Foundation, Seattle, WA

SPEAKER

Pharmacometrics @ 45; What's Next?

Carl C. Peck, MD, UCSF Center for Drug Development Science, San Luis Obispo, CA

3:00 PM – 4:30 PM

WORKSHOP

Leveraging Limited Data for Innovative Drug Development and Utilization Analyses

VIRGINIA

COMMUNITIES

Pharmacometrics & Pharmacokinetics (PMK)

D D R U

CHAIR

Anita Grover, PhD, BioMarin, Novato, CA

SPEAKERS

Dose Selection for Intracerebroventricular Cerliponase Alfa (BMN 190) in Children with CLN2 Disease: A Rare Genetic Disease

Joshua Henshaw, PhD, BioMarin, Novato, CA

Optimizing Maternal Influenza Immunization Timing to Best Protect Infants

Michael Dodds, PhD, Quantitative Solutions, Seattle, WA

Model-Based Biomarker Qualification: Optimizing Decision-Making in Polycystic Kidney Disease

Klaus Romero, MD, The Critical Path Institute, Tucson, AZ

Upon completion of this Workshop, the attendee should be able to:

- Understand a range of novel drug development and utilization questions where traditional data sources aren't available and quantitative tools have been successfully employed; and
- Discuss alternative and novel data sources and techniques for leveraging those sources to inform outcomes in the clinical pharmacology space.

4:15 PM – 5:15 PM

AWARD LECTURES

Leon I. Goldberg Early Investigator Award Lecture

MARRIOTT 1/2

AWARD PRESENTER

Craig W. Hendrix, MD, Johns Hopkins University, Baltimore, MD

SPEAKER

Elucidating the Pharmacology and Toxicology of Anti-HIV Drug Metabolites

Namandje N. Bumpus, PhD, Johns Hopkins University School of Medicine, Baltimore, MD

AWARD PRESENTER

Issam Zineh, PharmD, MPH, US Food and Drug Administration, Silver Spring, MD

SPEAKER

Precision Medicine: The New Normal

Michael Pacanowski, PharmD, MPH, OCP, US Food and Drug Administration, Silver Spring, MD

D Discovery R Regulation

D Development U Utilization

SATURDAY, MARCH 18, 2017

7:30 AM – 9:00 AM

SPECIAL EDUCATION SESSION

Publish or Perish: Getting in the Game, and Getting the Most Out of Your Published Works

VIRGINIA

CHAIRS

Catherine Sherwin, PhD, University of Utah School of Medicine, Salt Lake City, UT

Jennifer Goldman, MD, Children's Mercy Hospital, Kansas City, MO

SPEAKERS

Navigating to Find the Right Journal
John A. Wagner, MD, PhD, Takeda Pharmaceuticals, Cambridge, MA

Optimizing and Tracking the Impact of Your Published Article
Morna Conway, PhD, Morna Conway, Inc., Shelbyville, TN

Why Do I Need to Publish My Work?
Susan Abdel-Rahman, PharmD, Children's Mercy Hospitals & Clinics, Kansas City, MO

Upon completion of this Special Education Session, the attendee should be able to:

- Identify the right journal to publish one's work;
- Learn skills to negotiate and determine authorship;
- Identify strategies on how to respond to reviewers' comments; and
- Become familiar with methods for measuring the impact of your work: Impact Factor and other measures of citation, Altmetric, downloads and other Metrics

7:30 AM – 9:30 AM

SPECIAL SESSION

Subject Safety in First-in-Human (FIH) Studies: Perspectives, Pragmatism, and Practice

MARRIOTT 1/2

COMMUNITIES

Early Development & Drug Safety (EDDS)

CHAIRS

Sarah Robertson, PharmD, Vertex Pharmaceuticals, Boston, MA

Aubrey Stoch, MD, Merck & Co., Kenilworth, NJ

Richard L. Lalonde, PharmD, Pfizer, Groton, CT

SPEAKERS

First-in-Human Studies: Practical Aspects of Design and Control
Jim Bush, MB ChB, PhD, Covance Clinical Research Unit, Leeds, United Kingdom

BIA 10-2474 Accident: Biotrial Crisis Management – Facts, Impact & Lessons
Jean-Marc Gandon, PharmD, Biotrial, Rennes, France

Death (or SAE) in First-in-Human Studies: What Next? A Regulatory Perspective
Jonathan P. Jarow, MD, US Food and Drug Administration, Silver Spring, MD

When First-in-Human Studies Results in Death: Legal and Regulatory Lessons
Robin Fretwell Wilson, BA, JD, University of Illinois College of Law, Champaign, IL

An Industry View of First-in-Human Studies: Where Can We Improve?
Sarah Robertson, PharmD, Vertex Pharmaceuticals, Inc., Boston, MA

Upon completion of this Special Session, the attendee should be able to;

- Review current best practices for the safe conduct of FIH studies for novel therapeutic compounds; and

SATURDAY, MARCH 18, 2017

- Engage scientists in open dialogue about current challenges to standard FIH study practices and potential areas of improvement in light of the 2016 incident in France.

9:45 AM – 10:45 AM

STATE OF THE ART LECTURE
MARRIOTT 1/2

CHAIR
Julie A. Johnson, PharmD, University of Florida, Gainesville, FL

SPEAKER

In Silico Mechanistic Modeling: The Future of Precision Medicine
V.A. Shiva Ayyadurai, PhD, The Inventor of Email & Chairman/CEO, CytoSolve, Inc., Cambridge, MA

11:00 AM – 12:00 PM

ORAL ABSTRACT SESSION
Regulators of Drug Transporters
VIRGINIA

CHAIRS
Lei Zhang, PhD, US Food and Drug Administration, Silver Spring, MD

Alexander G. Vandell, PharmD, PhD, Daiichi Sankyo, Edison, NJ

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OII-001
IN VITRO AND IN VIVO FUNCTIONAL TESTING OF SNPS IN THE 3'UTR OF CYP2B6.
Presenter: Kimberly Burgess, Indiana University School of Medicine

OII-002
CLINICALLY RELEVANT MULTIDRUG TRANSPORTERS ARE REGULATED BY DIFFERENT MICRORNAS ALONG THE HUMAN INTESTINE.
Presenter: Henrike Bruckmüller, PhD, University Hospital Schleswig-Holstein

OII-003
REGULATION OF HEPATIC TRANSPORTERS IN MICE DURING ACUTE INFLAMMATION: INVOLVEMENT OF NF-KB AND PREGNANE X RECEPTOR (PXR).
Presenter: Walaa Abualsunun, PharmD, University of Toronto

OII-004
SUBSTANTIAL ENHANCER ACTIVITY OF NON-CODING REGIONS IN ABCG2 (BREAST CANCER RESISTANCE PROTEIN, BCRP).
Presenter: Kit Wun Kathy Cheung, PharmD, University of California, San Francisco

11:00 AM – 12:00 PM

ORAL ABSTRACT SESSION
Drug Metabolizing Enzymes, Neonatal and Pediatric Pharmacology
MARYLAND

CHAIRS
Dionna Green, MD, US Food and Drug Administration, Silver Spring, MD

Susan I. Vear, MD, MSCI, National Children's Hospital, Columbus, OH

For complete abstract content download the ASCPT Annual Meeting Mobile App.

OIII-001
FEASIBILITY OF A PEDIATRIC MICRODOSE STUDY OF [^{14}C] MIDAZOLAM TO STUDY THE ONTOGENY OF CYP3A-MEDIATED DRUG METABOLISM.
Presenter: Bianca van Groen, Erasmus MC - Sophia Children's Hospital

OIII-002
MATERNAL AND FETAL METHADONE EXPOSURE: ASSOCIATIONS WITH NEONATAL ABSTINENCE SYNDROME.
Presenter: Ingrid Metzger, PhD, Indiana University School of Medicine

D Discovery R Regulation
D Development U Utilization

SATURDAY, MARCH 18, 2017

OIII-003
CAFFEINE CITRATE DOSING ADJUSTMENT TO MAINTAIN TARGET CAFFEINE CONCENTRATION IN PRETERM NEONATES.
Presenter: Gilbert Koch, PhD, University Children's Hospital Basel

OIII-004
AGE-DEPENDENT DEVELOPMENTAL CHANGES IN HEPATIC ORGANIC CATION TRANSPORTER 1 (OCT1) PROTEIN EXPRESSION IN NEONATES AND SMALL INFANTS.
Presenter: David Hahn, PhD, Cincinnati Childrens Hospital Medical Center

11:00 AM – 1:00 PM

SYMPOSIUM

Innovation at the Intersection of Clinical Trials and Real-World Data to Advance Patient Care

MARRIOTT 3

Communities: Drug Utilization & Outcomes (DUO), Pharmacometrics & Pharmacokinetics (PMK)

CHAIRS

Lokesh Jain, PhD, Merck & Co., Inc., Rahway, NJ

Brandon Swift, PhD, Quintiles, Morrisville, NC

SPEAKERS

Overview of Real-World Data: Where is the World Moving?
Aman Bhandari, PhD, Merck, Rahway, NJ

Transforming Clinical Drug Development through Real-World Evidence
Pravin Jadhav, PhD, FCP, MPH, Otsuka, Princeton, NJ

Clinical Trial to Real-World Evidence: Enabling the Shift to Value-Based Decisions
Dyfrig Hughes, PhD, Bangor University, United Kingdom

Real World Data in the Real World of Healthcare. Why Now?
Craig White, QuintilesIMS, Cambridge, MA

Upon completion of this Symposium, the attendee should be able to:

- Gain insights into the current and evolving space of real-world healthcare data, and discuss approaches on how this data can be used to inform drug development decisions to enable development of new treatments and cures with better treatment effectiveness, greater potential for differentiation from existing products, and reduced risk of market failure; and
- Highlight the role of integrated Pharmacokinetic-Pharmacodynamic-Pharmacoeconomic (PK-PD-PE) modeling in shifting the focus of pre-launch drug development strategy towards maximizing the value for all stakeholders (e.g., patient, payers), by informing decisions on target product profile, drug development, and clinical trial designs.

1:15 PM – 2:45 PM

WORKSHOP

Epigenetics in Drug Response

VIRGINIA

COMMUNITIES

Pharmacogenomics (PMG)

CHAIRS

Ingolf Cascorbi, MD, PhD, University of Kiel, Kiel, Germany

Matthias Schwab, MD, Dr. Margarete Fischer-Bosch Institute, Stuttgart, Germany

SPEAKERS

Regulation of ADME-Genes by miRNAs
Ingolf Cascorbi, MD, PhD, University of Kiel, Kiel, Germany

MicroRNAs and Cancer Resistance
Paolo Neviani, Children's Hospital Los Angeles, Los Angeles, CA

DNA-methylation of ADME genes
Matthias Schwab, MD, Dr. Margarete Fischer-Bosch Institute, Stuttgart, Germany

Upon completion of this Workshop, the attendee should be able to:

- Learn about the molecular characteristics of epigenetic processes such as DNA-methylation and histone-acetylation as well as post-transcriptional modifications by non-coding RNAs;
- Discuss how ADME genes are affected by epigenetic processes;
- Identify how genetic modification of ADME genes alter the interaction with miRNA;
- Identify how diseases lead to a modification of epigenetic processes and what are the consequences for ADME genes;
- Discuss how epigenetic modifications of drug targets and cellular excretion mechanisms contribute to multi drug resistance in cancer; and
- Discuss which drugs affect epigenetics e.g DNA-methylation and histone-acetylation and how to make best use of them.

1:15 PM – 3:15 PM

SYMPOSIUM

Reverse Translation Fueled by Quantitative Pharmacology: Informing Biology, Drug Development Decision-Making, and Therapeutic Optimization

MARRIOTT 3

Communities: Pharmacometrics & Pharmacokinetics (PMK), Biomarker & Translational Tools (BTT)

CHAIRS

Karthik Venkatakrishnan, PhD, Takeda Pharmaceuticals International Company, Cambridge, MA

Sreeneeranj Kasichayanula, PhD, Amgen, Thousand Oaks, CA

SPEAKERS

Reflections on the Practice of R&D: Balancing Academic Curiosity Analyzing Observations for a Lifetime, with Patient-Centricity and Market-Driven Necessities to Move Fast

Amin Rostami-Hodjegan, PharmD, PhD, University of Manchester, Manchester, United Kingdom

Using our Past to Help with the Future: How Early Clinical Development can be Guided by Prior Data

Anne Heatherington, PhD, Pfizer, Cambridge, MA

Role of Model-Based Meta-Analysis and Integration with Real World Data in Reverse Translation across the Drug Development Continuum

John Gibbs, PhD, AbbVie, Inc., North Chicago, IL

Data-Driven Detection, Corroboration, and Validation of Novel Drug Effects and Drug-Drug Interactions

Nicholas Tatonetti, PhD, Columbia University Medical Center, New York, NY

Upon completion of this Symposium, the attendee should be able to:

- Illustrate, using case studies, the power of QP approaches (e.g., systems modeling, model-based meta-analysis, network analysis) in distilling knowledge from diverse clinical data (e.g., electronic health records, clinical trial outcomes, patient-level data in diverse populations) to inform biology/ mechanism, enhance Proof-of-Concept strategies, enable principled decision-making in drug development, and understand biological determinants of drug safety to guide rational risk management; and
- Nurture a reverse translation mindset in contemporary translational medicine across the discovery-development-utilization continuum; understand perspectives from industry/ academia on critical success factors for

D Discovery
R Regulation
D Development
U Utilization

implementing a culture of reverse translation; and discuss opportunities and challenges for development of next-generation translational researchers and pharmacometricians that can collaboratively inform and realize the full potential of quantitative reverse translation.

1:15 PM – 3:15 PM

SYMPOSIUM

Gut Microbiome and Drug Response Phenotype

MARYLAND

COMMUNITIES

Pharmacometabolomics (PM)

CHAIRS

Rima Kaddurah-Daouk, PhD, Duke University Medical Center, Durham, NC

Wei Jia, PhD, University of Hawaii Cancer Center, Honolulu, HI

SPEAKERS

Metabolic Interactions Between the Gut Microbiome and Host, with Application to Assessing Drug Response Profile
Wei Jia, PhD, University of Hawaii Cancer Center, Honolulu, HI

Quantitative Prediction and Clinical Evaluation of Herb-Drug Interactions
Mary Paine, PhD, Washington State University, Pullman, WA

Microbiota Transplantation Restores Normal Fecal Bile Acid Composition in Antibiotic-resistant Clostridium difficile Infection
Chi Chen, PhD, University of Minnesota, Minneapolis, MN

Genomics and Metabonomics in Disease and Drug Metabolism
Yulan Wang, PhD, Chinese Academy of Sciences, Wuhan, China

Upon completion of this Symposium, the attendee should be able to:

- Highlight national and global initiatives involving gut microbiome and precision medicine, including the National Microbiome Initiative and the Precision Medicine Initiative, and the role that the clinical pharmacology community can play in shaping such initiatives; and
- Share tools used in implementing a gut microbiome-based precision medicine approach including clinical NGS bioinformatics, microbiome metabolomics, pharmacometabolomics, and use of medical records. Exemplify from studies with Roux-en-Y Gastric Bypass surgery, liver diseases, and gastrointestinal cancers.

PROGRAM & SCIENTIFIC AGENDA

SAVE THE DATE – 2018 PRE-CONFERENCES

FULL DAY PRE-CONFERENCE

Phase-0/Microdosing Stakeholder Meeting

CHAIR

Tal Burt, MD, Burt Consultancy, LLC, Durham, NC

CO-CHAIR

Le Vuong, PhD, LTV Consulting, Davis, CA,

GOAL:

To advance the utilization of Phase-0/ Microdosing studies in drug development.

OBJECTIVES:

1. To obtain input from major stakeholders (regulatory, academia, industry, patient advocacy, non-profit) on the value, prospects, and challenges of Phase-0/ Microdosing studies in drug development
2. To provide an update on the validation, applications, and utilization of Phase-0/ Microdosing studies
3. To establish guidelines for future applications and utilization and recommendations for further research and development of these approaches

MEETING FORMAT:

1-day, 8-hour meeting, including the following sections:

State-of-the-art presentations – 3 hours

Small-group topical discussions – 3 hours

Large-group consensus discussions – 2 hours

HALF-DAY PRE-CONFERENCES

Pediatric Drug Development in Oncology: Challenges and Opportunities

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CHAIRS

Konstantina M. Vanevski, MD
Director, Experimental Medicine and Early Clinical Leader
Bayer HealthCare LLC

Dionna Green, MD
Medical Officer, Pediatrics / Policy Lead, Guidance and Policy Team
US Food and Drug Administration

MEETING FORMAT:

The focus of this half-day Pre-conference, including a roundtable discussion, is to share the perspective of regulators (FDA), researchers (NIH & academia), and industry on the challenges for generating, identifying and/or selecting pre-clinical and clinical data that are essential to facilitate feasible studies that yield 'robust' data-sets, to support labeling of drugs for pediatric use in oncology.

Pharmacometrics Meets Health Economics: Quantitative Approaches in the Translation from Efficacy to Real World Effectiveness and to Cost-Effective Patient Care

CHAIR

Jing Liu, PhD, Pfizer, Groton, CT

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MEETING FORMAT:

A half-day Pre-conference program.

Opening remarks, 4-6 lectures and open discussion with a break in between.

D Discovery
R Regulation
D Development
U Utilization

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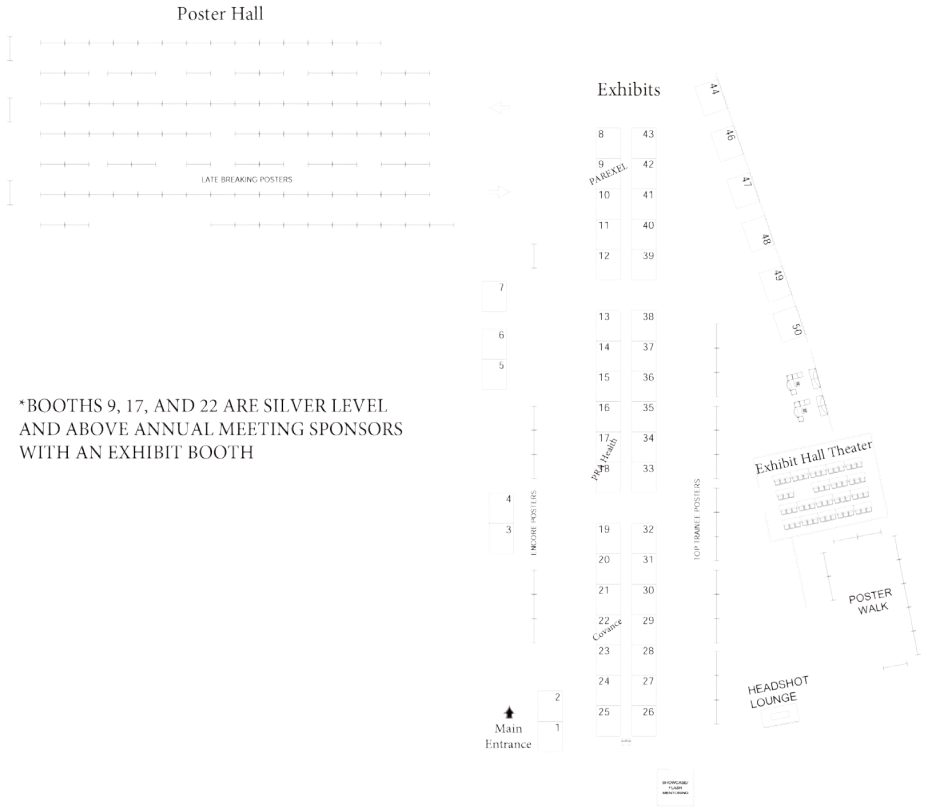

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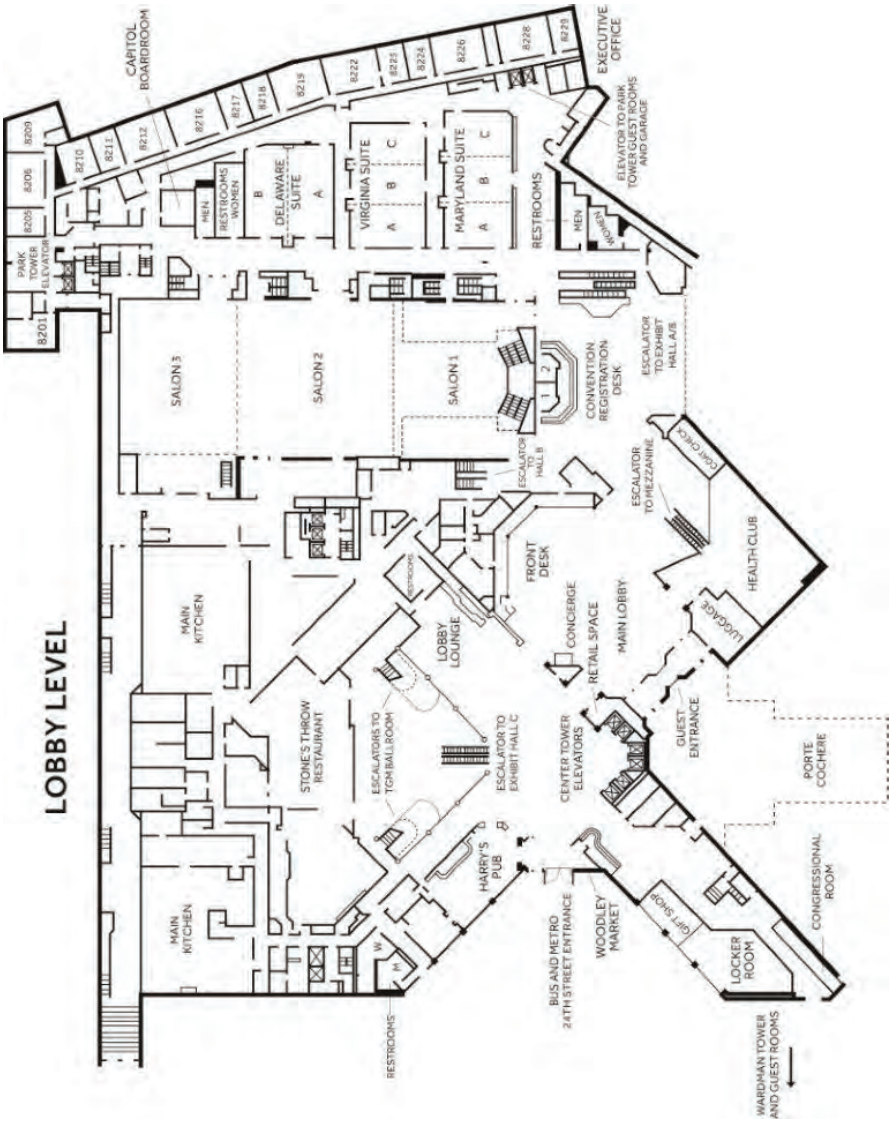
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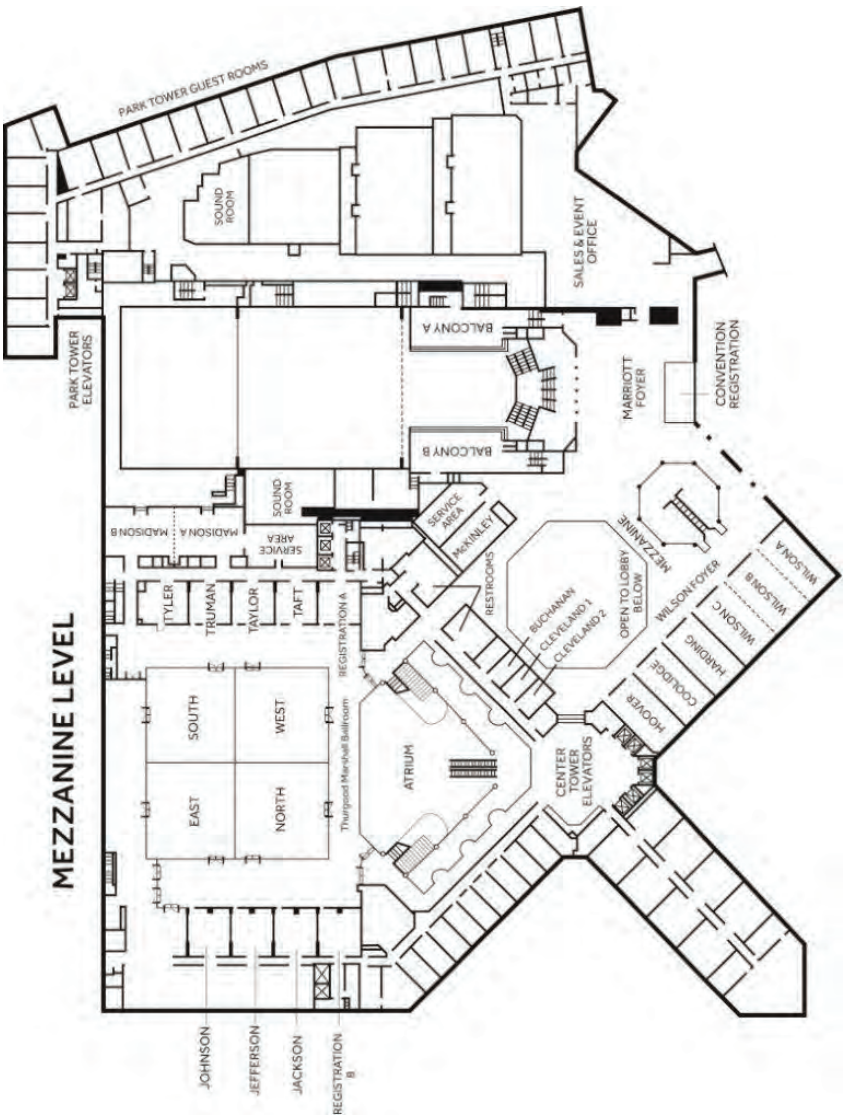
8229
MEN
WOMEN
RESTROOMS
DELAWARE SUITE
VIRGINIA SUITE
MARYLAND SUITE
SALON 3
SALON 2
SALON 1
CONVENTION REGISTRATION DESK
ESCALATOR TO EXHIBIT HALL A/B
ESCALATOR TO HALL B
ESCALATOR TO MEZZANINE
Gym Check
HEALTH CLUB
LUGGAGE
FRONT DESK
CONCIERGE
RETAIL SPACE
MAIN LOBBY
LOBBY LOUNGE
MAIN KITCHEN
STONE'S THROW RESTAURANT
ESCALATORS TO TGM BALLROOM
ESCALATOR TO EXHIBIT HALL C
CENTER TOWER ELEVATORS
GUEST ENTRANCE
PORTE COCHERE
HARRY'S PUB
BUS AND METRO 24TH STREET ENTRANCE
WOODLEY MARKET
GIFT SHOP
LOCKER ROOM
CONGRESSIONAL ROOM
WARDMAN TOWER AND GUEST ROOMS

SPONSORS & EXHIBITS

MEZZANINE LEVEL



POSTERS, POSTER WALKS, LATE-BREAKING AND ENCORE ABSTRACTS

ACKNOWLEDGMENTS

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ASCPT WISHES TO THANK THE ABSTRACT REVIEWERS FOR THEIR TIME AND EFFORT REVIEWING ABSTRACTS SUBMITTED FOR THE ASCPT 2017 ANNUAL MEETING.

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LATE-BREAKING POSTER SESSION

WEDNESDAY, MARCH 15, 2017
4:00 PM – 6:30 PM
EXHIBIT HALL A/B SOUTH

LB-001
PREDICTING EFFECTS OF CYP3A4 PERPETRATORS ON ABEMACICLIB AND ACTIVE METABOLITES EXPOSURE USING PHISIOLOGICALLY-BASED PHARMACOKINETIC MODELING.

M. Posada, K. Turner, P. Kulanthaivel, S. Hall, G. Dickinson; Eli Lilly, Indianapolis, IN, USA.

BACKGROUND: Abemaciclib, a selective inhibitor of cdk4/6, is metabolized mainly by CYP3A4. Clinical studies were performed to assess the impact of strong inhibitor, clarithromycin, and inducer, rifampicin. A PBPK model incorporating 3 active metabolites was built in Simcyp® to predict the effect of other CYP3A inhibitors and inducers.
METHODS: In humans, Clarithromycin increased abemaciclib exposure by 3.4-fold and rifampicin decreased it by 94%, hence informing the fraction metabolized via CYP3A4 in the model. An absolute bioavailability study informed the hepatic and gastric availability. *In vitro* data and a human disposition study determined the fraction and rate of formation of the 3 active metabolites, and absorption related parameters. All perpetrator models were verified using literature observations of midazolam and quinidine.
RESULTS: The model adequately reproduced the concentration-time profiles of abemaciclib and active metabolites. The predicted interaction ratios with rifampicin and clarithromycin were within 0.7 and 1.25 of observed. The predicted and observed AUC ratios for abemaciclib and active species are listed in the **table**.
CONCLUSION: The model predictions can be used to inform dosing recommendations to support prescribing practices.

Observed and Predicted AUC Ratios for abemaciclib with CYP3A inhibitors and inducers

Analyte	GEO Mean AUC Ratio (90%CI) STRONG CYP3A4 Inhibitors			MODERATE CYP3A4 Inhibitors	MODERATE CYP3A4 Inhibitors		
	Ketoconazole	Itraconazole	Clarithromycin Observed	Clarithromycin Predicted	Diltiazem	Verapamil	Carbamazepine
ABEM-aciclib	15.7 (14.2,17.3)	7.2 (6.9,7.4)	3.4 (2.9,4.0)	3.9 (3.6,4.2)	4.0 (3.7,4.2)	2.3 (2.2,2.5)	0.2 (0.18,0.22)
TOTAL Active Species	6.9	3.8	2.2	2.5	2.4	1.6	0.48

LB-002

PHARMACOGENETIC ASSOCIATION STUDY OF OXYCODONE IN PEDIATRIC SURGICAL PATIENTS.

R. Balyan[1], M. Mecoli[1], R. Venkatasubramanian[1], V. Chidambaran[1], N. Kamos[1], S. Clay[1], D. Moore[1], C.D. Glover[2], P. Szmuk[3], A. Vinks[1], S. Sadhasivam[1]; [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]Baylor College of Medicine, Houston, TX, USA, [3]UT Southwestern Medical Center, Dallas, TX, USA.

BACKGROUND: Use of opioid analgesics in children is a great concern due to incidences of respiratory depression and death. Following 2013 US Food and Drug Administration's warning against the use of codeine in children undergoing surgery, oxycodone is being prescribed as an alternative. This study aimed to study if oxycodone is a safer alternative to codeine in children by analyzing CYP2D6 genotype and oxycodone pharmacokinetic associations. Oxycodone is partly metabolized to the active metabolite oxymorphone by hepatic CYP2D6. Significant genetic variability in CYP2D6 affects oxymorphone formation and response to oxycodone.
METHODS: In a prospective observational study, 30 children (2-17 years) were administered oral oxycodone postoperatively, blood samples were collected for 24 h and plasma level were measured by LC-MS/MS. CYP2D6 genotype and oxycodone metabolism phenotype were determined based on allelic information such as CYP2D6 total activity score (TAS) and metabolism phenotype; poor (PM), intermediate (IM), extensive (EM) or ultrarapid (UM) metabolizer.
RESULTS: Significantly greater oxymorphone exposure was seen in EM subjects ($P = 0.02$ for C_{max}, $P = 0.007$ for $AUC_{0\text{-}6}$ and $P = 0.008$ for $AU_{C0\text{-}24}$) compared to PM/IM subjects. Similarly a higher TAS value was associated with greater oxymorphone exposure. Upon further analysis, higher oxymorphone / oxycodone exposure ratio were observed in EM subjects compared with PM/IM subjects ($P = 0.0007$ for C_{max}, $P = 0.0034$ for $AUC_{0\text{-}6}$ and $P = 0.0004$ for $AUC_{0\text{-}24}$).
CONCLUSION: The greater extent of conversion to oxymorphone was associated with higher TAS values. These findings suggest that oxymorphone generation and exposure is dependent upon underlying CYP2D6 phenotype. Further studies are needed to predict the occurrence of adverse event and tailor personalized dosing.

LB-003

RACIAL AND ETHNIC COMPOSITION OF CANCER CLINICAL TRIALS: HOW INCLUSIVE ARE WE?

L. Dickmann, J. Ware, J. Schutzman; Genentech, South San Francisco, CA, USA.

BACKGROUND: Although efforts have been made to encourage or even mandate the inclusion of minority populations in clinical studies, the proportion of minority patients enrolled in cancer trials has remained persistently low. The aim of this analysis was to investigate recent trends in racial and ethnic composition of cancer clinical trials.
METHODS: The sampling frame was any clinical study containing an oncology drug approved between January 1, 2010 and July 31, 2016. Data were taken from the US Food and Drug Administration Drug Trials Snapshot or statistical/medical reviews and from clinical trial publications in PubMed. Healthy volunteer studies were excluded and clinical trial identifiers were used to avoid duplication. Descriptive statistics were determined using either Excel or SAS v9.4.
RESULTS: In total, race and/or ethnicity information was available for 83,018 individuals from 256 studies. For studies specific to North America, information was obtained for 9,179 individuals from 81 studies. For all studies, 79.3% of patients identified as White/Caucasian, 13.5% as Asian, and 2.6% as Black/African American. For studies specific to North America, 86.4% of patients identified as White/Caucasian while only 1.8% identified as Asian and 7.6% as Black/African American. Further breakdown based on Hispanic ethnicity, cancer subtype and studies used for drug approval will also be presented.

CONCLUSION: Although progress has been made for inclusion of Asian populations on global cancer clinical trials, inclusion of other racial and ethnic groups remains low and is potentially declining compared to historical data.

LB-004

INTER-PATIENT VARIABILITY IN EVEROLIMUS PHARMACOKINETICS IN JAPANESE PATIENTS WITH ADVANCED BREAST CANCER.

M. Hirabatake[1], T. Mizuno[2], R. Miura[1], E. Hohokabe[3], S. Takebe[3], K. Hashimoto[3], Y. Kikawa[3], H. Kato[3], T. Hashida[1]; [1]Department of Pharmacy, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [3]Department of Breast Surgery, Kobe City Medical Center General Hospital, Kobe, Japan.

BACKGROUND: Everolimus (EVE) is a cornerstone drug for advanced breast cancer treatment. However, frequent EVE toxicity is a clinical problem, especially in Japanese patients. EVE toxicity results from exposure to high EVE concentration; however, limited data are available on EVE pharmacokinetics (PK) in breast cancer patients. In this study, we evaluated the PK and EVE toxicity in breast cancer patients.
METHODS: Eleven patients were enrolled until November 2015 to October 2016. Seven patients started EVE at 10 mg once daily, while 4 were administered a reduced dose of 5 mg. Blood samples were collected pre-dose and 1, 4, and 8 hours post-dose. EVE concentration was determined by validated latex-enhanced turbidimetric immunoassay. PK parameters were estimated with Bayesian estimation using MW/Pharm (Mediware). The toxicity was evaluated based on CTCAE Ver. 4.0.
RESULTS: The median (range) body weight and clearance estimates were 51.1 (39.0-61.5) kg and 9.6 (4.4-16.2) L/h, respectively. In 5 out of 7 patients, the dose was reduced from10 to 5 mg/day due to adverse events. Estimated trough concentration at an initial dose in patients treated with 10 mg/day was 19.1 (13.2-35.7) ng/mL, which is higher than the documented target range for renal transplantation patients (3-8 ng/mL). The estimated AUC at an initial dose tended to be higher in patients treated with reduced dose due to adverse events than in other patients (median: 850 vs. 617 ng·h/mL).
CONCLUSION: Large interindividual variability in the EVE PK was observed. Our results suggest that exposure to high EVE concentrations is associated with poor tolerability in Japanese breast cancer patients. Further clinical study is being planned to clarify the PK-PD relationship and identify the target concentration range for breast cancer patients.

LB-005

RELATIVE BIOAVAILABILITY OF A NOVEL ORAL PREDNISONE (PRED) FORMULATION.

N. Dormer[1], J. Moran[2], C. Shoults[1], D. Pierce[3], S. Abdel-Rahman[4], G. Kearns[3]; [1]Orbis Biosciences, Inc., Lenexa, KS, USA, [2]PinPoint Testing, LLC, Little Rock, AR, USA, [3]Arkansas Children's Research Institute, Little Rock, AR, USA, [4]Children's Mercy of Kansas City, Kansas City, MO, USA.

BACKGROUND: Existing PRED formulations have a bitter taste and are plagued by poor palatability and patient acceptance. We have demonstrated superior palatability of a novel microsphere formulation of PRED. We now report on its relative bioavailability (BA).
METHODS: 10 healthy adults (18-23 yr) participated in a 2 period crossover study comparing 10 mg oral doses of PRED microspheres (test or T formulation) to a marketed oral PRED tablet (reference or R formulation) in the fasting state. Blood samples (n=15) were obtained over a 12 hr period and both PRED and prednisolone quantitated using HPLC-MS/MS. C_{max} was estimated visually and AUC was determined via noncompartmental methods.
RESULTS: The log of unadjusted ratios (T/R; 90% confidence limits shown) were used to assess relative bioavailability by current US Food and Drug Administration criteria and confirmed with the difference of the adjusted log values. For both C_{max} and AUC, the

microsphere formulation met relative BA criteria for PRED. For prednisolone, only AUC met criteria for BA. C_{max} was lower (206.9 ± 94.4 vs. 263.4 ± 106.0 ng/mL) and T_{max} delayed (2.9 ± 0.5 vs. 1.8 ± 1.0 hr) in the T relative to the R formulation.
CONCLUSION: Total systemic exposures for PRED and prednisolone from a novel, taste neutral microsphere formulation are equivalent to those achieved after administration of a reference tablet.

BIOAVAILABILITY RESULTS

	PREDNISONE	PREDNISOLONE
	LN(T/R)	LN(T/R)
C_{MAX} (ng/ml)	0.810-1.097	0.647-0.938
AUC_{LAST} (ng/ml*h)	0.919-1.133	0.899-1.081
AUC_{TOT} (ng/ml*h)	0.944-1.180	0.917-1.107

LB-006

PHARMACOKINETICS OF A NEWLY-DEVELOPED ONCE-DAILY SUSTAINED RELEASE OF PREGABALIN: A MULTIPLE-DOSE, RANDOMIZED, OPEN-LABEL, 2-PERIOD CROSSOVER STUDY.

Y. Lim[1], S. Jang[1], W.-S. Na[1], H. Na[1], S. Nam[1], K. Jang[2], J.-Y. Jeon[2], D.-B. Park[2], M.-G. Kim[2]; [1]Yuhan Research Institute, Yuhan Corporation, Seoul, Republic of Korea, [2]Clinical Pharmacology Unit and Biomedical Research Institute, Chonbuk National University Hospital, Jeonju, Republic of Korea.

BACKGROUND: A new sustained release (SR) pregabalin formulation (YHD1119) designed for once-daily dosing has recently been developed to improve patient compliance. This study aimed to compare the pharmacokinetics between pregabalin SR and immediate release (IR) formulation after multiple oral doses in healthy subjects.
METHODS: A randomized, open-label, multiple-dose, two-treatment, two-period crossover study was conducted. Each subject received pregabalin SR 300 mg once-daily or IR 150 mg twice-daily for 3 consecutive days under fed conditions with a 12-day washout period. Blood samples were collected over 24 hours at steady state. Plasma concentrations of pregabalin were measured using LC-MS/MS. The AUC_{tau} and $C_{max,ss}$ for pregabalin were calculated using a noncompartmental method. Bioequivalence was assessed by determining whether 90% confidence intervals (CIs) of the geometric mean ratios (SR/IR) of AUC_{tau} and $C_{max,ss}$ were within 0.8 to 1.25.
RESULTS: A total of 31 healthy subjects completed the study. The mean (standard deviation [SD]) values of AUC_{tau} for SR and IR were 52111.79 (9254.59) and 53351.25 (7197.56) ng·hr/mL, respectively. The mean (SD) values of $C_{max,ss}$ for SR and IR were 4155.16 (703.84) and 3548.06 (490.57) ng/mL, respectively. The geometric mean ratios (90% CIs) were 0.9703 (0.9371-1.0046) for AUC_{tau} and 1.1639 (1.1040-1.2270) for $C_{max,ss}$. No serious AEs were reported and no significant difference in the incidence of AEs between pregabalin SR and pregabalin IR were detected.
CONCLUSION: Once-daily pregabalin SR 300 mg is bioequivalent to twice-daily pregabalin IR 150 mg. The pregabalin SR is expected to improve patient compliance.

LB-007

IDENTIFYING SOMATIC MUTATIONS ASSOCIATED WITH INTRINSIC RESISTANCE TO MULTI-TARGETED TYROSINE KINASE INHIBITORS.

N.K. Gillis; University of North Carolina, Chapel Hill, NC, USA.

BACKGROUND: Approximately 15%-30% of individuals with therapeutic indications for multi-targeted tyrosine kinase inhibitors (TKIs) fail to show even transitory benefit, demonstrating intrinsic resistance (IR). Early identification of inherently resistant tumors is essential to avoid exposure to non-effective therapies and unnecessary toxicities and to guide selection toward other therapies.
METHODS: We conducted a retrospective cohort study to identify somatic mutations associated with IR to multi-targeted TKIs. Adult patients treated with multi-targeted TKIs were classified as intrinsically resistant (progression at 1st imaging follow-up), non-resistant (no progression), or unknown (insufficient follow-up). Targeted exome or whole exome sequencing was performed using tumor FFPE samples (data collection completed 9/7/16 giving insufficient time for analysis by the 9/8 deadline). A candidate gene approach was employed to identify differences in mutations between resistant and non-resistant individuals.
RESULTS: A total of 51 individuals were included (median age 61 yo). The most prevalent tumor type was renal cell (48%). The majority received sorafenib (29%), sunitinib (27%), or pazopanib (41%). Thirty percent demonstrated IR. Median time to drug discontinuation was statistically different between resistant and non-resistant individuals (2.2 vs. 8.5 mo, $p < 0.001$). Five genes (*NTRK1, KDR, TGFBR2, PTPN11,* and *NOTCH2*) were more commonly mutated in resistant individuals (OR = 5.5, insufficient power). These genes have strong biologic plausibility supporting their potential roles in resistance to TKIs.
CONCLUSION: Somatic mutations in multi-targeted TKI drug targets may serve as biomarkers of IR to these agents. Future studies will further explore these associations.

LB-008

PHARMACOKINETICS OF DSTA4637S, AN ANTI-STAPHYLOCOCCUS AUREUS THIOMAB™ ANTIBODY ANTIBIOTIC CONJUGATE, IN HEALTHY VOLUNTEERS.

R. Deng, G. She, M. Carrasco-Triguero, O. Saad, A. Kamath, M. Peck, M. Rothenberg, N. Lewin-Koh, J. Tavel, W. Hanley; Genentech, South San Francisco, CA, USA.

BACKGROUND: DSTA4637S, an innovative THIOMAB™ antibody antibiotic conjugate, contains an anti-*S. aureus* mAb and a novel antibiotic dmDNA31, linked through a protease cleavable linker. It is being developed as a first-in-class therapeutic for patients with serious *S. aureus* infections.
METHODS: The pharmacokinetics (PK) of DSTA4673S was examined in a phase I, randomized, double-blind, placebo-controlled, single-ascending dose study in healthy volunteers (HVs). PK data of three analytes (DSTA4637S conjugate (measured as antibody conjugated dmDNA31, ac-dmDNA31), DSTA4637S total antibody (TAb) and unconjugated dmDNA31) were available from 20 PK evaluable subjects up to 85 days across five dose groups (5, 15, 50, 100 or 150 mg/kg, n=4 /cohort) with a single intravenous administration of DSTA4637S. The non-compartmental PK analysis was performed by Phoenix WinNonlin and finalized on September 26, 2016.
RESULTS: Concentrations of ac-dmDNA31 and TAb declined biphasically after C_{max} was reached at the end of the infusion. ac-dmDNA31 and TAb exhibited dose proportional PK from 5 to 150 mg/kg. For ac-dmDNA31 mean CL, terminal $t_{1/2}$ and V_{ss} ranged from 0.683 to 0.801 L/day (CV%: 8.30 to 22.4), 4.28 to 6.14 days (CV%: 0.50 to 14.4) and 3.82 to 5.31 L (CV%: 10.1 to 27.0). For Tab mean CL, terminal $t_{1/2}$ and V_{ss} ranged from 0.175 to 0.220 L/day (CV%: 5.20 to 30.9), 16.5 to 21.5 days (CV%: 5.90 to 29.6) and 4.51 to 6.06 L (CV%: 10.4 to 24.5). Mean terminal $t_{1/2}$ of unconjugated dmDNA31 (3.93 to 4.28 days) was similar to that of ac-dmDNA31, suggesting that dmDNA31 has the formation rate-limited kinetics. Across the doses unconjugated dmDNA31 exposure was very low, with mean C_{max} ~10000-fold lower than that of ac-dmDNA31.
CONCLUSION: DSTA4637S has acceptable PK profiles in HVs to support further clinical development.

LB-009

POPULATION PHARMACOKINETICS OF GENTAMICIN IN PEDIATRIC PATIENTS WITH CYSTIC FIBROSIS.

Y. Wang[1], X. Liu[1], H.S. Al-Sallami[2], J.T. Zobell[3], K. Korgenski[4], C.M. Sherwin[1]; [1]University of Utah, Salt Lake City, UT, USA, [2]University of Otago, Dunedin, New Zealand, [3]Intermountain Primary Children's Hospital, Salt Lake City, UT, USA, [4]Intermountain Healthcare, Salt Lake City, UT, USA.

BACKGROUND: This study aimed to investigate the potential influences of cystic fibrosis (CF) diagnosis among several other clinically relevant covariates on the pharmacokinetics (PK) of gentamicin (GENT) in pediatric population.
METHODS: The GENT concentration-time data and covariates were retrieved from Enterprise Data Warehouse maintained by Intermountain Healthcare (Data available/analyzed after Sep 30th). Pediatric patients (0-18 years old) from January 2006 to March 2015 received intravenous GENT (≥2 doses). Patients diagnosed with and those without CF but presenting similar demographic features were included. Population PK models were developed using NONMEM. Potential covariates were tested by performing scm in PsN.
RESULTS: A total of 115 observations from 56 patients were pooled for model building. The PK data were best described by a one-compartmental model with an additive error model. The estimated population plasma clearance (CL) (95% CI) was 0.18 L/h (0.16- 0.20 L/h), and volume of distribution (V) was 1.33 L (1.24- 1.42 L), with a between-subject variability of 17.5% and 14.9% (CV %), respectively. Stepwise covariate search returned body weight (BW) and creatinine clearance (CL_{CR}) as significant covariates. A power relationship was assumed relative to median BW and CL_{CR}. $\theta_{CL\text{-}BW}$ (95% CI) $\theta_{CL\text{-}CLCR,}$ and $\theta_{V\text{-}BW}$ were the exponents estimated to be 1.04 (0.93-1.15), 0.29 (0.08-0.49), and 0.81 (0.75-0.86), respectively. Diagnosis with CF was not identified as a significant covariate.
CONCLUSION: The population PK of GENT in current pediatric cohort was best described by a one-compartment model with first-order elimination. No significant differences in PK parameters were detected between patients with and those without CF. BW and CL_{CR} had significant influences on GENT PK.

LB-010

POPULATION PHARMACOKINETIC MODELING AND DOSING REGIMEN OPTIMIZATION OF INTRAVENOUS GENTAMICIN IN PEDIATRIC POPULATION.

Y. Wang[1], X. Liu[1], J. Olson[2], K. Korgenski[2], E.A. Thorell[1], C.M. Sherwin[1]; [1]University of Utah, Salt Lake City, UT, USA, [2]Intermountain Healthcare, Salt Lake City, UT, USA.

BACKGROUND: This study aimed to develop an optimal dosing regimen of intravenous gentamicin (GENT) for pediatric patients based on PK data, simulation, and clinical outcome.
METHODS: Data (available/analyzed after Sep 30th) were collected from pediatric patients (0-18 years old) received GENT (01/2006-03/2015). The popPK model was developed using NONMEM. The GENT peak (1-hr post-infusion) and trough levels after the first and last doses of a 10-day treatment were simulated following 120 different dosing regimens for one set of representative patient characteristics per age group. A Monte Carlo simulation (n=1000) was conducted for each dosing regimen. Criteria for target attainment were defined as 90% of the predicted troughs of ≤ 2 ug/mL and predicted peak: MIC ratio of ≥10. The MIC of GENT for infecting organisms evaluated were 0.5, 1, and 2 mg/L.
RESULTS: Based on predictions from our established popPK model, a dose of 2.5-3.5 mg/kg (MIC=0.5 mg/L), 4-7 mg/kg (MIC=1 mg/L), or 8.5-14 mg/kg (MIC=2 mg/L) of GENT with at least a 24 hr dosing interval should be employed to achieve therapeutic targets.
CONCLUSION: Our simulation results suggest higher doses with an extended dosing interval (24-48hr) to achieve therapeutic targets. Younger patients would require higher weight-adjusted GENT doses to achieve adequate peak and trough levels.

Dosage for single IV gentamicin

	MIC=0.5 mg/L			MIC=1 mg/L			MIC=2 mg/L		
ID	τ=24h, mg/kg	τ=36h, mg/kg	τ=48h, mg/kg	τ=24h, mg/kg	τ=36h, mg/kg	τ=48h, mg/kg	τ=24h, mg/kg	τ=36h, mg/kg	τ=48h, mg/kg
1	3.5	3.5	4	-	7.5	7.5	-	-	14
2	3.5	3.5	4	7	7	7	-	14	14
3	3	3	3	5.5	5.5	5.5	10.5	10.5	10.5
4	2.5	2.5	2.5	4.5	4.5	4.5	8.5	8.5	8.5

Dosage for multiple IV gentamicin, 10-day treatment

	MIC=0.5 mg/L			MIC=1 mg/L			MIC=2 mg/L		
ID	τ=24h, mg/kg	τ=36h, mg/kg	τ=48h, mg/kg	τ=24h, mg/kg	τ=36h, mg/kg	τ=48h, mg/kg	τ=24h, mg/kg	τ=36h, mg/kg	τ=48h, mg/kg
1	3	3.5	3.5	-	6.5	7	-	-	13.5
2	3.5	3.5	3.5	6.5	7	7	-	13.5	14
3	2.5	3	3	5	5.5	5.5	10.5	10.5	10.5
4	2.5	2.5	2.5	4	4.5	4.5	8.5	8.5	8.5

LB-011

DEVELOPMENT OF A PHARMACOKINETIC AND PHARMACODYNAMIC MODEL TO QUANTITATE THE EFFECT OF BIM23B065 ON A GROWTH HORMONE STIMULATION TEST.

M.J. van Esdonk[1], J. Stevens[1], M. Dehez[2], L. Pons[2], F.E. Stuurman[1], W. de Boon[1], P.H. van der Graaf[3], I. Paty[2], J. Burggraaf[1]; [1]Centre for Human Drug Research, Leiden, Netherlands, [2]Ipsen Innovation, 5 Avenue du Canada, 91940, Les Ulis, France, [3]Certara QSP, Canterbury, UK.

BACKGROUND: BIM23B065 belongs to a novel class of chimeric somatostatin-dopamine compounds. This study was performed to quantitate the relationship between the pharmacokinetics (PK) of BIM23B065 and its main metabolite (BIM23B133) and the secretion of growth hormone (GH) during a GH stimulation test (GHST) as a pharmacodynamic (PD) endpoint.
METHODS: A phase I, double-blind, randomized, placebo-controlled study was conducted in 63 healthy male volunteers. The study was performed in two parts; a single ascending dose (part A) with 5 cohorts (0.1 mg, 0.4 mg, 0.8 mg, 1.2 mg and 1.5 mg) and a 13 day multiple ascending dose which included a 6 day up-titration period (part B) with 3 cohorts (1.2 mg q.d., 0.8 mg b.i.d. and 1.0 mg b.i.d.). Each cohort consisted of 8 planned subjects of which 2 received placebo. GHSTs were conducted on day 7 and day 13 of part B. A population PK/PD analysis was performed on 453 plasma BIM23B065-, 589 plasma BIM23B133- and 276 plasma GH concentrations using NONMEM V7.3.
RESULTS: The PK profiles of BIM23B065 and BIM23B133 were best described using a 2-compartment model. The sensitivity to GHRH stimulation was decreased after treatment with BIM23B065. No differences in response to the GHST between the three treatment groups of part B could be identified. The median maximum GH concentrations following GHRH administration, after simulating 1000 individual subjects, was significantly decreased from 37.0 mU/L in non-treated subjects to 6.6 mU/L in treated subjects.
CONCLUSION: Using modeling and simulation techniques, we were able to quantitate the PK and the GH lowering effect of BIM23B065 following a GHST and showed that a maximum effect seems to be reached in all dose groups. Proof of pharmacology was shown here and will be further investigated in patients with excessive growth hormone.

LB-012

KPD VIRAL DYNAMICS MODEL BASED META-ANALYSIS FOR HCV NUCLEOSIDES AND NUCLEOSIDE PRODRUGS.

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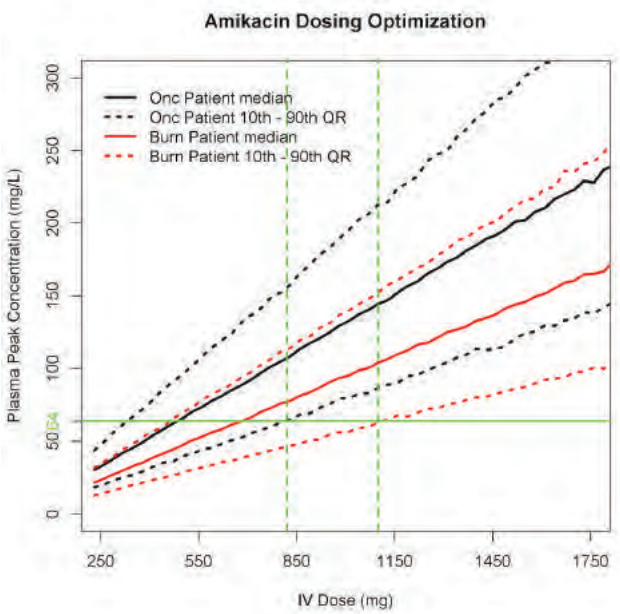
BACKGROUND: Anti-HCV nucleoside inhibitors are a promising therapeutic strategy, but development of this compound class has proven to be challenging. Some compounds have succeeded to achieve high levels of sustained viral response (SVR), while others have failed in the clinic for several different reasons, including a lack of efficacy in proof of concept studies and poor tolerability. Better predictive tools are needed to inform likelihood of success early in development and we present a model based framework for the same.
METHODS: We used a novel KPD-viral dynamics (VD) approach to characterize the curvilinear viral decline profile driven by nucleoside inhibitors. The model uses dose-driven kinetics and effect compartments to describe the delayed action of nucleosides. The clinical viral load decline profiles of 12 nucleosides obtained either from the literature or internal data were investigated for modeling.
RESULTS: Reasonable model fits to the viral load profiles were obtained and the viral system parameter estimates are in general agreement with literature. The viral load profile for each compound was described by a combination of drug-specific parameters i.e., estimated *in vivo* potency, liver decay half-life and lag half-life, each ranging between 4-1700 mg, 3-36 hr and 2-75 hr respectively. These parameters were sufficient to explain the heterogeneity (< 1 log to 5 log drop) in viral-response between compounds.
CONCLUSION: KPD approach is appropriate for nucleosides since the disposition of nucleosides is very complex. Being an intermediate approach between empirical PKPD and mechanistic plasma exposure driven viral dynamic modeling, application of KPD-VD is easily possible for clinical short term viral response assessment to inform likelihood of success and SVR prediction.

LB-013

DOSING OPTIMIZATION OF AMIKACIN IN PEDIATRIC PATIENTS WITH BURN INJURIES AND THOSE WITH ONCOLOGY CONDITIONS.

X. Liu[1], A. Smits[2], Y. Wang[1], S. Wead[3], R. Kagan[4], D. Healy[3], P. De Cock[5], K. Allegaert[2], C. Sherwin[1]; [1]Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA, [2]Neonatal Intensive Care Unit, UZ Leuven, Leuven, Belgium, [3]James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati, OH, USA, [4]The Shriners Hospitals for Children, Cincinnati, OH, USA, [5]Department of Pharmacy, Ghent University Hospital, Ghent, Belgium.

BACKGROUND: Disease status can lead to variable amikacin pharmacokinetics (PK) in children. This study aims to compare amikacin PK in children with burn injuries vs. oncology conditions and propose optimal dosing plans accordingly.
METHODS: PK data from children with burn injuries (group1, n=72, dosed at 10-20 mg/kg/day) and oncology conditions (group2, n=111, 20 mg/kg/day) were used and target C_{max} was determined (available and analyzed 10/30/2016). Population PK models were developed using NM7. Optimal dosing plans for each subpopulation were generated based on Monte Carlo simulation.
RESULTS: The data were best described by a 2-comp PK model with proportional residual error. Stepwise covariate search returned disease status as a significant covariate on central volume and clearance, among weight, age and creatinine clearance. Optimal dosing plans for typical patients (5 years, 20 kg, 120 mL/min per 1.73 m^2, burn vs. oncology) were developed. For single dose, green lines indicate minimal dosage when more than 90% patients reach example target C_{max} of 64 mg/L.



CONCLUSION: Our data suggest that disease-related characteristics besides patient-specific characteristics should be considered when dosing amikacin in critically ill pediatric patients, in order to optimize therapeutic concentration targeting.

LB-014

REGULATION OF UBIQUITINATION AND ACTIVATION OF AKT BY UDP-GLUCURONOSYLTRANSFERASE.

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BACKGROUND: UGT1A1 gene encodes a UDP (uridine diphosphate)-glucuronosyltransferase, an enzyme that transforms small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble, excretable metabolites by glucuronidation. Dysfunction of UGT1A1 induces disordered bilirubin metabolism and caused disease such as Gilbert syndrome. Although it has been extensively studied in drug metabolism, its role in tumor development remains largely unknown. Many cancers have shown a significant upregulation of UGT1A1, however, its role in carcinogenesis is not clear.
METHODS: Immunoprecipitation; Western blot.
RESULTS: UGT1A1 is significantly upregulated in lung cancer (16 fold) and bladder cancer (12 fold) tumors comparing to normal tissues based on the ONCOMINE database. Upregulation of UGT1A1 correlates with poor patients' overall survival. At the molecular level, we found that UGT1A1 positively regulated Akt activity. Specifically, UGT1A1 interacted with both Akt and TRAF6, leading to increased k63-linked ubiquitination of Akt. K63-linked Akt ubiquitination promoted Akt membrane localization and phosphorylation, thus activating Akt signaling pathway. Depletion of UGT1A1 resulted in attenuated interaction between Akt and TRAF6, suppressed Akt activity and decreased cancer cell proliferation.
CONCLUSION: Our studies identify a new role of UGT1A1 in tumor progression. UGT1A1 might function as an adaptor protein, which enhances the interaction between Akt and TRAF6, and boosts TRAF6 mediated ubiquitination and activation of Akt. Patient tumors with the high level of UGT1A1 are correlated with poor survival. Inhibition of UGT1A1 scaffolding function might be a potential strategy for cancer treatment.

LB-015

IMPACT OF ARTEMETHER-LUMEFANTRINE COMPARED TO NON-ARTEMISININS ON MALARIA TRANSMISSION: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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BACKGROUND: Artemisinin-based combination therapy (ACT) is first line for uncomplicated falciparum malaria due to its activity against multidrug resistant parasites. ACT disrupts transmission through an antigametocyte effect. The extent of this effect is uncertain.
METHODS: We searched PubMed, CENTRAL, and ClinicalTrials.gov for relevant studies. We included randomized controlled trials comparing artemether-lumefantrine (AL), the most widely deployed ACT, to non-ACTs. The primary outcomes were proportion of infectious mosquitoes in feeding studies and proportion of individuals with circulating gametocytes following AL for uncomplicated falciparum malaria. Analyses concluded in November, 2016.
RESULTS: 7,602 records were identified and 21 studies were eligible for inclusion. Most studies were conducted in sub-Saharan Africa (16 of 21) in children <5 yo. The most common non-ACT regimens were combinations of amodiaquine, chloroquine, sulfadoxine-pyrimethamine, and quinine. 2 trials carried out mosquito feeding studies to assess human-to-mosquito transmission. Both demonstrated a consistent effect favoring AL over non-ACT regimens with an OR 0.06 (95%CI: 0.00-0.99) at 7 days post-treatment and OR 0.56 (95%CI: 0.36-0.88) at 14 days. The pooled effect estimate for the proportion of AL-treated compared to non-ACT-treated study participants with circulating gametocytes at 7 days was OR 0.10 (95%CI: 0.06-0.17; I^2: 55%).
CONCLUSION: AL is markedly superior to non-ACT containing regimens for reducing

gametocyte carriage in patients with uncomplicated falciparum malaria. The transmission-limiting benefit of AL has relevance for policymakers planning optimal utilization of control strategies, including use for malaria prevention.

LB-016

EVALUATION OF HUMANIZED OATP1B1/1B3 MICE AND CYNOMOLGUS MONKEYS FOR PREDICTING PRAVASTATIN TRANSPORTER MEDIATED DRUG-DRUG INTERACTIONS.

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BACKGROUND: Organic anion transporting peptides (OATPs) contribute to the hepatic elimination of statins, and the inhibition of OATPs alters statins pharmacokinetics in the clinic. Regulatory agencies recommend conducting *in vitro* OATP inhibition studies for new drugs and provide decision trees for when clinical drug-drug interaction (DDI) studies should be conducted based on *in vitro* data. This study assesses and compares the utility of humanized OATP1B1/1B3 mice and cynomolgus monkeys as *in vivo* preclinical models in predicting the effect of OATP inhibition on the disposition of pravastatin in human.
METHODS: The inhibition of OATP1B1/1B3-mediated probe substrates transport by cyclosporine and rifampicin was assessed *in vitro* in cells expressing human or cynomolgus monkey (cyno) OATP1B1/1B3 (The data were analyzed on November 1st). *In vivo* studies were conducted in humanized OATP1B1/1B3 mice and cynomolgus monkeys receiving pravastatin orally alone or with inhibitors.
RESULTS: Rifampicin inhibited human OATP1B1, OATP1B3, cyno OATP1B1, and OATP1B3 mediated transport *in vitro* with IC_{50} values of 0.83, 1.83, 0.51, and 2.89 μM. Cyclosporine inhibited cyno OATP1B1 and OATP1B3 transport with IC_{50} values of 0.34 and 0.37 μM. In the humanized mice study, no significant change was observed in pravastatin dosed alone or with rifampicin (AUC: 0.67 ± 0.27 vs. 0.76 ± 0.25 μM·h; C_{max}: 0.64 ± 0.48 vs. 0.67 ± 0.23 μM). In cynomolgus monkey, AUC and C_{max} of pravastatin increased 22- and 36-fold when dosed with rifampicin, and 8- and 6-fold when dosed with cyclosporine.
CONCLUSION: Altered pravastatin disposition with OATP inhibitors in cynomolgus monkeys suggests the potential of the model to predict human DDI. However, the data suggests humanized mice may not be suitable for assessing OATP mediated DDI.

LB-017

HUMAN PHYSIOME ON A CHIP: APPLICATION OF MULTI-ORGAN *IN VITRO* PLATFORMS FOR QUANTITATIVE PHARMACOKINETIC INVESTIGATIONS.

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BACKGROUND: Investigation of the pharmacokinetics (PK) of a compound is of significant importance during the early stages of drug development. Recently, the need for more physiologically realistic *in vitro* models has fueled the emerging field of tissue engineered 3D cultures, also referred to as organs-on-chips, or MicroPhysiological Systems (MPS). We have lately developed fluidic platforms that can link multiple organ MPS together, allowing collection of high-content data for quantitative PK investigations.
METHODS: Diclofenac (DCF) PK were studied in a fluidic platform that interconnects a gut and a liver MPS. Several experiments were performed and PK data were collected in order to quantitatively characterize intestinal permeability and gut/liver metabolism and investigate the effect of gut-liver interaction on these processes. The PK of DCF were also investigated in a platform that housed 7 inter-connected organ MPS together (gut, liver, pancreas, lung, heart, brain and endometrium). Physiologically-based PK (PBPK) modeling was employed for the analysis of all the emerging in this work data (could not be analyzed before 9/8/2016, analysis finished at 11/4/2016).
RESULTS: In both the gut-liver and the 7-MPS experiments, DCF was absorbed across the gut epithelial barrier, distributed to the liver MPS and subsequently to a mixing chamber (that mimics

systemic circulation). DCF and its primary metabolite (4-OH-DCF) were detected across all the interacting organ MPS compartments. PBPK model predictions aligned well with the experimental data. Data analysis illustrated that DCF hepatic metabolism can be modulated after gut-liver interaction/crosstalk.
CONCLUSION: This work clearly illustrates the potential of multi-MPS technologies for quantitative PK investigations.

LB-018

A VALIDATED LC-MS/MS ASSAY TO MEASURE GANGLIOSIDE GD_2 AS A BIOMARKER FOR CHILDHOOD NEUROBLASTOMA.

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BACKGROUND: Gangliosides are found in the nervous system, where they account for ~10% of membrane lipid content. Ganglioside GD_2 is expressed on the surface of neuroblastoma (NBL), osteosarcoma and other tumors. Our aim is to develop a clinically validated assay to quantify GD_2 in plasma and serum for use as a tumor biomarker in NBL and other diseases where GD_2 is expressed.
METHODS: Plasma/serum standards spiked between 1-2500 ng/mL by serial dilution, QC samples prepared between 8-1600 ng/mL, and unknowns were extracted with 240 µL of MEOH containing 25 ng/mL internal standard. Supernatants were transferred to a 96 well plate and 10 µL were injected onto column. Two isoforms (fatty acid chains of 18 and 20 carbons) with m/z of 836 and 850 were measured using LC-MS/MS in negative ion mode.
RESULTS: Our assay was validated according to US Food and Drug Administration Guidelines with LLOQ of 10 ng/mL and matrix-based standard curve linear to 2500 ng/mL for both isoforms. Stability studies of QC samples showed GD_2 was stable at room temperature for at least 4 h and at -80 °C for at least 1 month. GD_2 was stable after 3 freeze/thaw cycles. We measured GD_2 concentration in serum samples from 4 children with high-risk NBL, ranging from 339-3080 ng/mL for C_{18} isoform and 17-95 ng/mL for C_{20} isoform.
CONCLUSION: We have developed a fully validated LC-MS/MS assay to measure the C_{18} and C_{20} isoforms of GD_2 in human plasma and serum. We demonstrated that GD_2 can be measured in patient samples using this assay. In future studies, GD_2 levels will be evaluated as tumor biomarker in patients with NBL to document the range of plasma GD_2 concentrations and correlate GD_2 level with tumor burden, determine effect of treatment on plasma GD_2 concentration, and correlate change in GD_2 concentration with response to treatment measured from imaging studies or histology.

LB-019

THE RELIABILITY OF HISTAMINE RESPONSE PHENOTYPE CLASSIFICATION: A POPULATION MODELING APPROACH.

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BACKGROUND: Previously we described histamine pharmacodynamic response phenotypes via histamine iontophoresis with laser Doppler (HILD)[1]. Histamine response phenotype may be important in guiding therapy for children with allergic/inflammatory disease. Therefore, we aimed to determine the reliability of phenotype classification within the same individual.
METHODS: HILD was performed per previously published method[1] in 19 children with allergic rhinitis on 2-3 separate occasions using convenience sampling. Response-time data were analyzed in NONMEM using a linked effect PKPD model (available and analyzed after 09/21/16). Hypo-, neutro- and hyper- response phenotypes were classified by examination of observed vs. predicted response plots and sum of residuals (predicted response minus observed response). Phenotype classification were assessed with test-retest reliability

statistic; interclass correlation coefficient (ICC).
RESULTS: Eleven children had evaluable data for more than one HILD test. All children with 3 tests (n=4/4) and most children with 2 tests (n=5/7) had consistent phenotype classification. Of the two children with altered phenotypes one child went from hyper- to hypo-response (sum of residuals +371 to -341), the second child went from hypo- to hyper-response (sum of residuals -125 to +250). The reliability of the phenotype classification was acceptable with an ICC of 0.77 (95% CI 0.44 - 0.93).
CONCLUSION: These preliminary results suggest HILD response phenotype classification is reliable in children with allergic rhinitis. Further exploration is needed to determine reliability in a larger cohort, contributions to changes in phenotype, and association between response phenotype and therapeutic response. [1] Jones *et al.*, (2013). JCP 53(7): 731-7.

LB-020

PREDICTING *IN VIVO* HEPATIC CLEARANCE FROM *IN VITRO* MICROSOMAL MEASURES.

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BACKGROUND: *In vitro* measures of drug metabolic clearance in human liver tissue do not adequately predict *in vivo* human drug metabolic clearance and we don't know why. Comparison between predicted and observed human metabolic clearance values indicate that *in vitro* metabolic clearance obtained from human liver microsomes under predict *in vivo* metabolic clearance on average by ~9 fold.
METHODS: Examining the basis for IVIVE predictions reveals that the liver was assumed to function as a homogeneous, rather than a heterologous environment composed of both aqueous and lipid components into which drugs distribute differentially. A new theoretical relationship is derived for BDDCS Class 1 drugs where transporter effects would be insignificant.
RESULTS: The equation describing the relationship between the *in vivo* hepatic clearance and the *in vitro* intrinsic clearance measured in a microsomal incubation includes a term $R_{ss,uu}$, the ratio of the steady-state unbound drug concentration *in vivo* in the hepatocyte water in contact with the enzyme to the average steady-state unbound concentration in whole liver. $R_{ss,uu}$ varies significantly from drug to drug and thus no universal IVIVE scaling factor will give successful predictions. At present, no methodology adequately predicts $R_{ss,uu}$. However, since it is a function of drug distribution within the liver and liver physiological characteristics (but not necessarily metabolic capacity and specificity), a drug's $R_{ss,uu}$ is expected to be similar across mammals and the IVIVE scaling factor in an animal model is expected to be relevant for humans. Human IVIVE for 7 drugs studied in rats and 6 drugs in dogs confirm this hypothesis.
DISCUSSION: The rationale for the poor and variable IVIVE predictions is presented together with a methodology to solve this problem.

LB-021

PARASITE CLEARANCE AND DRUG EFFICACY OF ARTEMETHER-LUMEFANTRINE FOR CHILDREN WITH UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA IN NORTHERN ZAMBIA.

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BACKGROUND: Case management of uncomplicated falciparum malaria with artemether-lumefantrine (AL) is a key component of malaria control in Zambia. Elucidation of local parasite dynamics and surveillance for drug resistance are pivotal to ensure continued progress.
METHODS: Single arm trial of AL for uncomplicated malaria in Zambia. Children aged 6-59 months were treated and followed for 5 weeks. Outcomes were parasite clearance rate and adequate clinical and parasitological response (ACPR). Parasite genotyping is ongoing as of September 8, 2016 with preliminary data available.
RESULTS: 100 children were enrolled between December 2014-July 2015 and treated with AL. Median age was 24.5 mo (IQR 16-42 mo). 81 children completed 35 day follow up. All parasites cleared by 72 hours, indicating absence of resistance. The median parasite clearance rate constant was 0.22 hr^{-1} (IQR 0.17-0.27 hr^{-1}). PCR-corrected ACPR was >90%, exceeding the threshold for drug efficacy. Assays of day 7 samples for lumefantrine concentrations are underway as input to a PD analysis.
CONCLUSION: AL remains effective for uncomplicated falciparum malaria in Nchelenge District. The estimated parasite clearance rate constant was consistent with previously reported values. Day 7 lumefantrine levels may correlate with protection against recurrent episodes.

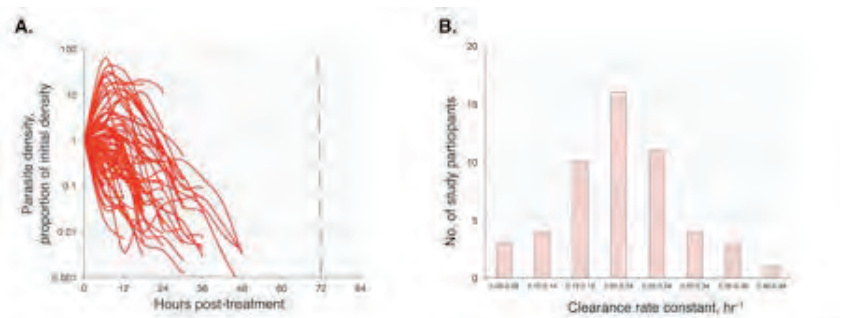

Figure 1. Parasite clearance curves, and distribution of parasite clearance rate constants, in children with uncomplicated *Pf* malaria treated with artemether-lumefantrine in Nchelenge District, Luapula Province, Zambia. **A.** Parasite clearance curves normalized to initial parasite density. 96% of participants cleared by 48 hours, and all cleared by 72 hours. **B.** Distribution of parasite clearance rate constants of parasite clearance curves (median: 0.22 hr^{-1}, IQR: 0.17-0.27 hr^{-1}).

LB-022

PHARMACOMETABOLOMIC APPROACHES FOR METFORMIN RESPONSE IN EARLY PHASE TYPE 2 DIABETES MELLITUS PATIENTS.

J.-E. Park[1], G.-H. Jung[2], I.-K. Lee[3], Y.-R. Yoon[4], **K.-H. Shin**[1]; [1]Kyungpook National University, Daegu, Republic of Korea, [2]Department of Internal Medicine, Changwon Fatima Hospital, Changwon, Republic of Korea, [3]Department of Endocrinology, Kyungpook National University Hospital, Daegu, Republic of Korea, [4]4Department of Biomedical Science, BK21 Plus KNU Bio-Medical Convergence Program for Creative Talent, Cell and Matrix Research Institute and Clinical Trial Center, Kyungpook National University Graduate School and Hospital, Daegu, Republic of Korea.

BACKGROUND: Metformin, a first line therapy for type 2 diabetes mellitus (T2DM), is known to improve insulin sensitivity and reduce gluconeogenesis in liver; however, little is known about biomarkers for metabolic changes or considerable variations in drug response in metformin treated patients. This study was aimed to determine metabolomics markers for metformin response in terms of mechanism and inter-individual variation.
METHODS: Twenty seven T2DM patients were enrolled and administered daily oral metformin for 6 months study periods. They were defined responders or non-responders according to the HbA1c changes in 3 months from baseline values. Blood and urine samples were collected before and 3 month and 6 month after drug starts. Urinary metabolites profiled by GC-MS and analyzed by multivariate statistical analysis using SIMCA 13. The significant metabolites were evaluated with ROC curves.
RESULTS: A total of 470 peaks detected and finally 11 candidates were listed. Among them three candidates were significantly downregulated in non-response group; citric acid (-139.79%), pseudouridine (-73910.60%) and hypoxanthine (-115.51%), and myoinositol (15.47%) was upregulated in the responders. The citric acid and pseudouridine were considered as potential predictable markers which showed 0.708 and 0.889 of AUC in ROC curve, respectively.
CONCLUSION: We found different metabolic profiles between responders and non-responders with pharmacometabolomic approach. These approaches might be helpful for development potential biomarkers for the drug response and inter-individual variability.

LB-023

PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION CAN GREATLY BENEFIT FROM A NOVEL ONCE-DAILY INTRAVENOUS BUSULFAN DOSING NOMOGRAM.

S.-J. Rhee[1], J. Lee[2], K.-S. Yu[1], I.-J. Jang[1], K. Hong[2], J. Choi[2], C. Hong[2], K. Park[2], H. Shin[2], S. Song[3], H. Kang[2], H. Lee[1]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [3]Department of Laboratory Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.

BACKGROUND: Busulfan, a bifunctional alkylating agent, has been used as a conditioning regimen prior to allogeneic hematopoietic stem cell transplantation (HSCT). The aims of this study were to derive a novel once-daily intravenous (IV) busulfan dosing nomogram for pediatric patients undergoing HSCT using a population pharmacokinetic (PK) model.
METHODS: A population PK analysis was performed using 2,183 busulfan concentrations in 137 pediatric patients (age: 0.6 - 22.2 years), who received IV busulfan once-daily for 4 days before undergoing HSCT. Based on the final population PK model, an optimal once-daily IV busulfan dosing nomogram was derived. The percentage of simulated patients achieving the daily target area under the concentration-time curve (AUC) by the new nomogram was compared with that by other busulfan dosing regimens. The data analysis was ongoing before September 8, 2016 and the results has been obtained after October 11, 2016.

RESULTS: A one-compartment open linear PK model incorporating patient's body surface area, age, dosing day, and aspartate aminotransferase as a significant covariate adequately described the concentration-time profiles of busulfan. An optimal dosing nomogram based on the PK model performed significantly better than the other dosing regimens, resulting in >60% of patients achieving the target AUC while the percentage of patients exceeding the toxic AUC level was kept minimal at <25% during the entire treatment period.
CONCLUSION: A novel once-daily busulfan dosing nomogram for pediatric patients undergoing HSCT is useful for clinicians, particularly in a setting where therapeutic drug monitoring service is not readily available.

LB-024

ON EARLY PEDIATRIC STUDY DESIGN: SAMPLE SIZE CALCULATION USING PBPK APPROACH WITHIN THE SIMCYP SIMULATOR.

K. Abduljalil, T. Johnson, **F. Salem**, M. Jamei; Simcyp, Sheffield, UK.

BACKGROUND: The PBPK approach provides the possibility to predict PK parameters and their variability within a population making it feasible to calculate the power of early clinical studies in children. The Aim of this work is to investigate the impact of UGT1A1 phenotypes on required sample size in children at different ages.
METHODS: A hypothetical Compound was used with elimination pathways of 75% liver UGT1A1, 1% Renal UGT1A1 in healthy adult volunteers. The Simcyp Pediatric Simulator V15R1 was used to generate three populations at 0.5, 5 and 20 years old subjects with 200 virtual subjects in each group using the default UGT1A1 polymorphisms, abundances and ontogeny. Extrapolated AUC_{-INF} were used as the PK parameter of interest. Two designs were considered, where either ages or age and UGT1A1 polymorphisms were set as entry criteria.
RESULTS: Calculations show that a study power of 80% can be achieved between 20-25 years adult and the 0.5 year population with about 30 subjects recruited randomly per arm. However for the 5 years old children, only 52% of study power can be achieved by recruiting 30 subjects. In the second scenario, where children phenotypes were considered, there were differences within the pediatric age group in sample size depending on their phenotypes. In relation to EM as the reference group, at the age of 0.5 year, about 50 PM subjects are required to reach 80% power, compared with 35 PM subjects in older children to reach the same level of power.
CONCLUSION: The calculated sample size in adult cannot be extrapolated to children, even for matched phenotypes as the net variability that drives the differences in children is a mixture of all system parameters, rather than the abundance or its associated variability for each phenotype.

LB-025

REGORAFENIB: A DDI-CASE-STUDY ON A BCRP-SPECIFIC EFFECT.

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BACKGROUND: Regorafenib is an oral multikinase inhibitor which has high efficacy in patients with gastrointestinal stroma tumors (GIST) and in metastatic colorectal cancer (mCRC). M-2 and M-5, the major metabolites, are pharmacologically active and showed similar kinase inhibition profiles. Therefore the inhibitory profile of regorafenib and the two metabolites at various transporters was evaluated.
METHODS: The inhibitory properties were investigated *in vitro* in cells overexpressing various human transporters. Two clinical DDI-studies were performed in a cancer patient population. Patients received either a single dose of 5 mg rosuvastatin or 0.5 mg digoxin prior to the start of the regorafenib treatment-cycle. On day 15 after the start of a 160 mg OD regorafenib-treatment another dose of rosuvastatin was administered and PK-samples were collected.
RESULTS: Regorafenib, M-2 and M-5 are potent inhibitors towards BCRP with IC_{50} values of 0.045 µM (regorafenib), 0.39 µM (M-2) and 0.15 µM (M-5). To a lesser extent regorafenib and M-2 exhibited also inhibitory potential towards P-gp (IC_{50} = 2.2 µM, 1.5 µM). According to guidelines by regulatory agencies two clinical drug-drug interaction studies were performed to evaluate the risk associated with P-gp and BCRP inhibition. Regorafenib did not influence C_{max} or AUC values of digoxin. In contrast, a 4.6-fold C_{max}-increase and a 3.9-fold AUC-increase were observed with rosuvastatin as victim drug.
CONCLUSION: Based on these results a clinical DDI involving P-gp with regorafenib as perpetrator is unlikely. However, a DDI involving BCRP was observed. These results show that BCRP-selective DDIs can result in significant AUC and C_{max} changes. The observed magnitude of the DDI-effect towards BCRP is above the predicted value.

LB-026

POPULATION PHARMACOKINETICS (POPPK) OF UMECLIDINIUM (UMEC) FOLLOWING AXILLARY ADMINISTRATION TO HEALTHY SUBJECTS (HS) AND HYPERHIDROSIS PATIENTS (HHP).

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BACKGROUND: UMEC, a long-acting muscarinic antagonist approved for chronic obstructive pulmonary disease (COPD), is being tested for primary hyperhidrosis. Our objectives were to model the PopPK of topical 1.85% (w/w) UMEC and to predict the adequacy of steady-state (SS) exposure at expected topical doses relative to that from the approved inhaled (INH) COPD dose of 62.5 mcg.
METHODS: A total of 29 subjects from 2 single dose IV or dermal studies in HS, and 1 repeat dose study in HHP were included in the analysis (GSK studies 117151, 202093, 4112008). PopPK modeling and covariate analysis were performed in NONMEM 7.3. Model selection was based on the objective function value, parameter estimate plausibility, diagnostic plots, and small relative standard error (RSE). Sensitivity analyses were performed to fix parameters with large RSE. Assuming dose linearity, the final model was used to simulate 500 SS plasma concentration profiles after daily and every other day topical administration of 5 formulation strengths (0.1, 0.25, 0.65, 1.15, and 1.85% w/w). AUC_{24} and AUC_{48} were calculated and compared to AUC of the 62.5 mcg INH dose.
RESULTS: The final model was a 2-compartment PK model with sequential zero-order followed by a 1st -order absorption process and linear elimination. No significant covariates were identified. The typical parameter values were: CL = 53.2 L/h, V1 = 7.44 L, Q = 43.1 L/h, V2 = 333 L, Ka = 0.012 h^{-1}, LAG = 2.56 h, $F_{absolute}$ = 0.0064, F2 (fraction of dose absorbed by zero-order process) = 0.119. The predicted SS exposure of topical UMEC was lower than after INH doses in all scenarios.
CONCLUSION: The predicted SS exposures for various topical regimens were less than that from the INH 62.5 mcg dose. The results are critical for selection of the phase IIB dose in HHP.

LB-027
Abstract presentation number not assigned.

LB-028
USE OF SYSTEMS TOXICOLOGY MODELING TO INVESTIGATE MECHANISMS OF LIVER ENZYME ELEVATIONS MEDIATED BY SOLITHROMYCIN AND OTHER MACROLIDES.

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BACKGROUND: Solithromycin (Soli), a 4th generation macrolide developed for the treatment of community acquired pneumonia, caused serum liver enzyme (ALT) elevations in clinical studies. A quantitative systems toxicology (QST) tool, DILIsym, was used to predict the occurrence and mechanisms of ALT elevations for Soli, erythromycin (Ery), clarithromycin (Clari), and telithromycin (Teli).
METHODS: *In vitro* assays were performed to assess effects of the macrolides on bile acid (BA) transport, mitochondrial function, and oxidative stress. These data were integrated with *in vivo* exposure using DILIsym; serum ALT responses were predicted in a simulated human population. (Teli/Clari work performed Sep-Oct, 2016).
RESULTS: DILIsym reasonably predicted the incidence of ALT elevations observed for Soli, Ery, and Clari; the predominant mechanism was reversible mitochondrial electron transport chain (ETC) inhibition for Soli and Clari, and BA transport inhibition for Ery (**Table 1**). ALT elevations by Teli were only predicted at the highest observed exposure combined with noncompetitive inhibition of BA transporters.
CONCLUSION: Mechanisms for ALT elevations vary among macrolides and Soli is similar to Clari in this regard. The simulation results were presented to the US Food and Drug Administration Ad Com for Soli on 11/4/16, a first to our knowledge for QST.

TABLE 1. Observed and simulated frequencies of ALT elevations and mechanisms for macrolides.

COMPOUND	PROTOCOL	OBSERVED peak ALT > 3X Upper Limit of Normal (ULN)	SIMULATED peak ALT > 3X ULN	PREDICTED Hy's Law Cases (ALT/AST >3xULN and Bilirubin >2xULN)	PREDOMINANT mechanism	MINOR mechanism
Solithromycin	ORAL (800 mg QD on day 1, 400 mg QD on days 2-5)	5.4% (22/411,all patients); 2.8% among patients with normal baseline ALT	3.9% (11/285)	0%	ETC inhibition	BA transporter inhibition
Solithromycin	IV-TO-ORAL (IV 400 mg on days 1-3, PO 800 mg QD on day 4, PO 400 mg QD on days 5-7)	9.1% (38/417, all patients); 6.6% among patients with normal baseline ALT	6.0% (17/285)	0%	ETC inhibition	BA transporter inhibition
Erythromycin	PO 500 mg QID 10 days	1-2%	2.8% (8/285)	0%	BA transporter inhibition	OXIDATIVE stress
Clarithromycin	PO 500 mg BID 7 days	1-2%	2.8% (8/285)	0%	ETC inhibition	BA transporter inhibition
Telithromycin	PO 800 mg QD 10 days	~0.5%	0%	0%	-	BA transporter inhibition

LB-029

RATES OF ALCOHOL BINGE EXPOSURE AS A RISK FACTOR FOR ALCOHOL USE DISORDER: A TIME TO EVENT ANALYSIS.

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BACKGROUND: Although several risk factors have been identified for alcohol use disorder (AUD), many individuals with these factors do not develop AUD. Identifying early phenotypic differences between vulnerable individuals and healthy controls could help identify those at higher risk. An important factor, the rate of alcohol consumption, particularly to binge levels of exposure, has received little attention. Using a carefully controlled experimental paradigm, we tested the hypothesis that risk factors for AUD, including family history of alcoholism, male sex, impulsivity, and low level of response to alcohol, would predict a faster rate of consumption.
METHODS: This cross-sectional study included 159 young social drinkers who completed a laboratory session in which they self-administered alcohol intravenously. Cox proportional hazards models were used to determine whether risk factors for AUD were associated with the rate of achieving a binge-level exposure, defined as a breath alcohol concentration above 80mg%, during the session.
RESULTS: Greater number of relatives with alcoholism (hazard ratio=1.04, 95% CI 1.02 to 1.07), male sex (hazard ratio=1.74, 95% CI 1.03 to 2.93), and higher impulsivity (hazard ratio=1.17, 95% CI 1.00 to 1.37), were all associated with a higher rate of binging throughout the session. Participants with all 3 risk factors had the highest rate of binging throughout the session compared to the lowest risk group (hazard ratio=5.27, 95% CI 1.81 to 15.30).
CONCLUSION: Rapid consumption of alcohol to binge levels may be an early indicator of AUD vulnerability and should be evaluated as part of a thorough clinical assessment.

LB-030

EVALUATION OF DRUG-DRUG INTERACTIONS (DDIS) FOR DRUGS EXHIBITING TIME-DEPENDENT INHIBITION (TDI): A CASE STUDY OF CRIZOTINIB.

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BACKGROUND: There are challenges with evaluating DDIs for oncology drugs exhibiting TDI. Crizotinib (CRZ), a targeted therapy for ALK(+)/ROS1(+) non-small cell lung cancer, is primarily metabolized via CYP3A. It is also a time-dependent CYP3A inhibitor as well as an inducer. A study in healthy volunteers showed that co-administration with a strong CYP3A inhibitor (ketoconazole) resulted in a 320% increase in AUC_{inf} after a single 150 mg CRZ dose. The current study was conducted to estimate the effect of a strong CYP3A inhibitor on CRZ AUC_{ss} after multiple dosing in patients with solid tumors.
METHODS: Patients were given CRZ 250 mg QD and itraconazole (ITZ) 200 mg QD from Days 1 to 16, followed by CRZ 250 mg QD alone from Days 16 to 29. Pharmacokinetics (PK) of CRZ and its metabolite were characterized on Day 15 and 29. Plasma concentrations of ITZ and its metabolites were also measured. A mixed effect model was used to estimate the effect of ITZ on CRZ AUC_{ss}. To compare with the clinical observation, the effect of ITZ on CRZ AUC_{ss} was predicted using net effect equations incorporating single-dose CRZ PK with *in vitro* CYP3A TDI and induction by CRZ, and reversible CYP3A inhibition by ITZ and its metabolites.
RESULTS: Data from 11 patients indicated that co-administered ITZ increased CRZ AUCss by 57%, which was similar to the model-predicted effect (~ 60% increase in CRZ AUC_{ss}).
CONCLUSION: The effect of strong CYP3A inhibitor on multiple-dose CRZ AUC_{ss} was weaker than the effect on single-dose CRZ AUC_{inf}. This can be explained by our model, where non-CYP3A metabolism pathways become more dominant in CRZ metabolism due to auto-inhibition of CYP3A as observed after multiple-dosing of CRZ. The reliable prediction for the net effect of a CYP3A inhibitor on a TDI drug may obviate the need to conduct multiple-dose DDI studies.

LB-031

POPULATION PHARMACOKINETIC MODEL FOR VANCOMYCIN IN PEDIATRIC BURN PATIENTS.

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BACKGROUND: Morbidity and mortality caused by infection in burn patients can be prevented in part by proper dosing of antibiotics such as vancomycin. However, optimizing vancomycin dosing is challenging in special populations such as pediatric burn patients. A pharmacokinetic (PK) model of vancomycin utilizing burn patient-specific parameters can aid in dosing and improve patient outcomes.
METHODS: A retrospective study analyzed 115 pediatric burn patients aged 0.17 to 18 years at Shriners Hospital for Children in Cincinnati, Ohio. Samples were taken between January 2007 and December 2009; analysis was completed in November 2016. Vancomycin was administered via an IV bolus and blood samples were taken prior to subsequent dose administration, between 6 and 12 hours after the IV bolus. Population pharmacokinetics among patients were then determined using a single trough sampling approach. A PK model was developed using Monolix standalone version 2016R1. The covariate model was selected based on statistically significant improvements of Objective Function Values (OFV) and visual inspection of diagnostic plots.
RESULTS: A one compartment model was used to estimate steady state distribution volume. The mean population volume and clearance were calculated to be 0.821 L/h (95%CI 0.661-0.985) and 0.124 L/h/kg (95%CI 0.110-0.138) respectively. All three covariates included in the model were centered relative to their median values. The distribution volume was found to be dependent on weight, while vancomycin clearance was influenced by age and creatinine clearance.
CONCLUSION: A dosing regimen for pediatric burn patients which considers patient weight, age and creatinine clearance can potentially be used to achieve desired vancomycin trough levels and recommended AUC/MIC ratios ≥ 400.

LB-032

FULLY DIFFERENTIATED SH-SY5Y CELLS AS AN *IN VITRO* MODEL TO ASSESS PACLITAXEL-INDUCED PERIPHERAL NEUROPATHY.

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BACKGROUND: Paclitaxel-induced peripheral neuropathy (PIPN)is a common and dose-limiting toxicity in the treatment of cancer. We aimed to establish an *in vitro* model for this toxicity using a widely available human cell line and investigated the effect of paclitaxel on these cells.
METHODS: SH-SY5Y cells were differentiated sequentially by 5 days treatment with 10 µM retinoic acid followed by 5 days treatment with 10 ng/ml BDNF. Immunocytochemistry revealed that this led to fully differentiated SH-SY5Y cells expressing the neuronal markers TUJ1 and MAP2. All subsequent experiments were performed on fully differentiated SH-SY5Y cells. Paclitaxel toxicity was assessed using a CellTiter-Glo assay. Mitochondrial membrane potential was investigated using a JC-10 assay. mRNA expression of EPHA family members(EPHA3/5/10) and the TRP channels (TRPV1 and TRPA1) was measured at different dosesof paclitaxel (1µM, 5µM, 10µM, 50µM). Calcium imaging was performed on Nikon Time Lapse epifluorescence microscope to reflect global calcium change caused by paclitaxel.

RESULTS: Fully differentiated SH-SY5Y cellsexpressTUJ1, EPHA10 and TRPV1; EPHA3 and 5 expression were not detected. We observed a trend of increased expression of TRPV1 in response to increasing paclitaxel concentrations. Calcium imaging confirmed that 10 µM paclitaxel could induce cytosolic calcium oscillations on differentiated SH-SY5Y cells. Mitochondrial membrane potential also changed in response to increasing paclitaxel concentrations.
CONCLUSION: We show that SH-SY5Y cells can be an easy and convenient tool to study PIPN. This model can be used to examine the molecular mechanism of PIPN and may help devise new strategies for the management of this common and problematic side effect.

LB-033

CHILDREN AT RISK OF SUBOPTIMAL DOSING OF ORAL PARACETAMOL? RESULTS OF A PEDIATRIC ORAL BIOAVAILABILITY MICRO DOSING STUDY.

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BACKGROUND: APAP is one of the most commonly used analgesic and antipyretic drugs in children but surprisingly its oral bioavailability (F) has never been determined in children. Based on adult studies, nearly complete bioavailability has traditionally been assumed, but comparing pediatric data from separate oral and IV pharmacokinetic (PK) studies suggest F around 70%. The aim of this study is to determine oral bioavailability of paracetamol and its interindividual variability using a microdosing study in pediatric patients.
METHODS: Oral bioavailability microdosing population PK study Participants: patients < 6 yrs old admitted to pediatric ICU and receiving therapeutic APAP iv 15 mg/kg. Intervention: a single microdose (3 µg/kg) of [^{14}C] paracetamol given orally at the same time as iv therapeutic dose Data collection: Blood was sampled for PK analysis, 8 times up to 24h post dose. Data analysis: Analysis of cold APAP was done with LC-MS and [^{14}C] APAP with AMS. LC-MS results became available summer 2016, after which NONMEM PK analysis was performed to estimate PK, to finish early November.
RESULTS: In 47 patients with median age: 6.8 (IQR 2-21) months, mean population oral bioavailability was 72% (range 12% to 90%). Bodyweight was the best predictor of clearance and volume of distribution. There was no significant effect of age on F. Median body weight was 7.4 kg (range 2 to 23kg) corresponding to a population clearance and volume of distribution from 0.51 L/h to 6.62 L/h and from 3L to 21L respectively. All internal validation steps of the model were successful.
CONCLUSION: We describe a successful oral bioavailability study using [^{14}C] microdosing in children. APAP F is lower than usually assumed, with a large variability. This puts children. at risk of therapy failure with oral APAP.

LB-034

CANCER INCIDENCE AFTER RADIOIODINE TREATMENT FOR HYPERTHYROIDISM.

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BACKGROUND: Concerns had been raised about cancer risk associated with radioactive iodine treatment for benign thyroid disease.
METHODS: Using the database of Clalit Health Services, the largest HMO in Israel, we carried out an historical cohort study of all patients newly diagnosed with benign thyroid disease since 1.1.2002, who have been treated with an oral thionamide or radioiodine treatment. We followed them until July 2016. We performed a time-dependent multivariable cox regression analysis for the association of any new diagnosis of cancer, to radioiodine treatment exposure.

RESULTS: 18,503 patients, newly treated for benign thyroid disease and without history of malignancy were included in the analysis. Of them, 15,434 were included in the thionamide-only group and 3069 in the radioiodine-exposed group. 628 patients were diagnosed with cancer during 124,787 person-years of follow-up (mean follow-up of 6.74 years). 102 incident cancer cases were diagnosed in the radioiodine-exposed group (3.32%), and 526 (3.41%) incident cancer cases diagnosed in the thionamide group, with no difference between groups in a multivariate analysis. There were 22 incident cases of non-Hodgkin's lymphoma. We found higher risk for non-Hodgkin's lymphoma in the radioiodine-exposed patients. In a Cox regression analysis, risk ratio, associated with radioiodine exposure, for developing non-Hodgkin's lymphoma was 2.51 (95% CI 1.05-5.99)(p=0.04). We did not find higher risk for the other specific cancer types.
CONCLUSION: There is no increase in overall cancer incidence in those treated for hyperthyroidism with radioiodine in a mean follow-up of 6.74 years. However, radioiodine-exposure is associated with increased relative risk for non-Hodgkin's lymphoma.

LB-035

CHARACTERIZATION OF THE EFFECTS OF PH ON THE PHYSICOCHEMICAL PROPERTIES OF CRLX101 - A NOVEL INVESTIGATIONAL NANOPARTICLE-DRUG CONJUGATE (NDC).

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BACKGROUND: CRLX101 is a nanoparticle-drug conjugate (NDC) of the topoisomerase I inhibitor, camptothecin (CPT). Cystitis, a side effect associated with CPT, has been observed in some patients after CRLX101 administration. CPT-induced cystitis is attributable to the re-activation of the lactone form of CPT within the low pH environment of the bladder. Urine alkalinization has been considered to increase urinary pH and prevent cystitis; however, the rate of CPT release from CRLX101 is increased at higher pH. A better understanding of CPT release from CRLX101 and the associated ratio of lactone to carboxylate forms is needed following urine alkalinization.
METHODS: An HPLC-FL assay was developed to simultaneously detect both lactone and carboxylate species of CPT (excitation wavelength of 380 nm, emission wavelength of 527 nm). The total release of CPT from intact CRLX101 NDCs and the resulting ratio of lactone to carboxylate species of CPT was measured at varying pH concentrations in urine. Assay validation was not completed until after September 8th, 2016.
RESULTS: An approximate 4-fold increase in the rate of CPT release was measured as the pH increased from 4 to 9. Despite the increase in total unconjugated CPT, the ratio of CPT species favored the inactive carboxylate form at pH values greater than 7.5. The lactone species did not significantly increase over the pH gradient.
CONCLUSION: These findings suggest that at higher pH, the majority of released CPT from CRLX101 NDCs is in the inactive carboxylate form, thus supporting the rationale for alkalinizing the urine to a pH greater than 7.5 to mitigate CPT-induced cystitis. The clinical utility of urine alkalinization with CRLX101 administration will be further addressed via the characterization of patient-derived samples.

LB-036

DOES BIRTH CHANGE THE GESTATIONAL TRAJECTORY OF UGT2B7 ACTIVITY? INSIGHT FROM PREMATURE NEONATES WITH SIMILAR POST-MENSTRUAL AGE AND DIFFERENT GESTATIONAL AGE AT BIRTH.

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BACKGROUND: There has been an ongoing debate on the effect of birth vs. getationl age (GA) on the ontogeny of drug metabolising enzymes. This may have clinical implications in determining the dosage in young infants who have similar post-natal age (PNA) but varying GA due to being born prematurely. To address this it is necessary to compare the metabolic capacity of infants with similar PNA but different GA and vice versa.
METHODS: To investigate impact of birth on the trajectory of UGT2B7 ontogeny, clearance values of zidovudine and morphine were deconvoluted back to intrinsic clearance ($CLu_{int,H}$) per mg of liver microsomal protein. An *in vivo* ontogeny function for UGT2B7 was derived using the best-fit model for paediatric to adult zidovudine $CLu_{int,H}$ ratio with age and the model as validated using $CLu_{int,H}$ ratio from morphine.
RESULTS: The new model described an increase in relative $CLu_{int,H}$ during neonatal life as a function of both GA and PNA, indicating an impact by birth which could not be accounted only based on GA. UGT2B7 activity in very preterm neonates shows faster development during the postnatal period compared to babies in the womb. Accordingly, at GA=24 weeks the $CLu_{int,H}$ ratio was 3×10^{-4} and 4×10^{-2} on days 1 and 28 PNA. However, for babies born at GA= 40 weeks the $CLu_{int,H}$ ratio was 9×10^{-3} that is less than a 28 days old premature baby born at 24 GA weeks.
CONCLUSION: When implementing enzyme ontogeny functions in PBPK models, it is important to consider the GA of premature neonates on the speed of maturation of pathways and also the PNA at which differences in development are no longer apparent. This ontogeny function requires further validation in a preterm PBPK model.

LB-037

IMPACT OF RADIO(CHEMO)THERAPY ON IMMUNE CELL COMPOSITION AND FUNCTION IN CERVICAL CANCER PATIENTS.

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BACKGROUND: New combination treatment paradigms in oncology currently explored consist of standard treatments and immunotherapy including so-called checkpoint blockers. The objective of this study was to evaluate the impact of standard radio(chemo)therapy on the immune system of cervical cancer patients.
METHODS: The effects of radiotherapy without/with concurrent cisplatin (67% of patients) on the immune system was studied in 30 patients with cervical cancer of whom 67% received weekly Cisplatin. Serial blood sampling was done for immunomonitoring which included composition of lymphocyte and myeloid-cell populations, expression of co-stimulatory molecules, T-cell reactivity, antigen presenting cell function, and the response to *in vitro* incubation with Nivolumab.
RESULTS: Radio(chemo)therapy significantly decreased the numbers of circulating white blood cells during treatment. Within 48 hrs after the 1st fraction a decrease of 27% was observed (from 1.92 x 10^9/L at baseline to 1.39 x 10^9/L after the 2nd fraction; $p<0.001$), and lasted at least until 3 weeks after completion of treatment. The capacity of the T-cells to respond to antigenic/mitogenic stimulation was significantly impaired upon treatment.

Furthermore, $CD4^+$ and $CD8^+$ T-cells dropped and $CD4^+$ T-cells displayed an up to 2.7 fold increased expression of programmed cell death-1 (PD-1), but this was not accompanied by increased capacity to proliferate. Radio(chemo)therapy was associated with an increase in circulating macrophages and myeloid-derived suppressor cells (MDSCs) and an impaired capacity of APCs to stimulate allogeneic T-cells.
CONCLUSION: Standard radio(chemo)therapy profoundly suppresses the immune system in cervical cancer patients, and may restrict its combination with immunotherapy.

LB-038
WITHDRAWN

LB-039
HERITABLE *OCT1* DEFICIENCY AS A RISK FACTOR FOR FENOTEROL TOXICITY.

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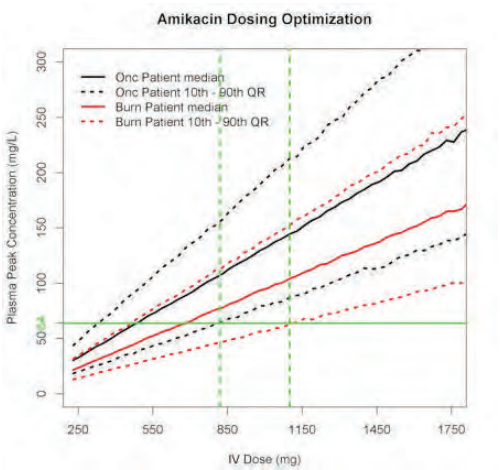
BACKGROUND: The $beta_2$ adrenoreceptor agonist fenoterol, which is used in the treatment of asthma and as a tocolytic agent, can cause severe and even fatal adverse effects. Here, we analyzed whether heritable deficiency of the hepatic organic cation transporter OCT1 (present in 3% of Europeans and White Americans) may affect fenoterol pharmacokinetics and increased risk of adverse effects.
METHODS: We analyzed fenoterol transport in OCT1-overexpressing HEK293 cells and in primary human hepatocytes and performed pharmacokinetic/pharmacodynamic analysis afer a 2-hours infusion of 180 µg fenoterol to 39 healthy individuals preselected for their *OCT1* genotypes.
RESULTS: Fenoterol was transported with high affinity by OCT1 (K_M of 1.8 µM). This transport was completely missing in *OCT1*5* and *OCT1*6* allelic-variants and was strongly reduced in *OCT1*3* and *OCT1*4*. Fenoterol uptake in primary human hepatocytes was reduced by 3-fold by the OCT inhibitor MPP+. More importantly, in healthy volunteers the systemic exposure (AUC) and the maximal plasma concentrations were close to 2-fold higher in individuals with OCT1 deficiency (n=5) compared to the rest of the studied population (n= 33, P= 10^{-5}). The higher systemic exposure in individuals with OCT1 deficiency was related to a 13 bpm stronger increase in heart rates (p = 0.002), 46 mg/dl higher plasma glucose ($p=10^{-4}$), and plasma potassium was by 0.3 mM lower (p=0.007).
CONCLUSION: Due to heritable OCT1 deficiency 3% of the Europeans and White Americans have significantly higher exposure to fenoterol and are at higher risk of toxicity. Heritable OCT1 deficiency may be an important reason behind the excess mortality related to fenoterol treatment and should be considered by fenoterol administration.



LB-040

IMPACT OF EXTENDED DURATION OF ARTESUNATE ON PARASITOLOGICAL OUTCOME IN A CYTOCIDAL MURINE MALARIA MODEL.

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BACKGROUND: Artemisinin combination therapies are a key pillar in global malaria control, relying upon a rapid reduction in parasitemia by artemisinins and killing of residual parasites by a partner compound. The short plasma half-life of the artemisinins and the 3 day dosing duration result in most of the artemisinin being cleared during a single 48-hour asexual cycle of *P. falciparum*. We hypothesized that extending the duration of artemisinin treatment results in a greater log reduction in the number of parasites, making a difference between cure and no cure with partner compounds.
METHODS: We adapted a novel murine model of malaria, which utilizes a luciferase-reporter *P. berghei* at high parasitemia, to study cytocidal activity. We investigated the effect of 2 different artemisinin duration regimens on parasite clearance and mouse survival. Monotherapy and combination therapy were investigated. We compared the cytocidal activity of the same total dose of artemisinin administered at once or over 7 days (9/29/16).
RESULTS: Increasing the duration of artemisinin monotherapy from 1 life cycle to 3 life cycles resulted in a greater reduction in total parasite number as evidenced by a 3 day delay in recrudescence. The same total dose of artemisinin administered at a single time point resulted in recrudescence by day 10, but was curative when spread out across 7 days. In combination with partner drugs amodiaquine and piperaquine, the 3 life cycle duration cures 75% and 100% of mice, respectively, whereas 0% and 33% cure is achieved with the 1 life cycle duration of artemisinin.
CONCLUSION: Our data suggests that, keeping total dose constant, greater parasite killing can be achieved by extending the duration of artemisinin compounds. This work may have relevance for current antimalarial dosing guidelines.

LB-041

IMPACT OF CYP3A4/5 POLYMORPHISMS ON TACROLIMUS (TAC) EXPOSURE IN ALLOGENEIC STEM CELL TRANSPLANT (ALLO SCT) RECIPIENTS.

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BACKGROUND: Large inter-patient variability in TAC exposure exists, partly due to pharmacogenetics. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines provide dosing recommendations based on *CYP3A5* genotype; however, these are based solely on solid organ transplant studies. We aimed to investigate the impact of *CYP3A4/5* polymorphisms on TAC exposure in allo SCT patients.
METHODS: Buccal swabs were collected from allo SCT patients between 07/03/14 and 11/01/2016. DNA was extracted using the MagMAX™ DNA kit. Ion AmpliSeq™ PGx Panel was used to genotype for polymorphisms in *CYP3A5 (*3, *6, *7)* and *CYP3A4 (*1B, *22)*. TAC infusion started at 0.03 mg/kg on day +5 post-transplant. Levels were drawn every 2 days to guide dosing (target 5-15 ng/mL). The prevalence of out of range steady state concentrations (SSC) (4th day after starting TAC) between phenotypes was compared using the Chi-squared test. The student t-test and ANOVA were used to compare mean TAC SSC.
RESULTS: Of 46 patients (67.4% Caucasians and 28.2% African Americans), 4.3%, 67.5% and 28.2% were CYP3A4 intermediate (IM), normal (NM) and ultra-rapid (UM) metabolizers, respectively, whereas 76% were CYP3A5 poor metabolizers (PMs). No patients had sub-therapeutic TAC SSC. About 46% and 71% of CYP3A5 NM/IMs and PMs had supra-therapeutic TAC SSC (P=0.15). The mean TAC SSC in CYP3A5 NM/IMs and PMs was 14.9 ± 3.6 and 16.8 ± 4.1 ng/mL, respectively (P=0.21). The prevalence of supra-therapeutic TAC

SSC in CYP3A4 IM, NM, and UMs was 100%, 67.5% and 38%, respectively (P=0.04). The mean TAC SSC in CYP3A4 IM, NM and UMs was 19.7 ± 3.9, 17 ± 3.7, and 13.9 ± 3.9 ng/mL, respectively (P=0.02).
CONCLUSION: *CYP3A4* appears to be an important determinant of TAC exposure. Given the trend, more patients will be recruited to discern the role of *CYP3A5*.

LB-042

A PBPK MODEL FOR COBICISTAT, A POTENTIAL STRONG CYP3A4 INHIBITOR FOR CLINICAL DDI STUDIES WITH CYP3A4 VICTIM DRUGS.

L. Almond, A.B. Ke, K. Rowland-Yeo; Simcyp (a Certara Company), Sheffield, UK.

BACKGROUND: Since the use of ketoconazole was discontinued, investigators have assessed and proposed alternative strong CYP3A4 inhibitors for use in Phase I clinical DDI studies. One such alternative is Cobicistat (COBI), a potent CYP3A4 inactivator that was developed specifically as a pharmacokinetic booster. We present a PBPK model for COBI that can be used to assess the DDI liability of drugs in development that are metabolised by CYP3A4.
METHODS: The aim was to develop the PBPK model of COBI as a perpetrator using prior clinical and *in vitro* data to recover the multiple dose (MD) exposure after dosing of 100mg and 200mg QD. *In vitro* inactivation parameters, corrected for non-specific binding, were incorporated into the model and the predicted interaction with midazolam (10 trials of age matched virtual subjects; Simcyp Version 15) at both dose levels was compared to corresponding observed data.
RESULTS: The developed model was able to recover the MD exposure of COBI after 100 and 300 mg QD; predicted and observed AUC(0,**T**) values were 3.44 *and* 3.41 and 16.1 *and* 16.2 mg/L.h, respectively. The predicted midazolam AUC(0,inf) ratios were within 1.25 fold of the observed for both regimens; ratios were 13.4 and 12.9, and 19.0 and 20.7 for 100 and 200mg QD, respectively. The predicted midazolam C_{max} ratios were within 2-fold of observed.
CONCLUSION: Although the model presented here is not fully mechanistic, in that it does not consider auto-inhibition or other issues relating to its complex disposition, this "fit-for-purpose model" can be used to further investigate the potential of COBI as a perpetrator of CYP3A4-mediated interactions. Ongoing verification of the model using CYP3A4 substrate drugs (e.g. atazanavir) and drugs in development can help ensure prediction accuracy of the DDI liability of COBI.

LB-043

PHARMACOGENOMIC VARIABILITY OF SPASTICITY RESPONSE WITH ORAL BACLOFEN IN CHILDREN WITH CEREBRAL PALSY.

M. McLaughlin[1], Y. He[2], J. Brunstrom-Hernandez[3], L. Thio[4], B. Carleton[5], A. Gaedigk[1], A. Lewandowski[6], H. Dai[1], W. Jusko[7], J. Leeder[1]; [1]Children's Mercy Hospital, Kansas City, MO, USA, [2]Food and Drug Administration, Silver Spring, MD, USA, [3]1 CP Place, Plano, TX, USA, [4]St. Louis Children's Hospital, St. Louis, MO, USA, [5]University of British Columbia, Vancouver, BC, Canada, [6]The EMMES Corporation, Rockville, MD, USA, [7]University of Buffalo, Buffalo, NY, USA.

BACKGROUND: Oral baclofen is the most used oral medication to treat pediatric patients with spasticity; however, variations in clinical response limit the ability to anticipate therapeutic benefit.
METHODS: This pharmacogenomic add-on study evaluates variability in clinical response from participants in an oral baclofen pharmacokinetic study. Of 61 participants aged 2-16 with a known diagnosis of spastic cerebral palsy who participated in a PK/PD trial, 34 underwent genetic analysis comprising 307 genes (4,535 single-nucleotide polymorphisms (SNPs)) and had sufficient pharmacodynamics data for inclusion in this study. Participants underwent open label titration of oral baclofen during the 12 week study period with pharmacodynamic evaluation by the Modified Tardieu Scale (MTS) score for hamstring

spasticity. The MTS score was collected at baseline and during 11 follow-up visits as a part of the pharmacokinetic study. Associations between genotype and phenotypes of oral baclofen doses with clinical endpoints (improvement from baseline in hamstring R1 spastic catch assessed using mean MTS scores) were determined by univariate analysis with correction for multiple testing by false discovery rate (FDR). Analysis of this data set was completed November 8, 2016 and not able to be analyzed prior to September 8, 2016.
RESULTS: After adjustment for FDR, MTS was associated with SNPs in *ABCC12* (rs16945874), *SLC28A1* (rs1542283 and rs16974641), and *PPARD* (rs7770619 and rs6906237) ($p<0.05$). Four participants who were heterozygous for all three SNPs had the largest improvement in MTS angle.
CONCLUSION: SNPs in *ABCC12*, *SLC28A1*, and *PPARD* were associated with improved clinical responses; however, these findings will need to be replicated in a larger cohort to determine their effect on spasticity.

LB-044

THE QUEST FOR BIOMARKERS IN ONCOLOGY: AN OPPORTUNITY FOR QUANTITATIVE CLINICAL PHARMACOLOGY APPROACHES.

Y. Lien[1], V.D. Sharma[1], S. Basu[1], H. Yang[1], W. Wang[2], H. Zhou[2], S. Ait-Oudhia[1], S. Schmidt[1];
[1]University of Florida, Orlando, FL, USA, [2]Biologics Clinical Pharmacology, Spring House, PA, USA.

BACKGROUND: Targets for monoclonal antibodies (mAbs) on are on the cell surface, circulating in plasma as soluble antigens (SAs), or both. While it is well-accepted that SAs impact the mAbs' pharmacokinetics, it is currently unclear whether their plasma concentration can be a surrogate driver for target site kinetics. Here we have developed a user-friendly modeling framework that allows to examine SAs as surrogates to the PK of mAbs at the target site.
METHODS: An integrative step-wise PK approach was used. First, the original target-mediated disposition model was reproduced for mAbs (Model#1). Second, Model#1 was extended to include SAs tissue distribution (Model#2). Third, the FcRn-mediated elimination of mAbs was integrated into Model#2 (Model#3). Fourth, the SAs target-mediated clearance was added to Model#3 (Model#4). For each of these models, simulations were performed to determine the impact of target occupancy and engagement, free ligand and SAs on the PK of mAbs at the target site. Modeling was performed in Berkeley Madonna. A user-friendly R application interface was created for each of the four models.
RESULTS: Model-based simulations using our developed framework shows: 1) A longer circulating half-life and a prolonged interstitial tissue distribution for mAbs with FcRn's impact. 2) The influence of the SAs on the late phase of mAbs PK profiles, clearances, and tissue distributions. 3) The effect of SAs on lowering the target occupancy on membrane bound receptors.
CONCLUSION: A mechanistic modeling framework was developed and successfully applied to examine the influence of SAs on the PK of mAbs at the target site. It can serve to guide drug development process from design *in silico* to clinical trials support and decisions.

LB-045

BENCH-TO-BEDSIDE QUANTITATIVE SYSTEMS PHARMACOLOGY APPROACH TO EXAMINE THE MTOR SIGNALING PATHWAY IN HEPATOCELLULAR CARCINOMA.

A. Ande, M. Chaar, S. Ait-Oudhia; University of Florida, Orlando, FL, USA.

BACKGROUND: Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide. The mTOR signaling pathway is identified as a promising target given its role in cellular proliferation, migration, and angiogenesis. Dysregulation of this pathway is common in HCC patients. Here, we aimed to: 1) dissect the circuitry of this pathway in HCC patients and 2) build a bench-to-bedside quantitative system pharmacology (QSP) model that predicts HCC patients' response to mTOR inhibitors.
METHODS: A step-wise, multiscale, bottom-up QSP approach was adopted. First, data were extracted from literature including, the time course of: key proteins dynamics in the PI3K/AKT/mTOR pathway, HCC cells (Huh7) viability and apoptosis, tumor growth volume in HCC xenograft mice, and patients' free survival profiles. In addition, we conducted *in vitro*

experiments to collect the time course of cell proliferation and cell cycle phase data upon treating Huh7 cells with the prototype mTOR inhibitor, Everolimus (EVE) at 0.1, 1, and 10 μM.
RESULTS: Based on our protein signaling network and developed QSP model, EVE inhibited mTOR phosphorylation, which in turn inhibited the downstream phosphorylation of S6. In turn, S6 counter activated the phosphorylation of AKT through IRS signaling. We connected this protein signaling meshwork to the cellular responses including, inhibition of cell proliferation, apoptosis, and the cell cycle model using the cell cycle analysis data.
CONCLUSION: A translational multiscale QSP model was successfully developed. This model can not only predict the clinical efficacy of EVE, but also be used as a platform for related drugs and to evaluate the efficacy of combination targeted-therapy in the mTOR pathway to effectively treat HCC.

LB-046

CETHROMYCIN COMPLETELY CURES *P. BERGHEI* LIVER STAGE MALARIA INITIATED BY MOSQUITO BITES.

D. Sullivan[1], G. Kennedy[1], L. Walker[1], R. Evans[1], N. Kaludov[2]; [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]AliquantumRX, Baltimore, MD, USA.

BACKGROUND: Prophylaxis of malaria in travelers to malaria endemic countries is limited to atovoquone/proguanil, doxycycline, mefloquine and rarely primaquine. We investigated the liver stage activity of cethromycin in the *P. berghei* liver stage model initiated by mosquito bites. Cethromycin was identified by a quantum based computational approach sifting through millions of molecules for liver stage malaria activity. Cethromycin is a molecular hybrid of a nonsubstituted quinoline nucleus joined to an erythromycin scaffold a 2-erythromycin-quinoline. *In vitro* data previously indicated reduction in *P. berghei* liver stage parasites by real time PCR assays on infected livers at less than human equivalent single doses.
METHODS: Murine *Plasmodium* mosquito infections were used.
RESULTS: Here we demonstrate complete cure of *P. berghei* infection by single oral dose of 60 mg/kg in mice which is equivalent to the 5 mg/kg human dose of 300 mg a day used in bacterial pneumonia studies. Azithromycin at 60 mg/kg single oral dose was not curative. Both quinoline and erythromycin alone at 120 mg/kg for two doses as well as control mice resulted in patent blood stage parasitemia in all mice. Cethromycin at 30 mg/kg was also curative as well as single oral 60 mg/kg given before mosquito infection. Similar to azithromycin, cethromycin was active against blood stages but inactive against transmissible gametocytes.
CONCLUSION: Cethromycin has been evaluated for efficacy against bacterial pneumonia in more than 2,000 patients with good safety profiles. Additional studies will characterize minimum curative dose, blood stage activity and pharmacokinetics in the liver. Cethromycin has potential for rapid clinical development for casual malaria prophylaxis.

LB-047

TRENDS OF CALCINEURIN INHIBITOR USE IN PEDIATRIC IMMUNOSUPPRESSION.

K. Job[1], B. Hillyard[1], C. Sanders[1], J.E. Rower[1], E. Korgenski[2], C.M. Sherwin[1]; [1]Clinical Pharmacology, Department of Pediatrics, University of Utah, Salt Lake City, UT, USA, [2]Intermountain Healthcare, Salt Lake City, UT, USA.

BACKGROUND: Calcineurin inhibitors (CNI) are fundamental to immunosuppressant therapy in pediatric transplant (Tx) recipients to prevent organ rejection The rationale behind the clinical use of tacrolimus (Tac) and cyclosporine (CsA) use in children is poorly described, particularly with regards to Tx type. This retrospective study evaluates CNI use in pediatric patients.
METHODS: Data was obtained retrospectively from the Intermountain Health Electronic Data Warehouse. We included 262 patients receiving Tac (2006-2014) and 102 pediatric patients receiving CsA (2006-2015) for heart, bone marrow, liver, or kidney transplant. Data was analyzed using SAS 9.2 and Rstudio. Comparisons were made by age, dose amount, and formulation. CsA analyses were ongoing as of 9/8/16.

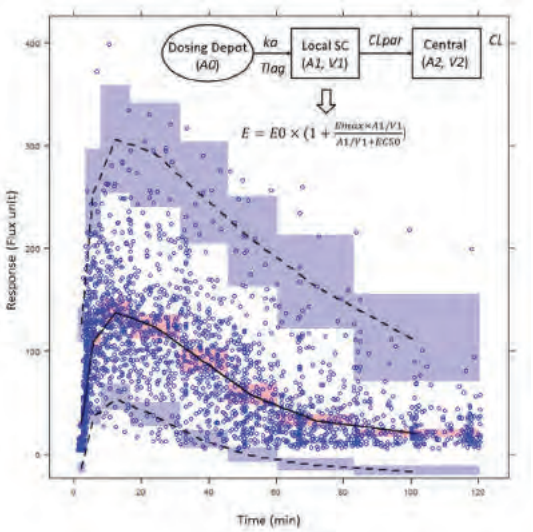
RESULTS: Patients were evenly split by sex, primarily white (~90%), and between 0-19 years of age. Liver Tx patients were generally given larger dosages of Tac and more frequently administered brand Tac formulations. Frequency of generic Tac formulation use has increased since 2011 across all transplant types. Larger CsA doses were administered in patients under 6 years of age ($p < 0.01$). Target attainment was generally poor for both Tac and CsA, but varied across Tx types. Notably, ~60% of heart Tx measurements were outside target the target of 12-16 ng/mL.
CONCLUSION: Generic Tac formulations are less frequently prescribed to liver Tx patients, likely due to drug metabolization and toxicity concerns. CsA use persists for transplant indications, particularly in BMT patients, but has generally declined due to nephrotoxicity concerns. Age-dependent dosing and poor target attainment suggests need for further CNI PK study.

LB-048

POPULATION PHARMACOKINETIC/PHARMACODYNAMIC MODELING OF HISTAMINE RESPONSE MEASURED BY HISTAMINE IONTOPHORESIS LASER DOPPLER.

X. Liu[1], B. Jones[2], J. Roberts[1], C. Sherwin[1]; [1]Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA, [2]Division of Allergy Asthma and Immunology, Children's Mercy Hospital, Kansas City, MO, USA.

BACKGROUND: Histamine iontophoresis with laser Doppler monitoring (HILD) method provides objective, dynamic, and robust measurements (40Hz over 2 hours) of the epicutaneous histamine response. We aimed to develop an algorithm to reduce HILD data in size and demonstrate the feasibility of using the reduced data for population pharmacometric analysis.
METHODS: Children with a diagnosis of asthma (n=169) were enrolled from outpatient clinics at the Children's Mercy Hospital and underwent HILD in identical fashion. An averaging algorithm was developed in R packages. Population models were developed using NONMEM7.
RESULTS: The averaging algorithm reduced each individual data (up to 3600 data points) to 10 - 15 data points while characterizing the actual histamine response. The reduced data was pooled and described by a PK/PD linked-effect model that represents the local histamine response. The model featured a local distribution compartment with absorption lag time (Tlag) and direct PD response, and accurately described the histamine response and population variability (**Figure**).
CONCLUSION: The richly sampled HILD data was reduced to a suitable size for pharmacometric analysis using an averaging algorithm. This study has demonstrated the feasibility of modeling HILD data for pharmacodynamic response.



ENCORE POSTER SESSION

WEDNESDAY, MARCH 15

4:00 PM – 6:30 PM

E-001

CAPTURING DEVELOPMENTAL CHANGE IN SIROLIMUS CLEARANCE AND ITS UNDERLYING MECHANISM: A PRACTICAL APPROACH USING LONGITUDINAL PHARMACOKINETIC DATA.

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BACKGROUND: Through participation in a prospective phase II concentrations-controlled clinical trial of sirolimus (NCT00975819), we longitudinally collected sirolimus concentrations in very young pediatric patients (aged 1.1 months to 4 years). Using these data, we captured the developmental change in sirolimus clearance (CL) and evaluated its underlying mechanism.
METHODS: 316 sirolimus concentrations were obtained from 24 young pediatric patients over a four-year study period. Sirolimus metabolite concentrations were separately determined by LC-MS/MS. Individual sirolimus CL estimates at each sampling point were generated using Bayesian estimation (MW/Pharm, ver. 3.8). The relationship between sirolimus CL estimates and age at each sampling point was analyzed with NONMEM (ver. 7.2). PBPK modeling was conducted on the Simcyp pediatric platform (ver. 14) that takes age-dependent anatomical and physiological changes into account.
RESULTS: The relationship between allometrically scaled sirolimus CL estimates and age was described by a sigmoidal E_{max} model. Formation of 25-OH-sirolimus and 16-*O*-demethylsirolimus, which were both CYP3A metabolites, increased in a similar age-dependent manner. Time to CL at half of the matured level was estimated at 62.9 weeks of postmenstrual age in the population analysis. This time was close to the 61.3 weeks estimated by the pediatric PBPK modeling.
CONCLUSION: The population estimates on developmental change in sirolimus CL will facilitate age-appropriate dosing in future patients. This study using multiple approaches supports the conclusion that the developmental change in sirolimus CL can be explained by parallel increases in CYP3A metabolic activity as a result of size increases (growth) and CYP3A protein expression (maturation).

E-002

DETAILED EVALUATION OF PK-BASED DRUG-DRUG INTERACTION DATA CONTAINED IN NEW DRUG AND BIOLOGIC LICENSE APPLICATIONS OF DRUGS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION IN 2015.

J. Yu, Z. Zhou, K. Owens, T. Ritchie, I. Ragueneau-Majlessi; University of Washington, Seattle, WA, USA.

BACKGROUND: The aim of the present work was to systematically evaluate PK-based DDI data available in the 33 NDAs and 12 BLAs approved by the US Food and Drug Administration in 2015.
METHODS: Using the University of Washington Drug Interaction Database©, all drug metabolism, transport, pharmacokinetic, and DDI data available in the regulatory documentation were analyzed to highlight the significant findings.
RESULTS: *In vitro*, a majority of the NMEs were found to be substrates or inhibitors/inducers of at least one DME or transporter, with CYP3A being the most represented enzyme. *In vivo*, 95 clinical DDI studies displayed positive PK results with an AUC ratio = 1.25 for inhibition or = 0.8 for induction. When considered as victims, 21 NMEs had at least one positive clinical DDI, with three NMEs found to be sensitive substrates of CYP3A (AUC ratio = 5 when coadministered with strong inhibitors): cobimetinib, isavuconazole (the active metabolite of prodrug isavuconazonium),

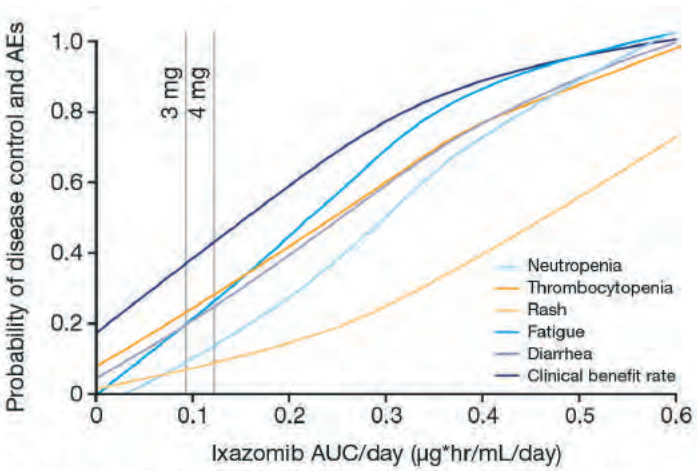
and ivabradine. As perpetrators, nine NMEs showed positive inhibition and three NMEs showed positive induction, some of these clinical interactions involving both enzymes and transporters. The most significant changes for inhibition and induction were observed with rolapitant, a moderate inhibitor of CYP2D6, and lumacaftor, a strong inducer of CYP3A. PBPK simulations and PGx studies were used for six and eight NMEs, respectively, to inform dosing recommendations. The effects of hepatic or renal impairment on the drugs' PK were also evaluated to support drug administration in these specific populations.
CONCLUSION: The evaluation showed that most of the NMEs were extensively studied both *in vitro* and *in vivo*, and their drug interaction profiles were well characterized, with a continued effort in transporter-based DDIs and PBPK modeling and simulations.

E-003

EXPOSURE-SAFETY-EFFICACY ANALYSIS OF IXAZOMIB IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): DOSE SELECTION FOR PHASE III TRIAL OF IXAZOMIB MAINTENANCE THERAPY.

N. Gupta, R. Labotka, G. Liu, K. Venkatakrishnan; Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA.

BACKGROUND: This analysis aimed to identify the appropriate dose for the oral proteasome inhibitor ixazomib in the phase III TOURMALINE-MM3 study of single-agent ixazomib vs placebo as maintenance therapy in MM patients who have responded to induction therapy followed by HDT/ASCT (NCT02181413).
METHODS: Logistic regression analyses examined the relationship between ixazomib exposure (AUC/day, derived from a population PK analysis) and safety (grade ≥3 hematologic [anemia, neutropenia, thrombocytopenia] and grade ≥2 nonhematologic [diarrhea, fatigue, rash, peripheral neuropathy] adverse events) or efficacy (best response ≥stable disease [SD]) using data from a phase I dose-escalation study in 44 patients with RRMM (dose range 0.48-3.95 mg/m^2).
RESULTS: Significant relationships to ixazomib exposure were observed for probability of diarrhea, fatigue, rash, thrombocytopenia, neutropenia, and response of ≥SD ($p<0.05$, **Figure 1**). At a starting dose of 3 mg weekly, the model predicted 19% grade ≥2 diarrhea, 19% grade ≥2 fatigue, 8% grade ≥2 rash, 23% grade ≥3 thrombocytopenia, 10% grade ≥3 neutropenia, and 37% ≥SD.
CONCLUSION: Based on these findings, ixazomib maintenance therapy in the ongoing TOURMALINE-MM3 study is initiated at a dose of 3 mg weekly, increasing to 4 mg if tolerated after 4 cycles to gain maximum clinical benefit.



E-004

PHASE I/IB PHARMACOKINETICS AND SAFETY STUDY OF IXAZOMIB IN MULTIPLE MYELOMA PATIENTS WITH SEVERE RENAL IMPAIRMENT/END-STAGE RENAL DISEASE REQUIRING HEMODIALYSIS (ESRD).

N. Gupta[1], M.J. Hanley[1], R.D. Harvey[2], A. Badros[3], B. Lipe[4], V. Kukreti[5], J.G. Berdeja[6], H. Yang[1], M. Qian[1], X. Zhang[1], K. Venkatakrishnan[1], A. Chari[7]; [1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA, [2]Winship Cancer Institute of Emory University, Atlanta, GA, USA, [3]University of Maryland, Baltimore, MD, USA, [4]University of Rochester, Rochester, NY, USA, [5]Princess Margaret Cancer Center, Toronto, ON, Canada, [6]Sarah Cannon Research Institute, Nashville, TN, USA, [7]Mount Sinai School of Medicine, New York, NY, USA.

BACKGROUND: This study (NCT01830816) characterized ixazomib PK in patients (pts) with multiple myeloma (MM) and severe renal impairment (sRI) or ESRD, to provide posology recommendations.
METHODS: 38 pts with normal renal function (NRF, creatinine clearance [CrCl] =90mL/min), sRI (CrCL<30 mL/min), or ESRD were PK-evaluable. Blood samples were collected before and at multiple time points after a single 3 mg ixazomib dose. For ESRD pts, pre- and post-dialyzer plasma samples were collected. The impact of RI on ixazomib PK was estimated using an ANOVA model. AEs were assessed using NCI CTCAE version 4.03.
RESULTS: Ixazomib was highly bound to plasma proteins (~99%) in all groups. Unbound and total systemic ixazomib exposures were 38% and 39% higher, respectively, in sRI or ESRD pts vs. pts with NRF (**Table 1**). Pre- and post-dialyzer ixazomib concentrations were similar in ESRD pts. AE incidence was comparable across groups, except for anemia; incidences of grade 3/4 and serious AEs were greater in the sRI and ESRD groups.
CONCLUSION: These data support a reduced ixazomib dose of 3 mg in pts with sRI/ESRD, administered without regard to dialysis timing, and informed labeling of ixazomib, which is approved in the USA and Canada in combination with lenalidomide-dexamethasone for the treatment of pts with MM who have received at least one prior therapy.

Table: Geometric least squares mean ratios (90% CIs) for unbound C_{max} and AUC_{0-last}

	Geometric least-squares mean ratio (90% CI)		
Parameter	**sRI *vs* NRF**	**ESRD *vs* NRF**	**sRI/ESRD combined *vs* NRF**
Unbound C_{max}, ng/ml	1.60 (0.99–2.58)	0.71 (0.38–1.34)	1.25 (0.79–1.98)
Unbound AUC_{0-last}, h.ng/ml	1.39 (0.88–2.20)	1.34 (0.78–2.31)	1.38 (0.93–2.04)
Total C_{max}, ng/ml	1.76 (1.11–2.78)	0.73 (0.40–1.33)	1.35 (0.86–2.10)
Total AUC_{0-last} h.ng/ml	1.41 (1.01–1.98)	1.36 (0.92–2.02)	1.39 (1.04–1.86)

E-005

CHARACTERIZATION OF NON-T CELL-INFLAMED BLADDER CANCER TO ENHANCE IMMUNOTHERAPY RESPONSE.

R.F. Sweis, S. Spranger, R. Bao, G.P. Paner, W.M. Stadler, G.D. Steinberg, T.F. Gajewski; University of Chicago, Chicago, IL, USA.

BACKGROUND: Response to immunotherapy and improved survival are linked to a T cell-inflamed tumor microenvironment characterized by CD8+ tumor-infiltrating T cells and expression of a chemokine/interferon gene signature. Anti-PD1 therapy leads to durable responses, but only in a minority of patients. To identify predictive biomarkers and better understand mechanisms of resistance, we characterized activated molecular pathways in non-T cell-inflamed bladder cancers.
METHODS: RNA seq and somatic mutation data from 267 bladder cancers in TCGA were downloaded. Immune subtypes were identified using consensus clustering with 725 genes derived from a T cell signature. Differentially expressed genes were detected by ANOVA with a FDR $q<0.01$ and fold change>2.0. Enriched pathways were identified by Ingenuity Pathway Analysis. Somatic variants were converted to VCF format and tabulated.
RESULTS: A T cell-inflamed phenotype was found in 36% of bladder tumors, while 33% were non-inflamed. Expression of CD8A positively correlated with inhibitory molecules PDL1, IDO1, FOXP3, TIM3, and LAG3 (all $p < 0.0001$). Non-inflamed tumors contained 730 over-expressed genes and activation of regulators Wnt/ß-catenin and peroxisome proliferator-activated receptor gamma (PPARG) (both $p = 0.003$). Mutational burden was not different between groups ($p = 0.80$). FGFR3 was the most commonly mutated gene exclusive to non-inflamed tumors, ($p < 0.0001$). Expression of WNT7B, PPARG, and FGFR3 inversely correlated with CD8A (all $p < 0.0001$).
CONCLUSION: Bladder tumors are characterized by T cell-inflamed and non-inflamed phenotypes, with no difference in mutational density. ß-catenin, PPARG, and FGFR3 pathways correlate with T cell exclusion and are potential targetable mechanisms of immunotherapy resistance.

E-006

CROSS-ARM BINDING EFFICIENCY OF AN EGFR X C-MET BISPECIFIC ANTIBODY.

S. Zheng, S. Moores, S. Jarantow, J. Pardinas, M. Chiu, H. Zhou, W. Wang; Janssen R&D, Spring House, PA, USA.

BACKGROUND: Multispecific proteins, such as bispecific antibodies (BsAbs), that bind to two different ligands are becoming increasingly important therapeutic agents. Such BsAbs can exhibit markedly increased target binding and target residence time when both pharmacophores bind simultaneously to their targets. The cross-arm binding efficiency (χ) describes an increase in apparent affinity when a BsAb binds to the second target or receptor (R2) following its binding to the first target or receptor (R1) on the same cell. χ is an intrinsic characteristic of a BsAb mostly related to the binding epitopes on R1 and R2. χ can have significant impacts on the binding to R2 for BsAbs targeting two receptors on the same cell.
METHODS: JNJ-61186372, a BsAb that targets epidermal growth factor receptor (EGFR) and c-Met, was used as the model compound for establishing a computational method to characterize χ. The model was developed using NONMEM (V7.2).
RESULTS: The χ for JNJ-61186372 was successfully determined via fitting of *in vitro* cell binding data to a ligand binding model that incorporated χ. The model-derived χ value was used to predict the binding of JNJ-61186372 to individual EGFR and c-Met receptors on tumor cell lines, and the results agreed well with the observed IC_{50} for EGFR and c-Met phosphorylation inhibition by JNJ-61186372. Consistent with the model, JNJ-61186372 was shown to be more effective than the combination therapy of anti-EGFR and anti-c-Met monovalent antibodies at the same dose level in a mouse xenograft model.
CONCLUSION: Our results showed that χ is an important characteristic of BsAbs, and should be considered for rationale design of BsAbs targeting two membrane bound targets on the same cell.

E-007

MECHANISM-BASED INACTIVATION OF CYTOCHROME P450 2A6 BY IMPERATORIN ISOLATED FROM CNIDIUM MONNIERI.

M.-J. Kim, J.-G. Ha, S.-E. Yoo, **H.-S. Kim**, J.-G. Shin, D.-H. Kim; Inje University College of Medicine, Busan, Republic of Korea.

BACKGROUND: Cnidium monnieri is a well-known traditional Chinese medicine, which has been used for the treatment of various diseases such as arthritis, osteoporosis, tumors, and skin disease. The purpose of this study was to investigate the irreversible inhibition of Cnidium monnieri extracts and its major ingredient, imperatorin on cytochrome P450 (CYP) 2A6-mediated coumarin 7-hydroxylation.
METHODS: Seventy percent ethanolic extracts of Cnidium monnieri and its major ingredients, osthole, imperatorin, and isoimperatorin were evaluated for their inhibitory effects of CYP isoforms in human liver microsomes and recombinant CYP2A6 with liquid chromatography-tendem mass spectrometry (LC-MS/MS).
RESULTS: The extracts of Cnidium monnieri and imperatorin strongly inhibited CYP2A6-mediated coumarin 7-hydroxylation. The IC_{50} value of imperatorin was 11.7-fold reduced after pre-incubation with microsomes in the presence of NADPH, suggesting that imperatorin is a mechanism-based inactivator. The inhibition of coumarin 7-hydroxylase activity by imperatorin was not restored to the control level by nucleophiles or extensive dialysis. In addition, the inactivation was protected by the addition of pilocarpine, a competitive inhibitor of CYP2A6. The K_I value of imperatorin to CYP2A6 was 3.2 μM with a maximal rate constant for inactivation (k_{inact}) value of 0.101 min^{-1}. The estimated partition ratio was approximately 4.2.
CONCLUSION: These results indicate that imperatorin is a potent mechanism-based inhibitor of CYP2A6. *In vivo* interactions between imperatorin and CYP2A6 substrates need to be evaluated whether the inhibition of CYP2A6 by imperatorin is clinically relevant.

E-008

URINE COLORIMETRY TO DETECT LOW RIFAMPIN EXPOSURE DURING TUBERCULOSIS THERAPY: A PROOF-OF-CONCEPT STUDY.

I. Zentner[1], H. Schlecht[2], L. Khensouvann[2], N. Tamuhla[3], M. Kutzler[2], V. Ivaturi[4], J. Pasipanodya[5], T. Gumbo[5], C. Peloquin[6], G. Bisson[7], C. Vinnard[1]; [1]Rutgers, The State University of New Jersey, Pennington, NJ, USA, [2]Drexel University College of Medicine, Philadelphia, PA, USA, [3]Botswana-Upenn Partnership, Gaborone, Botswana, [4]University of Maryland, Baltimore, MD, USA, [5]Baylor Research Institute, Dallas, TX, USA, [6]University of Florida College of Pharmacy, Gainsville, FL, USA, [7]Penn Center for AIDS Research, Philadelphia, PA, USA.

BACKGROUND: The cost and complexity of current approaches to therapeutic drug monitoring during tuberculosis (TB) therapy limits widespread use in areas of greatest need. We sought to determine whether urine colorimetry could have a novel application as a form of therapeutic drug monitoring during anti-TB therapy.
METHODS: Among healthy volunteers, we evaluated 3 dose sizes of rifampin (150 mg, 300 mg, and 600 mg), performed intensive pharmacokinetic sampling, and collected a timed urine void at 4 h post-dosing. The absorbance peak at 475 nm was measured after rifamycin extraction. The optimal cutoff was evaluated in a study of 39 HIV/TB patients undergoing TB treatment in Botswana.
RESULTS: In the derivation study, a urine colorimetric assay value of 4.0×10^{-2} Abs, using a timed void 4 h after dosing, demonstrated a sensitivity of 92 % and specificity of 60 % to detect a peak rifampin concentration (C_{max}) under 8 mg/L, with an area under the ROC curve of 0.92. In the validation study, this cutoff was specific (100 %) but insensitive (28 %). We observed similar test characteristics for a target C_{max} target of 6.6 mg/L, and a target area under the drug concentration-versus-time curve (AUC_{0-8}) target of 24.1 mg per hour/L.
CONCLUSION: The urine colorimetric assay was specific but insensitive to detect low rifampin serum concentrations among HIV/TB patients. In future work we will attempt to optimize sampling times and assay performance, with the goal of delivering a method that can translate into a point-of-care assessment of rifampin exposure during anti-TB therapy.

E-009

MODEL QUALIFICATION APPROACHES FOR QUANTITATIVE SYSTEMS PHARMACOLOGY AND MECHANISTIC PHYSIOLOGICAL MODELS.

C. Friedrich; Rosa & Co., San Carlos, CA, USA.

BACKGROUND: Quantitative Systems Pharmacology (QSP) has emerged as a powerful approach in model-informed drug development. QSP is an umbrella term for mathematical modeling that considers drug MOA in the context of biological disease mechanisms to improve understanding of human biology and pharmacology. Specific QSP modeling methods vary, and there is currently no one unifying qualification method (1). Several recent publications discuss QSP model qualification (2-4). Mechanistic physiological models are one established QSP approach in which biological mechanisms and drug MOA are represented by appropriate equations (usually ordinary differential equations) and parameters. Whole-system behavior can then be simulated to gain insights into the connections between mechanisms and outcomes. Here, we compare and contrast newly proposed QSP qualification approaches with the Model Qualification Method (MQM, **Figure 1**) for Rosa's PhysioPD™ Research Platforms.
METHODS: Recent publications discussing QSP model qualification (2-4) were analyzed and compared with the MQM.
RESULTS: The MQM comprises eight criteria addressing relevance, uncertainty, variability, and consistency with test data. QSP qualification approaches proposed recently share several themes with each other and the MQM, and add useful details and examples for addressing several of the MQM criteria. The MQM is broader and includes additional criteria, particularly

regarding biological uncertainty, that are not addressed in other published approaches.
CONCLUSION: The MQM developed for mechanistic physiological models can serve as a framework for qualifying QSP models. Use of the MQM would complement and enhance other proposed approaches. The industry may be converging on a set of QSP qualification criteria.

E-010

PHARMACOKINETICS OF METFORMIN IN PATIENTS RECEIVING REGULAR HEMODIAFILTRATION.

F. Smith[1], S. Kumar[1], T. Furlong[2], S. Gangaram[1], J. Greenfield[3], **S. Stocker**[4], G. Graham[4], K. Williams[4], R. Day[4];
[1]School of Medical Sciences, UNSW, Sydney, Australia, [2]Department of Nephrology, St Vincent's Hospital, Sydney, Australia, [3]Department of Endocrinology, St Vincent's Hospital, Sydney, Australia, [4]Department of Clinical Pharmacology & Toxicology, St Vincent's Hospital, Sydney, Australia.

BACKGROUND: The cardioprotective effects of the anti-hyperglycaemic agent, metformin, may be beneficial for type 2 diabetes mellitus patients (T2DM) with end-stage kidney disease. . However, metformin is contraindicated in this population due to concerns that the drug may accumulate and cause lactic acidosis. This study investigated the pharmacokinetics and safety of metformin in patients with T2DM receiving chronic haemodialysis.
METHODS: Patients (n=4) received metformin (500 mg IR) after haemodialysis (3 sessions a week; 1500 mg/week) for 12 weeks. Dose reductions were made if plasma metformin concentrations approached 5 mg/L. Multiple plasma samples were collected during dialysis sessions and after dosage (Weeks 1-4, 8, 12) for determination of biochemical parameters and/or metformin concentrations. Metformin concentrations were measured by HPLC.
RESULTS: During haemodialysis plasma metformin concentrations were decreased by 52 to 74%, and metformin clearance ranged from 123 to 179 mL/min. Mean extraction ratios of metformin from erythrocytes ranged from -0.15 to 0.28. Plasma metformin concentrations were generally constant between dialysis sessions, indicating minimal endogenous clearance. The mean metformin area under the curve was 2.7 times greater for patients than healthy subjects dosed (3000 mg/day) to steady state (133 vs. 49.2 mg.h/L, respectively). Metformin plasma concentrations did not exceed 5 mg/L, and there was no relationship with plasma lactate concentrations.
CONCLUSION: Dialysis readily cleared metformin from plasma, but not red blood cells. This suggests that reduced doses of metformin can be safety administered to T2DM haemodialysis patients, providing these patients with not only glycaemic control, but also cardiovascular benefits.

E-011

THE PREDICTION OF THE RELATIVE IMPORTANCE OF CYP3A/P-GLYCOPROTEIN TO THE NONLINEAR INTESTINAL ABSORPTION OF DRUGS BY ADVANCED COMPARTMENTAL ABSORPTION AND TRANSIT MODEL.

K. Maeda[1], J. Takano[2], M.B. Bolger[3], Y. Sugiyama[4]; [1]The University of Tokyo, Tokyo, Japan, [2]Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan, [3]Simulations Plus, Inc., Lancaster, CA, USA, [4]RIKEN, Kanagawa, Japan.

BACKGROUND: Intestinal CYP3A and P-glycoprotein (P-gp) decrease the intestinal absorption of substrate drugs. Since substrate specificity of CYP3A often overlaps that of P-gp, and estimation of their saturation in the intestine is difficult, dose-dependent FaFg (fraction of the administered drugs that reach the portal blood) of substrate drugs and the relative importance of CYP3A and P-gp have not been well clarified.
METHODS: We aimed to establish an Advanced Compartmental Absorption and Transit (ACAT) model with optimized parameters to quantitatively estimate the importance of P-gp and CYP3A in the non-linear pharmacokinetics, and predict the FaFg of substrate drugs. The scaling factors of V_{max} for CYP3A (SF_{CYP3A}) and P-gp ($SF_{P\text{-}gp}$) were simultaneously optimized to best explain the FaFg of selective and dual CYP3A and/or P-gp substrate drugs.
RESULTS: The best overall predictability of FaFg values of these drugs was achieved when considering both SF_{CYP3A} and $SF_{P\text{-}gp}$. The simulation clarified the relative importance of CYP3A and P-gp in the intestinal absorption. In particular, the non-linear intestinal absorption of verapamil was caused by the saturation of intestinal CYP3A, whereas that of quinidine was governed by the saturation of both CYP3A and P-gp. In addition, the dose-dependent FaFg of selective and dual CYP3A and/or P-gp substrate drugs were well-predicted.
CONCLUSION: We propose a methodology for predicting the FaFg of drugs from *in vitro* assays using a mathematical model with carefully optimized SF_{CYP3A} and $SF_{P\text{-}gp}$ values.

E-012

ASTROLABE: A TOOL FOR RAPID, AUTOMATED GENOTYPE ASSIGNMENTS OF CYP2C9, CYP2C19 AND CYP2D6 FROM NEXT GENERATION SEQUENCING (NGS) DATA.

A. Gaedigk, G.P. Twist, S.E. Soden, E.G. Farrow, N.A. Miller; Children's Mercy Kansas City, Kansas City, MO, USA.

BACKGROUND: NGS is increasingly used to characterize pharmacogene variation. To facilitate haplotype calling and phenotype prediction, we have developed a probabilistic scoring system, Astrolabe (initially called 'Constellation') and applied it to the highly polymorphic *CYP2D6* gene locus (Twist et al 2016, Gen Med 1:15007). This Encore Presentation describes upgrades and expansion of Astrolabe to include two other genes with CPIC guidelines.
METHODS: The Study was approved by the Children's Mercy IRB and included an extended number of subjects (3 HapMap; 73 patients/parents). Allele definitions for *CYP2C9* and *19* are according to the P450 Nomenclature Database. To improve call rates, selected *CYP2D6* alleles were resequenced to obtain complete gene sequences. All but one subject were extensively characterized with orthogonal methods for all 3 genes to validate Astrolabe diplotype calls. Original WGS data were reanalyzed with the DRAGEN Bio-IT processor (Edico Genome) to improve variation call quality Astrolabe is available at www.childrensmercy.org/genomesoftwareportal/.
RESULTS: When compared with genotyping Astrolabe correctly called *CYP2D6, CYP2C9* and *CYP2C19* diplotypes for 70/76 (92%), 69/75 (92%) and 71/75 (95%) subjects, respectively. Astrolabe accurately identified the *CYP2D6*5* gene deletion (n=5) and gene duplications (n=2). Phenotype predictions between genotype and Astrolabe calls were consistent for >95% of subjects.
CONCLUSION: When combined with rapid WGS methods, Astrolabe can provide provisional phenotype prediction within 26 hours. Improved haplotype definitions will increase Astrolabe call accuracy. Other NGS platforms including a targeted pharmacogene panel are currently being evaluated and further expansions to other pharmacogenes are underway.

E-013

LEVOFLOXACIN-INDUCED QT PROLONGATION DEPENDS ON THE TIME OF DRUG ADMINISTRATION.

L. Kervezee[1], V. Gotta[2], J. Stevens[1], W. Birkhoff[1], I.M. Kamerling[1], M. Danhof[2], J.H. Meijer[3], J. Burggraaf[1]; [1]Centre for Human Drug Research, Leiden, Netherlands, [2]Leiden Academic Center for Drug Research, Leiden, Netherlands, [3]Leiden Univ Medical Center, Leiden, Netherlands.

BACKGROUND: Many physiological processes exhibit diurnal rhythmicity. Hence, the exposure, effectiveness and side effects of a drug may vary with the time of the day. We investigated the effect of dosing time on drug-induced, heart-rate corrected, QT (QTc) interval on the electrocardiogram (ECG).
METHODS: In a randomized, cross-over, trial 12 healthy male subjects received the QTc-prolonging drug levofloxacin at 02:00, 06:00, 10:00, 14:00, 18:00 and 22:00 at six separate occasions. Blood samples and ECG recordings were collected at regular intervals after drug administration. A pharmacokinetic-pharmacodynamic modeling approach was used to determine variations in drug exposure, heart rate and daily variation in baseline QTc and the effect of dosing time on the QTc interval.
RESULTS: The relationship between the concentration of levofloxacin and the QTc interval shows a 24-hour sinusoidal rhythm. Simulations show that the extent of levofloxacin-induced QTc prolongation depends on dosing time, with the largest effect at 14:00 (1.73 [95% prediction interval: 1.56-1.90] ms per mg/L) and the smallest effect at 06:00 (-0.04 [-0.19-0.12] ms per mg/L).
CONCLUSION: These results suggest that the extent of drug-induced QTc prolongation may depend on the time of day, introducing a potential bias in the assessment of drug-induced QTc prolongation and potentially resulting in a misjudgment of the risk to patients. This phenomenon should be explored further.

TRANSLATIONAL AND PRECISION MEDICINE (TPM) AND DEVELOPMENT, REGULATORY, AND OUTCOMES (DRO) POSTER SESSION

THURSDAY, MARCH 16, 2017

4:30 PM – 6:30 PM

PI-001

DETERGENT-FREE FORMULATION OF NANOSOMAL DOCETAXEL LIPID SUSPENSION (NDLS): A RANDOMIZED TRIAL TO EVALUATE EXPOSURE/ RESPONSE IN WOMEN WITH METASTATIC BREAST CANCER (MBC).

A. Ahmad[1], S. Sheikh[1], M. Gopichand[2], H. Ayre[3], A. Khatri[4], V. Mahobia[5], G. Patel[6], S. Malik[7], K. Rathnam[8], M. S[9], S. Gupta[10], N. Sharma[11], R.A. H[12], D.S. Domadia[13], P. Kale[14], R. Patel[13], P. Patel[15], M. Khan[15], I. Ahmad[1]; [1]Jina Pharmaceuticals, Libertyville, IL, USA, [2]City Cancer Centre, Vijawada, India, [3]Unique Hospital Multispeciality & Research Institute, Surat, India, [4]Samvedna Hospital, Varansi, India, [5]Govt. Medical College & Hospital, Nagpur, India, [6]Apple Hospital, Surat, India, [7]General Hospital & Cancer Centre, Hyderabad, India, [8]Meenakshi Mission Hospital & Reserach Centre, Madurai, India, [9]K. R. Hospital, Mysore Medical College & Research, Mysore, India, [10]King George's Medical University, Lucknow, India, [11]Acharya Tulsi Regional Cancer Treatment & Research Institute, Bikaner, India, [12]Srinivasam Cancer Care Hospital, Bangalore, India, [13]Lambda Therapeutic Research, Ahmedabad, India, [14]Lambda Therapeutic Research, Ahmdeabad, India, [15]Intas Pharmaceuticals Ltd., Ahmedabad, India.

PI-002

SUBPHENOTYPES IN MAJOR DEPRESSIVE DISORDER TO BETTER CHARACTERIZE PHARMACOGENOMIC ANTIDEPRESSANT TREATMENT RESPONSE.

A.T. Ahmed[1], M.A. Frye[1], A. Rush[2], W.V. Bobo[1], J. Biernacka[1], D. Hall Flavin[1], G.D. Jenkins[1], A. Batzle[1], M.K. Skime[1], L. Wang[1], W. Craighead[3], H.S. Mayberg[3], R.M. Weinshilboum[1], R.F. Kaddurah-Daouk[2], B.W. Dunlop[3]; [1]Mayo Clinic, Rochester, MN, USA, [2]Duke University School of Medicine, Durham, NC, USA, [3]Emory University School of Medicine,, Atlanta, GA, USA.

PI-003

IMMUNOTHERAPY FOR HER2 POSITIVE BREAST CANCER.

T.R. Vaidya, S. Ait-Oudhia; College of Pharmacy, University of Florida, Orlando, FL, USA.

PI-004

REAL-WORLD PHARMACOGENOMICS-BASED PATIENT CARE.

J. Alfonsi, R. Kim, W. Teft, P. Dool; University of Western Ontario, London, ON, Canada.

PI-005

ULTRA-RAPID BIOCHAPERONE LISPRO AMELIORATES POSTPRANDIAL BLOOD GLUCOSE (PPG) CONTROL COMPARED TO HUMALOG IN SUBJECTS WITH TYPE 1 DIABETES MELLITUS.

G. Andersen[1], G. Meiffren[2], B. Alluis[2], A. Ranson[2], R. Soula[2], M. Gaudier[2], O. Soula[2], C. Kazda[3], T. Heise[1], S. Bruce[2]; [1]Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany, [2]Adocia, Lyon, France, [3]Eli Lilly and Co., Neuilly-sur-Seine Cedex, France.

PI-006

GENETIC VARIANTS IN KIF15 ARE ASSOCIATED WITH *MYCN*-AMPLIFIED NEUROBLASTOMA.

M.A. Applebaum[1], E. Hungate[1], A. Skol[1], Z. Vaksman[2], M. Diamond[2], L. McDaniel[2], S. Volchenboum[1], B. Stranger[1], S. Diskin[2], J. Maris[2], K. Onel[1], S. Cohn[1]; [1]University of Chicago, Chicago, IL, USA, [2]University of Pennsylvania, Philadelphia, PA, USA.

POSTERS, POSTER WALKS, LATE-BREAKING AND ENCORE ABSTRACTS

PI-007

STATISTICAL ANALYSIS TO COMPARE VARIOUS *IN VITRO* CRITERIA FOR PREDICTING P-GLYCOPROTEIN TRANSPORTER MEDIATED DRUG-DRUG INTERACTIONS *IN VIVO*.

V. Arya[1], T. Zhou[2], X. Yang[1], J. Vaidyanathan[1], L. Zhang[1]; [1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA, [2]US Food and Drug Administration, Silver Spring, MD, USA.

PI-008

STATISTICAL ANALYSIS TO COMPARE VARIOUS *IN VITRO* CRITERIA FOR PREDICTING ORGANIC ANION TRANSPORTING POLYPEPTIDES 1B1 (OATP1B1)-MEDIATED DRUG INTERACTIONS *IN VIVO*.

V. Arya[1], J. Vaidyanathan[1], K. Yoshida[2], X. Yang[1], L. Zhang[1]; [1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA, [2]US Food and Drug Administration (ORISE Fellow), Silver Spring, MD, USA.

PI-009

EVALUATION OF RIFAXIMIN, A NOVEL P-GLYCOPROTEIN SUBSTRATE FOR CONSIDERATION IN DRUG-DRUG INTERACTION STUDIES: AN INTEGRATED ASSESSMENT OF PRECLINICAL AND CLINICAL DATA.

P. Bapat[1], E.L. Reyner[2], E.G. Plise[2], J. Cheong[2], K. Yoshida[2], L. Salphati[2], J.A. Ware[2]; [1]University of Toronto, Toronto, ON, Canada, [2]Genentech, Inc., South San Francisco, CA, USA.

PI-010

PHYSIOLOGICALLY BASED ABSORPTION MODELING AS A TOOL TO EVALUATE THE BIOEQUIVALENCE OF METOPROLOL ER PRODUCTS.

S. Basu[1], H. Yang[1], S. Schmidt[1], L. Fang[2], L. Lesko[1]; [1]University of Florida, Orlando, FL, USA, [2]US Food and Drug Administration, Office of Generic Drugs, Silver Spring, FL, USA.

PI-011

RECTAL OMEPRAZOLE IN YOUNG INFANTS: THE MAGIC BULLET?

P. Bestebreurtje[1], B. de Koning[2], C.A. Knibbe[3], D. Tibboel[2], S.N. de Wildt[4]; [1]Tergooi Hospital, Hilversum, Netherlands, [2]Erasmus MC Sophia, Rotterdam, Netherlands, [3]Leiden University & Antonius Hospital, Leiden & NIeuwegein, Netherlands, [4]Radboud University & Erasmus MC Sophia, Nijmegen & Rotterdam, Netherlands.

PI-012

POINT-OF-CARE PROVIDER USE OF PHARMACOGENOMIC (PGX) RESULTS DURING PRESCRIBING IMPACTS PATIENT (PT) RECALL OF MEDICATION RECOMMENDATIONS.

B.A. Borden, S.M. Lee, K. Danahey, P. Galecki, P. Yukman, M.J. Ratain, P.H. O'Donnell; The University of Chicago, Chicago, IL, USA.

PI-013

A MULTIFACETED INTERVENTION TO REDUCE DRUG-RELATED COMPLICATIONS IN SURGICAL PATIENTS (THE P-REVIEW STUDY).

J. Bos[1], P.M. van den Bemt[2], W. Kievit[3], J.L. Pot[4], J.E. Nagtegaal[4], A. Wieringa[5], M.M. van der Westerlaken[4], G. van der Wilt[3], P.A. de Smet[1], C. Kramers[3]; [1]Canisius Wilhelmina Hospital, Nijmegen, Netherlands, [2]Erasmus University Medical Centre, Rotterdam, Netherlands, [3]Radboud University Medical Centre, Nijmegen, Netherlands, [4]Meander Medical Centre, Amersfoort, Netherlands, [5]Isala Hospital, Zwolle, Netherlands.

PI-014

ASSOCIATION OF UGT1A1*80 ON BILIRUBIN LEVELS IN HEALTHY VOLUNTEERS TREATED WITH EFAVIRENZ.

K.S. Burgess, I.F. Metzger, J. Lu, N. Thong, T.C. Skaar, Z. Desta; Indiana University School of Medicine, Indianapolis, IN, USA.

PI-015

IMPROVING TREATMENT COMPLIANCE WITH A NOVEL MOBILE DIARY APP IN EARLY PHASE CLINICAL TRIALS.

J.F. Pinckaers[1], T. van der Kolk[1], G.K. Hogendoorn[1], R. Rijneveld[1], S. Kouwenhoven[2], G. Feiss[3], A.F. Cohen[1], **K. Burggraaf**[1], R. Rissmann[1]; [1]Centre for Human Drug Research, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Cutanea Life Sciences, Wayne, PA, USA.

PI-016

INTRA-TARGET MICRODOSING (ITM), A NOVEL DRUG DEVELOPMENT APPROACH: PROOF-OF-CONCEPT IN HUMANS.

T. Burt[1], D.B. MacLeod[2], L. Kihak[3], T. Hawk[2], T. Turkington[2], A. Santoro[2], D.K. DeMasi[2], M. Feinglos[2], R.J. Noveck[2], M. Rowland[4]; [1]Burt Consultancy, Durham, NC, USA, [2]Duke University, Durham, NC, USA, [3]Siemens Medical Solutions USA, Inc., Knoxville, TN, USA, [4]Manchester University, Manchester, UK.

PI-017

USE OF MODELING AND SIMULATION TO SUPPORT THE USE OF C.E.R.A. (CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR) IN PEDIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASE.

P. Chanu[1], N. Frey[2]; [1]Genentech/Roche (current) and Certara Strategic Consulting (during analysis), Lyon, France, [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland.

PI-018

DOES SECRETORY CLEARANCE FOLLOW GLOMERULAR FILTRATION RATE IN CHRONIC KIDNEY DISEASES (CKD)? IMPLICATIONS FOR DRUG DOSAGE ADJUSTMENTS.

A. Chapron, D.D. Shen, B.R. Kestenbaum, J. Himmelfarb, C.K. Yeung; University of Washington, Seattle, WA, USA.

PI-019

IMPACT OF GASTRIC PH ON THE PHARMACOKINETICS OF TASELISIB (GDC-0032): INTEGRATION OF PBPK AND RETROSPECTIVE CLINICAL TRIAL ANALYSIS TO INFORM CLINICAL DECISION MAKING.

S. Cheeti[1], J. Suchomel[1], K. Yoshida[1], N. Kotani[2], M. Nakamura[2], J. Tanaka[2], B. Vora[1], L. Salphati[1], K. Faber[1], J. Hsu[1], T.J. Stout[1], M.C. Wei[1], J.A. Ware[1]; [1]Genentech, Inc., South San Francisco, CA, USA, [2]Chugai Pharmaceutical Co., Ltd., Tokyo, Japan.

PI-020

NON-SPECIFIC BINDING AFFECTS TKI-TRANSPORTER INTERACTIONS.

M. Chen, A.A. Gibson, N. Pabla, A. Sparreboom, S.D. Baker; The Ohio State University, Columbus, OH, USA.

PI-021

HIGH-DIMENSIONAL DRUG INTERACTION SCREENING AND VALIDATION USING HEALTH RECORD DATABASES AND PHYSIOLOGICALLY BASED PHARMACOKINETICS MODELS .

C.-W. Chiang, P. Zhang, X. Wang, Z. Desta, S.K. Quinney, L. Li; Indiana University - Purdue University Indianapolis, Indianapolis, IN, USA.

PI-022

VISUALIZATION TECHNIQUE FOR FAERS-BASED ADVERSE EVENT PREDICTION.

B. Cicali, G. Badea, K. Bain, C.H. Knowlton, J. Turgeon; Tabula Rasa HealthCare, Moorestown, NJ, USA.

POSTERS, POSTER WALKS, LATE-BREAKING AND ENCORE ABSTRACTS

PI-023

IMPACT OF BETWEEN-SUBJECT, WITHIN-SUBJECT AND BETWEEN-OCCASION VARIABILITY ON THERAPEUTIC SUCCESS FOR NARROW THERAPEUTIC INDEX DRUGS: A BIOEQUIVALENCE PERSPECTIVE.

E. Dahmane, M. Gopalakrishnan, L. Fang, J. Gobburu, V. Ivaturi; University of Maryland Baltimore, School of Pharmacy, Baltimore, MD, USA.

PI-024

EVALUATION OF ANTIBIOTIC INTERACTIONS: A CASE EXAMPLE WITH TIME KILL CURVE EXPERIMENTS.

A.N. Deitchman[1], A. Broeker[1], J. Kast[1], S.G. Wicha[2], R.S. Singh[1], H. Derendorf[1]; [1]University of Florida, Gainesville, FL, USA, [2]Uppsala University, Uppsala, Sweden.

PI-025

FREQUENCY OF CYP2D6 ALLELES INCLUDING STRUCTURAL VARIANTS IN THE UNITED STATES.

A.L. Del Tredici[1], A. Malhotra[1], M. Dedek[1], F. Espin[1], D. Roach[1], G.-D. Zhu[1], J. Voland[1], T.A. Moreno[1], A. Gaedigk[2]; [1]Millennium Health, LLC, San Diego, CA, USA, [2]Children's Mercy-Kansas City, Kansas City, MO, USA.

PI-026

DOSE SELECTION IN ENTRY INTO HUMAN (EIH) STUDIES: LEARNINGS FROM A RETROSPECTIVE SURVEY ON EIH STUDIES WITH SMALL MOLECULES CONDUCTED BETWEEN 2004 AND 2014 AT HOFFMANN-LAROCHE.

M.-L. Delporte, R.W. Peck, N.J. Parrott, C. Weber, T. Lave, B. Ricci; Hoffmann-LaRoche, Basel, Switzerland.

PI-027

EVALUATION OF *KDR* RS34231037 AS PREDICTOR OF SUNITINIB EFFICACY IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA.

M. Apellániz-Ruiz[1], **M.H. Diekstra**[2], J. María Roldán[3], E. Boven[4], D. Castellano[5], H. Gelderblom[6], R.H. Mathijssen[7], J.J. Swen[2], S. Böhringer[8], J. García-Donás[9], B. Rini[10], H.-J. Guchelaar[2], C. Rodríguez-Antona[11]; [1]Hereditary Endocrine Cancer Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain, [2]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands, [3]Hereditary Endocrine Cancer Group, Spanish National Cancer Research Centre (CNIO),, Madrid, Spain, [4]Medical Oncology, VU University Medical Center, Amsterdam, Netherlands, [5]Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain, [6]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands, [7]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [8]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, Netherlands, [9]Oncology Unit, Clara Campal Comprehensive Cancer Centre, Madrid, Spain, [10]Department of Solid Tumour Oncology, Cleveland Clinic Foundation (CCF) Taussig Cancer Institute, Cleveland, OH, USA, [11]Hereditary Endocrine Cancer Group, Spanish National Cancer Research Centre (CNIO), ISCIII Center for Biomedical Research on Rare Diseases (CIBERER), Madrid, Spain.

PI-028

APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL (PBPK) TO PREDICT PH-DEPENDENT DRUG-DRUG INTERACTION (DDI) FOR WEAK BASE DRUGS (WBDS).

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PI-029

A GWAS OF RESISTANT HYPERTENSION IN THE INTERNATIONAL VERAPAMIL SR-TRANDOLAPRIL STUDY (INVEST) AND SECONDARY PREVENTION OF SUBCORTICAL STROKES (SPS3).

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PI-030

ALEMTUZUMAB PK IN PEDIATRIC PATIENTS UNDERGOING REDUCED INTENSITY ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT): TOWARD DOSE INDIVIDUALIZATION.

C. Emoto[1], R.A. Marsh[2], L. Neumeier[2], P.A. Mehta[2], A.A. Vinks[1], T. Fukuda[1]; [1]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

PI-031

VANCOMYCIN DYNAMIC PBPK MODELING TO ASSESS PHARMACOKINETIC PROFILES ASSOCIATED WITH CHANGES IN MULTIPLE PHYSIOLOGICAL PARAMETERS.

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PI-032

CROSS INDUSTRY COMPARISON OF CLINICAL PHARMACOLOGY STUDY DESIGN, ENROLLMENT, AND TOTAL PACKAGE COST ANALYSIS FOR APPROVED ONCOLOGY DRUGS.

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PI-033

VONOPRAZAN-BASED DUAL THERAPY WITH AMOXICILLIN IS AS EFFECTIVE AS THE TRIPLE THERAPY FOR ERADICATION OF H. PYLORI.

T. Furuta, T. Kagami, T. Suzuki, H. Ichikawa, M. Yamade, K. Umemura; Hamamatsu University School of Medicine, Hamamatsu, Japan.

PI-034

FUNCTIONAL CHARACTERIZATION OF RARE *CYP2D6* ALLELIC VARIANTS *IN VIVO*.

A. Gaedigk, G.P. Twist, N.A. Miller, E.G. Farrow, J.A. Lowry, S.E. Soden; Children's Mercy Kansas City, Kansas City, MO, USA.

PI-035

ESTABLISHING AN *IN VITRO* DISSOLUTION "SAFE SPACE" FOR MK-3682B FIXED-DOSE COMBINATION (FDC) TABLETS.

W. Gao, S. Glasgow, L. Arrington, J. Kuiper, J. Miller, D. Harris, F. Kesisoglou, G. Garrett, B. Davit; Merck & Co., West Point, PA, USA.

PI-036

POPULATION PHARMACOKINETIC/ PHARMACODYNAMIC MODELING OF DACOMITINIB EXPOSURE ON QT INTERVALS IN PATIENTS (PTS) WITH ADVANCED NSCLC.

N. Giri[1], S. Quinn[2], E. Sbar[3], A. Ruiz-Garcia[1]; [1]Pfizer Inc., San Diego, CA, USA, [2]Pfizer Inc., Cambridge, MA, USA, [3]Pfizer Inc., Collegeville, PA, USA.

PI-037

ADVERSE DRUG REACTION CAUSALITY ASSESSMENT TOOLS FOR DRUG-INDUCED STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS: ROOM FOR IMPROVEMENT.

J.L. Goldman[1], W.-H. Chung[2], B. Lee[1], W. Hoetzenecker[3], R.G. Micheletti[4], S. Usdin Yasuda[5], D.J. Margolis[6], N.H. Shear[7], J.P. Struewing[8], M. Pirmohamed[9]; [1]Children's Mercy Hospital, Kansas City, MO, USA, [2]Chang Gung Memorial Hospital, Taipei, Linko and Keelung, Taipei, Taiwan, [3]University of Zurich, Zurich, Switzerland, [4]Hospital of the University of Pennsylvania, Philadelphia, PA, USA, [5]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA, [6]University of Pennsylvania, Philadelphia, PA, USA, [7]Sunnybrook Health Sciences Centre and University of Toronto, Toronto, ON, Canada, [8]National Human Genome Research Institute, Bethesda, MD, USA, [9]University of Liverpool, Liverpool, UK.

PI-038

INFLUENCE OF TYPE 2 DIABETES ON CYTOCHROMES P450 ENZYMES MEDIATED DRUG METABOLISM.

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PI-039

ASSESSMENT OF THE EFFECT OF HMGCR VARIANT ALLELES ON RESPONSE TO ATORVASTATIN TREATMENT IN TYPE 2 DIABETIC EGYPTIAN PATIENTS.

A.A. Guemei, S.B. Abdel-Kader, I.H. Diab, M.H. Megallaa, M.K. Barakat; School of Medicine, Alexandria University, Alexandria, Egypt.

PI-040

A PHASE I MASS BALANCE STUDY OF IXAZOMIB, AN ORAL PROTEASOME INHIBITOR (PI), USING ACCELERATOR MASS SPECTROMETRY (AMS) IN PATIENTS WITH ADVANCED SOLID TUMORS.

N. Gupta[1], S. Zhang[1], S. Pusalkar[1], D.A. Noe[1], M. Plesescu[1], M.J. Hanley[1], S. Chowdhury[1], B. Wang[1], K. Venkatakrishnan[1], D.R. Shepard[2]; [1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA, [2]Cleveland Clinic, Cleveland, OH, USA.

PI-041

MODELING POPULATION PK AND PENETRATION OF STANDARD ANTI-TB DRUGS IN PULMONARY LESIONS FROM ADULTS WITH ACTIVE TB.

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PI-042

CHARACTERIZATION OF THE PHARMACOKINETICS OF IXAZOMIB IN CHINESE PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA IN THE CHINA CONTINUATION OF THE TOURMALINE-MM1 STUDY.

M.J. Hanley[1], N. Gupta[1], J. Hou[2], Y. Xu[3], J. Jin[4], X. Chen[5], B. Wang[1], H. Wang[6], H. van de Velde[1], K. Venkatakrishnan[1]; [1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA, [2]ChangZheng Hospital, Shanghai, China, [3]Chinese Academy of Medical Science & Peking Union Medical College, Tianjin, China, [4]First Hospital Affiliated Zhe Jiang Medical University, Zhejiang, China, [5]Xijing Hospital, Xi'an, China, [6]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Beijing, China.

PI-043

TYROSINE PHOSPHORYLATION MEDIATED REGULATION OF OCT1 AND MATE1 FUNCTION.

S. Hu, N. Pabla, A.A. Gibson, S.D. Baker, A. Sparreboom; The Ohio State University, Columbus, OH, USA.

PI-044

PHARMACOKINETICS AND PHARMACODYNAMICS OF GEMIGLIPTIN/ROSUVASTATIN FIXED-DOSE COMBINATION COMPARED WITH LOOSE COMBINATION OF INDIVIDUAL TABLETS IN HEALTHY SUBJECTS.

I. Hwang[1], S.-I. Park[1], K. Park[1], S. Yoon[1], J. Jung[2], S. Lee[1], H. Lee[1], K.-S. Yu[1]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]LG Life Sciences, Seoul, Republic of Korea.

PI-045

STATEWIDE SURVEY ON PUBLIC PERCEPTION OF PROVIDER INFLUENCE ON PHARMACOGENETIC TESTING.

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PI-046

EFFECTIVENESS OF COMMUNITY-BASED HBA1C SCREEN AS A CLINICAL STUDY RECRUITMENT TOOL.

S.H. Jaycox, M. Esposito, S. Paglialunga; Celerion, Tempe, AZ, USA.

PI-047

DEVELOPMENT OF PREEMPTIVE GENOTYPING METHODS USING MULTIPLEX SINGLE BASE EXTENSION.

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PI-048

ORGANIC ANION TRANSPORTER POLYPEPTIDE (OATP) MEDIATED DRUG INTERACTIONS BETWEEN RIFAMPIN AND LINEZOLID, *IN VITRO.*

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PI-049

THE EFFECTS OF FAMPRIDINE ON EYE MOVEMENTS IN MULTIPLE SCLEROSIS PATIENTS WITH INTERNUCLEAR OPHTHALMOPLEGIA.

K. Kanhai[1], Y.L. Wagenaar[1], J.A. Nij Bijvank[2], E.S. Klaassen[1], K. Lim[1], S.C. Bergheanu[1], A. Petzold[2], A. Verma[3], R. van Rijn[2], G. Groeneveld[1]; [1]Centre for Human Drug Research, Leiden, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Biogen, Boston, MA, USA.

PI-050

ANTIBIOTICS IN SPACE: POTENTIAL IMPACT OF THE SPACEFLIGHT ENVIRONMENT ON CIPROFLOXACIN EFFICACY AGAINST *E. COLI.*

J. Kast[1], E.L. Schuck[1], A.N. Deitchman[1], L. Putcha[2]*, H. Derendorf[1]; [1]University of Florida, Gainesville, FL, USA, [2]NASA Johnson Space Center, *Author is deceased, Houston, TX, USA.

PI-051

PALATABILITY OF A NOVEL ORAL PREDNISONE FORMULATION: A MATTER OF GOOD TASTE.

G. Kearns[1], S. Bai[1], C. Shoults[2], D. Pierce[3], N. Dormer[2]; [1]Arkansas Children's Research Institute, Little Rock, AR, USA, [2]Orbis Biosciences, Inc., Lenexa, KS, USA, [3]Arkansas Children's Hospital, Little Rock, AR, USA.

PI-052

WHITE MATTER CONNECTIVITY RELATED TO AMISULPRIDE TREATMENT RESPONSE IN PATIENTS WITH SCHIZOPHRENIA.

M.-K. Kim, K. Lim, S.-H. Lee; Bundang CHA Medical Center, CHA University, Seoul, Republic of Korea.

PI-053

PLASMA LEUKOTRIENE E4 AND PERIPHERAL EOSINOPHILS CAN REFLECT PRIOR IN ELDERLY ASTHMATICS.

G.-Y. Ban[1], Y.-M. Ye[1], **A. Kim[2]**, S.-H. Kim[3], G.-Y. Hur[4], J.-H. Kim[5], J.-J. Shim[4], K. Cho[6], J.-Y. Cho[6], H.-S. Park[1]; [1]Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea, Republic of, [2]Clinical Trial Center, Ajou University School of Medicine, Suwon, Republic of Korea, [3]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea, [4]Department of Internal Medicine, Korea University Guro Hospital, Seoul, Republic of Korea, [5]Department of Internal Medicine, Hallym University School of Medicine, Anyang, Republic of Korea, [6]Department of Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea.

PI-054

A SURVEY OF THE EFFECTS OF SOFT FOOD VEHICLES ON PHARMACOKINETICS FOR THE ALTERNATIVE DOSING METHOD.

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PI-055

THE PHARMACOGENOMIC EFFECTS ON PHARMACOKINETICS AND PHARMACODYNAMICS OF BOSENTAN.

H.-S. Kim, M. Oh, E.-Y. Kim, J.-G. Shin; Inje University College of Medicine, Busan, Republic of Korea.

PI-056
EFFECTS OF SEX, AGE AND HORMONE ON DISTRIBUTION OF METABOLIC MARKERS PREDICTING HEPATIC CYP3A ACTIVITY IN HEALTHY KOREANS.
A.H. Kim, J. Lee, S. Yoon, S. Lee, K.-S. Yu, I.-J. Jang, J.-Y. Cho; Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea.

PI-057
ANALYSIS OF ADULT IN-HOSPITAL MEDICATIONS FOR CLINICALLY ACTIONABLE PHARMACOGENOMIC (PGX) INFORMATION.
Y. Lee[1], K. Danahey[1], G. Moscoe[2], L. Kreidich[3], M.J. Ratain[1], D.O. Meltzer[1], P.H. O'Donnell[1]; [1]The University of Chicago, Chicago, IL, USA, [2]Asante Three Rivers Medical Center, Grant Pass, OR, USA, [3]The University of Chicago Medicine, Chicago, IL, USA.

PI-058
DOSE-RESPONSE RELATIONSHIP OF FIMASARTAN IN COMBINATION WITH HYDROCHLOROTHIAZIDE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION.
H. Lee[1], H. Chung[1], H. Yoo[1], S. Yoon[2], S. Yoon[1], H. Lee[1]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, Republic of Korea.

PI-059
FUNCTIONAL CHARACTERIZATION OF ETHIONAMIDE AND PROTHIONAMIDE BY MDR1, MRP1/2, *IN VITRO*.
Y. Lee[1], S. Lim[1], M. Cho[1], Y. Yoon[2], D. Lee[2], M. Parvez[1], **H. Shin**[1], J.-G. Shin[1]; [1]Department of Pharmacology and Pharmacogenomics Research Center, Inje University, Busan, Republic of Korea, [2]Inje University Busan Paik Hospital, Busan, Republic of Korea.

PI-060
LORATADINE, A POTENT INHIBITOR OF LACTIC ACID TRANSPORTERS MCT1 AND MCT4 IN HUMAN SKELETAL MUSCLE CELLS.
Y. Leung, J. Turgeon, V. Michaud; Université de Montréal, Montreal, QC, Canada.

PI-061
PROSPECTIVE EVALUATION OF GENETIC VARIATION IN *PEAR1* REVEALS ASPIRIN-DEPENDENT EFFECTS ON PLATELET AGGREGATION PATHWAYS.
J.P. Lewis, J.D. Backman, L.M. Yerges-Armstrong, R.B. Horenstein, S. Newcomer, S. Shaub, M. Morrisey, P. Donnelly, M. Drolet, K. Tanner, M.A. Pavlovich, J.R. O'Connell, B.D. Mitchell; University of Maryland, Baltimore, Baltimore, MD, USA.

PI-062
MECHANISTIC UNDERSTANDING OF THE BLOOD-BRAIN BARRIER PENETRATION OF AZD1775 IN GLIOBLASTOMA PATIENTS: A PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING APPROACH.
J. Li[1], J. Wu[1], X. Bao[1], Y. Xie[1], A. Sparreboom[2], N. Sanai[3]; [1]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA, [2]College of Pharmacy & Comprehensive Cancer Center, Ohio State University, Columbus, OH, USA, [3]Barrow Neurological Institute, St. Joseph's Hospital & Medical Center, Phoenix, AZ, USA.

PI-063
APPLICATION OF PBPK MODELING TO PREDICT FOOD EFFECT ON ORAL DRUG ABSORPTION: A REVIEW OF SCIENTIFIC PUBLICATIONS AND REGULATORY SUBMISSIONS.
M. Li, Y. Pan, P. Zhao; US Food and Drug Administration, Silver Spring, MD, USA.

PI-064

A REVIEW OF SIX OPIOID ANALGESICS WITH ABUSE-DETERRENT LABELING.

W. Li[1], S.C. Nallani[1], S.N. Calderon[2], E. Fields[3], S.H. Hertz[3], Y. Xu[1], C.G. Sahajwalla[1]; [1]DCP2, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA, [2]Controlled Substance Staff, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA, [3]Division of Anesthesia Analgesia and Addiction Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA.

PI-065

APPLICATION OF BOOTSTRAP METHOD IN BIOEQUIVALENCE STUDY FOR ORAL GENERIC PRODRUG PRODUCTS.

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PI-066

PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING OF DRUG-DRUG INTERACTION (DDI) BETWEEN TEMSIROLIMUS AND ITS METABOLITE SIROLIMUS WITH MIDAZOLAM.

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PI-067

META-ANALYSIS ON THE ASSOCIATION OF *VEGFR1* GENETIC VARIANTS WITH SUNITINIB OUTCOME IN METASTATIC RENAL CELL CARCINOMA PATIENTS.

X. Liu[1], J. Swen[1], E. Boven[2], D. Castellano[3], H. Gelderblom[1], R. Mathijssen[4], C. Rodríguez-Antona[5], J. García-Donas[6], B. Rini[7], H.-J. Guchelaar[1]; [1]Leiden University Medical Center, Leiden, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [5]Spanish National Cancer Research Centre, Madrid, Spain, [6]Clara Campal Comprehensive Cancer Center, Madrid, Spain, [7]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA.

PI-068

SNP-DEPENDENT *CYP1A1* INDUCTION: GENETIC VARIATION NEAR BUT NOT IN XRES MODULATES ARYL HYDROCARBON RECEPTOR FUNCTION.

D. Liu, S. Qin, K. Krishna, L. Wang, R. Weinshilboum; Mayo Clinic, Rochester, MN, USA.

PI-069

VORICONAZOLE-INDUCED QT PROLONGATION - CLINICAL CHARACTERISTICS AND RISK FACTORS.

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PI-070

THE ROLE OF ORGANIC CATION TRANSPORTER 3 (OCT3, *SLC22A3*) IN THE PHARMACOKINETICS OF EPINEPHRINE.

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PI-071

PLACEBO-RESPONSE IN ANALGESIC CLINICAL TRIALS.

A.A. Manerikar, S.C. Nallani, E.W. Fields, Y. Xu, C.G. Sahajwalla; US Food and Drug Administration, Silver Spring, MD, USA.

PI-072

RELATIONSHIP BETWEEN RESPONSE RATES AND PROGRESSION-FREE SURVIVAL IN NON-HODGKIN'S LYMPHOMA.

N. Mangal[1], A.H. Salem[2], M. Li[3], R. Menon[2], K.J. Freise[2]; [1]Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando, FL, USA, [2]Clinical Pharmacology and Pharmacometrics, AbbVie, Inc., North Chicago, IL, USA, [3]Virginia Commonwealth University, Richmond, VA, USA.

PI-073

THE ASSOCIATION OF CYTOCHROMES P450 AND TRANSPORTER GENETIC VARIATION WITH STEADY-STATE ENDOXIFEN CONCENTRATION.

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PI-074

PHARMACOKINETICS OF MILRINONE IN INFANTS WITH ACUTE KIDNEY INJURY FOLLOWING CARDIAC SURGERY.

T. Mizuno[1], K.M. Gist[2], Z. Gao[1], E.C. King[1], S.L. Goldstein[1], A.A. Vinks[1]; [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]University of Colorado, Children's Hospital Colorado, Aurora, CO, USA.

PI-075

AN AGE-APPROPRIATE SIROLIMUS DOSE IN NEONATES AND INFANTS WITH COMPLICATED VASCULAR ANOMALIES: APPLICATION OF MODELING AND SIMULATION OF DEVELOPMENTAL CHANGES IN CLEARANCE.

T. Mizuno[1], T. Fukuda[1], C. Emoto[1], P.S. Mobberley-Schuman[1], A.M. Hammill[1], D.M. Adams[2], A.A. Vinks[1]; [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]Boston Children's Hospital and Harvard Medical School, Boston, MA, USA.

PI-076

EXPOSURE-RESPONSE ANALYSIS TO ASSESS THE EFFECT OF ABT-494 ON QT INTERVAL AND UTILIZATION OF A NON-PHARMACOLOGICAL APPROACH TO DEMONSTRATE ECG ASSAY SENSITIVITY.

M.-E.F. Mohamed, J. Zeng, P. Jiang, B. Hosmane, A.A. Othman; AbbVie, North Chicago, IL, USA.

PI-077

PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING TO EVALUATE DRUG-DRUG INTERACTION (DDI) RISK OF ALECTINIB.

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PI-078

NOVEL ANTIMALARIAL LEAD IDENTIFICATION USING *IN SILICO* PREDICTION METHODS AND SIMULATION.

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PI-079

THE INFLUENCE OF THE GENETIC POLYMORPHISMS OF EFFLUX TRANSPORTER ON DRV LEVELS IN PBMC AND PLASMA.

D. Nagano[1], T. Araki[1], K. Yanagisawa[2], Y. Ogawa[2], H. Uchiumi[2], Y. Nojima[2], K. Yamamoto[1]; [1]Departments of Clinical Pharmacology, Gunma University Graduate School of Medicine and Department of Pharmacy, Gunma University Hospital, Maebashi, Japan, [2]Departments of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Japan.

PI-080

CHANGES IN BLOOD CONCENTRATIONS OF TRACE METALS DURING THE FIRST CYCLE OF CDDP-BASED CHEMOTHERAPY.

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POSTERS, POSTER WALKS, LATE-BREAKING AND ENCORE ABSTRACTS

PI-081

IDENTIFICATION OF MAJOR CONTRIBUTORS TO INTER-INDIVIDUAL VARIABILITY IN CYP2D6-MEDIATED DRUG METABOLISM.

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PI-082

EXAMINING THE RELATIONSHIP BETWEEN ATHEROGENIC INDICES AND THE NON-INVASIVE FIBROSIS BIOMARKER FIB-4.

S. Paglialunga; Celerion, Tempe, AZ, USA.

PI-083

SOLUTE CARRIER FAMILY (SLC22) TRANSPORTERS MEDIATED SUBSTRATE CHARACTERIZATION OF 22 ANTI-TB DRUGS.

M. Parvez, N. Kaisar, Y. Lee, **H. Shin**, J. Jung, J.-G. Shin; Department of Pharmacology and PharmacoGenomics Research Center, Inje University College of Medicine, Busan, Republic of Korea.

PI-084

ORGANIC ANION TRANSPORTER (OATS) MEDIATED DRUG-INTERACTIONS BETWEEN ADEFOVIR /TENOFOVIR AND P-AMINO SALICYLIC ACID (PAS), *IN VITRO*.

M. Parvez, N. Kaisar, Y. Lee, **H. Shin**, J. Jung, J.-G. Shin; Department of Pharmacology and Pharmacogenomics Research Center, Inje University College of Medicine, Busan, Republic of Korea.

PI-085

DRUG-DRUG INTERACTION PREDICTION BETWEEN P-AMINO SALICYLIC ACID (PAS) AND TENOFOVIR USING A FULL PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL.

M. Parvez, N. Kaisar, M. Hasanuzzaman, **H. Shin**, J. Jung, J.-G. Shin; Department of Pharmacology and Pharmacogenomics Research Center, Inje University College of Medicine, Busan, Republic of Korea.

PI-086

PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF A NOVEL FACTOR XI_A INHIBITOR ADMINISTERED AS IV INFUSION IN NON-JAPANESE AND JAPANESE HEALTHY SUBJECTS.

V. Perera[1], C.E. Frost[1], C.L. Yones[1], Z. Wang[1], S. Dorizio[1], C. Russo[1], W. Chen[2], T. Ueno[3], M. Akimoto[3], B. Cirincione[1], X. Xu[1], D.A. Seiffert[1], M.M. Desouza[1], P. Mugnier[4], F. LaCreta[1], R.J. Frost[1]; [1]Early Clinical and Translational Research, Bristol-Myers Squibb Company, Princeton, NJ, USA, [2]Global Regulatory Safety and Biometrics, Bristol Myers Squibb Company, Princeton, NJ, USA, [3]Translational Research, Bristol Myers Squibb Company K.K, Tokyo, Japan, [4]Global Regulatory Safety and Biometrics, Bristol-Myers Squibb Company, Princeton, NJ, USA.

PI-087

EXPOSURE-RESPONSE ANALYSIS OF A NOVEL FACTOR XIA INHIBITOR USING ACTIVATED PARTIAL THROMBOPLASTIN TIME RATIO.

V. Perera, R.J. Frost, Z. Wang, T.S. Garimella, M. Bouillon-Pichault, X. Xu, C.E. Frost, J.M. Luettgen, D.A. Seiffert, M.M. Desouza, F. LaCreta, B. Cirincione; Early Clinical and Translational Research, Bristol-Myers Squibb Company, Princeton, NJ, USA.

PI-088

REVERSAL OF MECAMYLAMINE-INDUCED EFFECTS IN HEALTHY SUBJECTS BY NICOTINE RECEPTOR AGONISTS: COGNITIVE AND (ELECTRO) PHYSIOLOGICAL RESPONSES.

R. Alvarez-Jimenez, E.P. 't Hart, **S. Prins**, M. de Kam, J.M. van Gerven, A. Cohen, G. Groeneveld; Centre for Human Drug Research, Leiden, Netherlands.

PI-089

ASSESSMENT OF A BASIC MODEL FOR PREDICTING POTENTIAL CLINICAL DRUG INTERACTIONS MEDIATED BY CYP3A4 INHIBITION.

H. Qosa, B. Avaritt, D. Volpe; US Food and Drug Administration, Silver Spring, MD, USA.

PI-090
LITERATURE MINING OF PHARMACOKINETIC STUDIES OF ANTIDEPRESSANTS IN PREGNANCY.
S.K. Quinney[1], L.H. Kus[1], I.E. Su[1], S. Katta[2], D.M. Haas[1]; [1]Indiana University School of Medicine, Indianapolis, IN, USA, [2]Indiana University School of Informatics and Computing, Indianapolis, IN, USA.

PI-091
UTILIZATION OF INFORMATICS TOOLS TO MECHANISTICALLY ANALYZE DRUGS ASSOCIATED WITH SEROTONIN SYNDROME.
R. Racz, K. Burkhart; US Food and Drug Administration, Silver Spring, MD, USA.

PI-092
IMPLEMENTATION OF NEUROPSYCHIATRIC PHARMACOGENETICS AT CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER: 12 YEARS OF SUCCESSFUL PERSONALIZED MEDICINE.
L.B. Ramsey, L. Bronicki, C.A. Prows, S. Sadhasivam, M.T. Sorter, K. Zhang, T.A. Glauser, A.A. Vinks; Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

PI-093
CHARACTERIZATION OF NIVOLUMAB PHARMACOKINETICS (PK) INCORPORATING TIME-VARYING CLEARANCE (CL) IN CANCER PATIENTS.
J. Raybon, P. Statkevich, Y. Feng, L. Zhu, M. Hruska, A. Bello, S. Agrawal, A. Roy, G. Bajaj; Bristol-Myers Squibb, Princeton, NJ, USA.

PI-094
IMPACT OF A PHARMACOGENETICS SERVICE MODEL IN THE HOSPICE SETTING.
K.K. Reynolds[1], K. Richard[2], B.A. McNally[3], M.W. Linder[1]; [1]PGXL Laboratories and University of Louisville, Louisville, KY, USA, [2]ViaQuest, Inc, Dublin, OH, USA, [3]PGXL Laboratories, Louisville, KY, USA.

PI-095
POPULATION PHARMACOKINETICS OF HIGH-DOSE METHOTREXATE IN INFANTS WITH BRAIN TUMORS.
J. Roberts, T. Lin, J. Huang, A. Onar-Thomas, J. Panetta, V. Daryani, G. Robinson, A. Broniscer, A. Gajjar, C. Stewart; St. Jude Children's Research Hospital, Memphis, TN, USA.

PI-096
PATTERN OF EVENT-RELATED ADVERSE EVENTS AS A PREDICTOR FOR RISK OF TORSADES DE POINTES (TDP).
K. Romero[1], D. Woosley[2], T. Gallo[3], R.L. Woosley[4]; [1]Critical Path Institute, Tucson, AZ, USA, [2]AZCERT, Oro Valley, AZ, USA, [3]ACZERT, Marana, AZ, USA, [4]AZCERT, Marana, AZ, USA.

PI-097
IMPLEMENTING AN ENHANCED STANDARDIZED MEDICATION THERAPY MANAGEMENT APPROACH WITHIN A PRIMARY CARE SETTING.
E.J. Schwartz[1], J. Patel[2], P. Patel[2], H. Shah[2], A.M. Issa[3], J. Turgeon[1], O.V. Knowlton[1], C.H. Knowlton[1], K.T. Bain[1]; [1]TabulaRasa HealthCare, Moorestown, NJ, USA, [2]Elmwood Family Physicians, Marlton, NJ, USA, [3]University of the Sciences, Philadelphia, PA, USA.

PI-098
UTILIZING PBPK TO UNDERSTAND HEALTHY VOLUNTEER VS. CANCER PATIENTS PK.
E. Schwenger[1], G. Moorthy[1], E. Masson[1], H. Tomkinson[2], K. Vishwanathan[1]; [1]AstraZeneca, Waltham, MA, USA, [2]AstraZeneca, Cambridge, UK.

PI-099
PHARMACOKINETICS AND BIOEQUIVALENCE OF TELMISARTAN/S-AMLODIPINE COMBINATION TABLETS AND CO-ADMINISTRATION OF TELMISARTAN AND S-AMLODIPINE IN HEALTHY VOLUNTEERS.
S. Seong, W. Kang, B. Ohk, B. Kim, M.-R. Gwon, H.-J. Kim, H. Lee, Y.-R. Yoon; Kyungpook National University Hospital Clinical Trial Center, Daegu, Korea, Republic of.

POSTERS, POSTER WALKS, LATE-BREAKING AND ENCORE ABSTRACTS

PI-100

THIAZIDE INDUCED HYPERURICEMIA: NOVEL INSIGHTS FROM METABOLOMICS AND GENOMICS INTEGRATION IN THE PHARMACOGENOMIC EVALUATION OF ANTIHYPERTENSIVE RESPONSES 2 (PEAR 2) STUDY.

M.H. Shahin[1], G. Michailidis[2], Y. Gong[1], A.L. Beitelshees[3], A.B. Chapman[4], J.G. Gums[1], E. Boerwinkle[5], S.T. Turner[6], R.M. Cooper-DeHoff[1], J.A. Johnson[1]; [1]Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, College of Pharmacy, University of Florida, Gainesville, FL, USA, [2]Department of Statistics, University of Florida, Gainesville, FL, USA, [3]Department of Medicine, University of Maryland, Baltimore, MD, USA, [4]Department of Medicine, The University of Chicago, Chicago, IL, USA, [5]Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, TX, USA, [6]Department of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA.

PI-101

LEAN BODY WEIGHT (LBW) DOSING OF PANTOPRAZOLE IS APPROPRIATE FOR OBESE CHILDREN.

V. Shakhnovich[1], B. Smith[2], J. Guptill[3], L. James[4], D. Collier[5], H. Wu[6], C. Livingston[6], J. Zhao[6], G. Kearns[7]; [1]Children's Mercy Hospital, Kansas City, MO, USA, [2]Duke University Medical Center, Durham, NC, USA, [3]Duke Clinical Research Institute, Durham, NC, USA, [4]Arkansas Children's Hosital, Little Rock, AR, USA, [5]East Carolina University, Greenville, NC, USA, [6]Duke University Research Institute, Durham, NC, USA, [7]Arkansas Children's Hospital, Little Rock, AR, USA.

PI-102

ASSOCIATION OF FC-GAMMA RECEPTOR POLYMORPHISM CD16A AND CLINICAL BENEFITS OF ELOTUZUMAB IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE.

J. Sheng, B. Farsaci, O. Sy, C. Passey, M. Robbins, L. Zhu, M. Gupta; BMS, Princeton, NJ, USA.

PI-103

HOW DRUG-DRUG INTERACTIONS (DDIS) INFORM DRUG LABELING: A SURVEY OF APPROVED NEW MOLECULAR ENTITIES (NMES) FROM 1998 TO 2015.

T. Shugg, J. Xu, I.R. Younis; US Food and Drug Administration, Silver Spring, MD, USA.

PI-104

LETROZOLE INHIBITS HERG CURRENT AND REDUCES PROLIFERATION IN CULTURED GLIOBLASTOMA CELLS.

T. Shugg[1], N. Dave[2], J.D. Robarge[2], K. Pollok[2], B.R. Overholser[1]; [1]Purdue University, West Lafayette, IN, USA, [2]Indiana University School of Medicine, Indianapolis, IN, USA.

PI-105

REDUCED NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE ACTIVITY POTENTIATES THE TOXICITY OF METHOTREXATE THROUGH DEPLETION OF CELLULAR ATP.

R.K. Singh, R.S. Funk; University of Kansas, Kansas City, KS, USA.

PI-106

ASSOCIATION OF ADRB1 GENE DNA METHYLATION WITH ANTIHYPERTENSIVE RESPONSE TO METOPROLOL IN THE PHARMACOGENOMIC EVALUATION OF ANTIHYPERTENSIVE RESPONSES 2 (PEAR-2) STUDY.

M.H. Solayman[1], T.Y. Langaee[1], Y. Gong[1], S.T. Turner[2], A.B. Chapman[3], J.G. Gums[1], E. Boerwinkle[4], A.L. Beitelshees[5], L. El-Wakeel[6], M. El-Hamamsy[6], R.M. Cooper-DeHoff[1], O.A. Badary[6], J.A. Johnson[1]; [1]Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL, USA, [2]Division of Nephrology and Hypertension, Department of Medicine, College of Medicine, Mayo Clinic, Rochester, MN, USA, [3]The University of Chicago Medicine, Chicago, IL, USA, [4]The University of Texas Health Science Center at Houston (UTHealth) School of Public Health, Houston, TX, USA, [5]Department of Medicine, University of Maryland, Baltimore, MD, USA, [6]Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.

PI-107

DICLOXACILLIN AND FLUCLOXACILLIN INDUCE CYP3A4 AND CYP2C9 IN HUMAN HEPATOCYTES.

T.B. Stage[1], S. Wong[2], D.L. Kroetz[1], C. Khojasteh[2]; [1]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA, [2]DMPK, Genentech, Inc., 1 DNA Way, South San Francisco, USA, South San Francisco, CA, USA.

PI-108

MEDICATION-SPECIFIC LONG QT-JT INDEX AND PATIENT-SPECIFIC LONG QT-JT SCORE FOR ASSESSING RISK OF TORSADE DE POINTES: VALIDATION IN AN AMBULATORY POPULATION.

L.E. Steffen, G. Badea, B. Cicali, C.H. Knowlton, J. Turgeon; Tabula Rasa HealthCare, Moorestown, NJ, USA.

PI-109

PATIENT ATTITUDES TOWARDS PHARMACOGENETIC TESTING.

C. Stojinski[1], S. Ashokkumar[1], K. Monono[2], C. Carcuffe[2], K. Maslowski[2], W. Matthai[2], D.M. Kolansky[2], J. Giri[2], S. Tuteja[2]; [1]Drexel Univesity College of Medicine, Philadelphia, PA, USA, [2]University of Pennsylvania School of Medicine, Philadelphia, PA, USA.

PI-110

THE IMPACT OF RS505802 FOR *SLC22A12* ON OXIPURINOL AND URIC ACID DISPOSITION IN HMONG PATIENTS ON ALLOPURINOL FROM THE GENETICS OF HYPERURICEMIA THERAPY IN HMONG (GOUT-H) STUDY.

Y.M. Roman[1], K.A. Culhane-Pera[2], M.C. Lo[2], S. Yang[2], J. Yang[2], M. Lo[2], **R.J. Straka**[1]; [1]University of Minnesota, Minneapolis, MN, USA, [2]West Side Community Health Services, St. Paul, MN, USA.

PI-111

LIVER TARGETED CMX157 FOR THE TREATMENT OF CHRONIC HEPATITIS B: AN ASCENDING MULTIPLE DOSE STUDY IN HEALTHY VOLUNTEERS.

S. Chatsiricharoekul[1], P. Jutasompakorn[1], S. Niyomnaitham[1], T. Matkovits[2], M. Conover[2], J. Cobb[2], J. Greytok[2], **J. Sullivan-Bolyai**[2]; [1]Siriraj Hospital, Bangkok, Thailand, [2]ContraVir Pharmaceuticals, Edison, NJ, USA.

PI-112

PHARMCOKINETICS, SAFETY AND ANTIVIRAL ACTIVITY OF CMX157, A NOVEL PRODRUG OF TENOFOVIR, ADMINISTERED AS ASCENDING MULTIPLE DOSES TO HBV-INFECTED SUBJECTS.

T. Tanwandee[1], S. Nimanong[1], T. Matkovits[2], M. Conover[2], J. Cobb[2], J. Greytok[2], **J. Sullivan-Bolyai**[2]; [1]Siriraj Hospital, Bangkok, Thailand, [2]ContraVir Pharmaceuticals, Edison, NJ, USA.

PI-113

IN SILICO PREDICTION OF DRIVER MUTATIONS IN BREAST CANCER DRUG TARGETS AND THEIR DIRECT ACTIVATORS OR INACTIVATORS.

M. Swart, T. Skaar; Indiana University School of Medicine, Indianapolis, IN, USA.

PI-114

PRENATAL ANTIBIOTIC EXPOSURE AND CHILDHOOD ASTHMA: A POPULATION-BASED STUDY.

K. Loewen, B. Monchka, S.M. Mahmud, **G.W. 't Jong**, M.B. Azad; University of Manitoba, Winnipeg, MB, Canada.

PI-115

COADMINISTRATION OF CIMETIDINE WITH MIROGABALIN IN HEALTHY SUBJECTS: RESULTS FROM A PHASE I, RANDOMIZED, OPEN-LABEL, DRUG-DRUG INTERACTION STUDY.

M. Tachibana[1], N. Yamamura[2], C. Hsu[1], V. Warren[1], V. Dishy[1], H. Zahir[1]; [1]Daiichi Sankyo Inc, Edison, NJ, USA, [2]Daiichi Sankyo Inc, Tokyo, Japan.

PI-116

PREDICTORS OF VARIATION IN CYP2A6 MRNA, PROTEIN, AND ENZYME ACTIVITY IN A HUMAN LIVER BANK: INFLUENCE OF GENETIC AND NON-GENETIC FACTORS.

J.-A. Tanner[1], B. Prasad[2], K. Claw[2], P. Stapleton[2], D. Nickerson[2], A. Chaudhry[3], E.G. Schuetz[3], K.E. Thummel[2], R.F. Tyndale[1]; [1]University of Toronto, and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada, [2]University of Washington, Seattle, WA, USA, [3]St Jude Children's Research Hospital, Memphis, TN, USA.

PI-117

USING THE FOOD EFFECT TO SHOW ASSAY SENSITIVITY: ESTIMATION OF POWER USING SUBSAMPLING SIMULATIONS.

J. Taubel, S. Fernandes, G. Ferber; Richmond Pharmacology Ltd, London, UK.

PI-118

QT VARIATION OVER 24H: IMPACT OF FOOD EFFECT.

J. Taubel[1], S. Fernandes[1], D. Djumanov[1], G. Ferber[2]; [1]Richmond Pharmacology Ltd, London, UK, [2]Statistik Georg Ferber, Riehen, Switzerland.

PI-119

THE POWER OF PROVING QTC ASSAY SENSITIVITY: MOXIFLOXACIN VS. FOOD.

J. Taubel[1], S. Fernandes[1], G. Ferber[2]; [1]Richmond Pharmacology Ltd, London, UK, [2]Statistik Georg Ferber, Riehen, Switzerland.

PI-120

DETERMINING HEPATIC ENZYMES RESPONSIBLE FOR THE ACTIVATION OF TENOFOVIR ALAFENAMIDE FUMARATE.

T. Tran, J. Li, J. Shi, H. Zhu; University of Michigan, Ann Arbor, MI, USA.

PI-121

UNBIASED PROTEOMICS UNCOVERS NOVEL MECHANISM OF NIACIN'S HDL-C RESPONSE.

S. Tuteja, S. Rao, R.L. Dunbar, K. Trindade, S. DerOhannessian, D.J. Rader; University of Pennsylvania School of Medicine, Philadelphia, PA, USA.

PI-122

TOPICAL IONIC CONTRA VIRAL THERAPY REDUCES SIZE AND HPV-LOAD OF CUTANEOUS WARTS IN A PROOF-OF-CONCEPT RCT.

T. van der Kolk[1], G.K. Hogendoorn[1], S. Kouwenhoven[2], E.S. Klaassen[1], M.N. de Koning[3], J.N. Bouwes-Bavinck[2], G. Feiss[4], R. Rissmann[1], J. Burggraaf[1]; [1]Centre for Human Drug Research, Leiden, Netherlands, [2]Department of Dermatology, Leiden University Medical Centre, Leiden, Netherlands, [3]DDL Diagnostic Laboratory, Rijswijk, Netherlands, [4]Cutanea Life Science, Wayne, PA, USA.

PI-123

SKIN LESION QUANTIFICATION BY 3D PHOTOGRAPHY.

T. van der Kolk[1], G.K. Hogendoorn[1], C. Lemoine[2], G. Feiss[3], J. Burggraaf[1], R. Rissmann[1]; [1]Centre for Human Drug Research, Leiden, Netherlands, [2]Leiden University, Leiden, Netherlands, [3]Cutanea Life Sciences, Wayne, PA, USA.

PI-124

PROPHYLACTIC USE OF ENOXAPARIN IN MORBIDLY OBESE ADOLESCENTS DURING BARIATRIC SURGERY.

J.D. Vaughns[1], E.F. Williams[1], V. Ziesenitz[2], N. Hassan[1], G. Mikus[3], E. Nadler[1], J.N. van den Anker[1]; [1]Childrens National Health System, Washington, DC, USA, [2]University Children's Hospital, Basel, Switzerland, [3]Heidelberg University Hospital, Heidelberg, Germany.

PI-125

MARKERS OF GUT DYSFUNCTION DO NOT EXPLAIN VARIABILITY IN RIFAMPIN PHARMACOKINETICS IN HIV-ASSOCIATED TUBERCULOSIS.

C. Vinnard[1], S. Ravimohan[2], N. Tamuhla[3], V. Ivaturi[4], J. Pasipanodya[5], S. Srivastava[5], C. Modongo[3], N. Zetola[3], D. Weissman[2], T. Gumbo[5], G.P. Bisson[2]; [1]Rutgers, The State University of New Jersey, Newark, NJ, USA, [2]University of Pennsylvania School of Medicine, Philadelphia, PA, USA, [3]UPenn Botswana Partnership, Gaborone, Botswana, [4]University of Maryland, Baltimore, Baltimore, MD, USA, [5]Baylor University, Dallas, TX, USA.

PI-126

EFFECTS OF THE POTENT CYTOCHROME P450 3A4 INHIBITOR, ITRACONAZOLE, ON THE PHARMACOKINETICS OF BI 425809, A NEW GLYCINE TRANSPORTER 1 (GLYT1) INHIBITOR.

M. Desch[1], M. Goettel[2], S. Goetz[1], K.-H. Liesenfeld[1], T. Chan[3], J. Zhou[3], R. Sennewald[1], G. Wunderlich[4], **S. Wind**[1]; [1]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany, [2]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany, [3]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA, [4]Boehringer Ingelheim (Canada) Ltd, Burlington, ON, Canada.

PI-127

PHARMACOKINETIC INTERACTION OF BI 425809, A NEW GLYCINE TRANSPORTER 1 (GLYT1) INHIBITOR, WITH CYTOCHROME P450 (CYP) ISOENZYMES AND P-GLYCOPROTEIN (P-GP) PROBE DRUG.

M. Desch[1], H. Schmitt[1], K. Hohl[1], K.-H. Liesenfeld[1], T. Chan[2], J. Zhou[2], F. Müller[1], G. Wunderlich[3], **S. Wind**[1]; [1]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany, [2]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA, [3]Boehringer Ingelheim (Canada) Ltd, Burlington, ON, Canada.

PI-128

EVALUATION OF THE FACTORS AFFECTING TEICOPLANIN SERUM CONCENTRATION IN NEONATES AND CHILDREN.

T. Yamada[1], H. Nishio[2], M. Ochiai[2], S. Ishida[1], Y. Wakasugi[1], K. Suetsugu[1], T. Tsuji[1], A. Kanaya[1], T. Hara[2], S. Masuda[1]; [1]Department of Pharmacy, Kyushu University Hospital, Fukuoka, Japan, [2]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

PI-129

PREDICTION OF HUMAN PHARMACOKINETICS (PK) OF ANTIBODY-DRUG CONJUGATES (ADCS) FROM SIMPLE ALLOMETRY OF NONCLINICAL DATA.

J. Yang, B. Zhao, G. Jang; Seattle Genetics, Inc., Bothell, WA, USA.

PI-130

THERAPEUTIC DRUG MONITORING OF DOCETAXEL: A CASE REPORT OF ADMINISTRATION OF DOCETAXEL FOR BREAST CANCER PATIENT RECEIVING RIFAMPICIN AND CLARITHROMYCIN TREATMENT FOR NTM.

H. Yashima[1], T. Araki[1], Y. Ishikawa[1], S. Oshima[2], D. Nagano[3], K. Obayashi[2], J. Horiguchi[4], K. Yamamoto[1]; [1]Department of Clinical Pharmacology, Gunma University Graduate School of Medicine and Department of Pharmacy, Gunma University Hospital, Maebashi, Japan, [2]Department of Pharmacy, Gunma University Hospital, Maebashi, Japan, [3]Department of Clinical Pharmacology, Gunma University Graduate School of Medicine, Maebashi, Japan, [4]Breast and Endocrine Surgery Gunma University Hospital, Maebashi, Japan.

PI-131

TUMOR GROWTH DYNAMIC (TGD) MODELING AND SAFETY ANALYSIS OF NIVOLUMAB (NIVO) PLUS IPILIMUMAB (IPI) IN FIRST-LINE (1L) PATIENTS (PTS) WITH NON-SMALL CELL LUNG CANCER (NSCLC).

X. Zhao, Y. Feng, X. Wang, T.C. Young, S. Maier, A. Bello, A. Roy, S. Agrawal; Bristol-Myers Squibb, Princeton, NJ, USA.

PI-132

NEW SUBMISSIONS TO THE US FOOD AND DRUG ADMINISTRATION (2014-2016) CONFIRMED THE PREDICTIVE PERFORMANCE OF PBPK FOR THE EFFECT OF CYP 3A MODULATORS ON SUBSTRATE DRUGS.

V. Hsu, Y. Pan, **P. Zhao;** US Food and Drug Administration, Silver Spring, MD, USA.

PI-133

BENEFIT-RISK ANALYSIS TO SUPPORT DOSE SELECTION OF IPATASERTIB IN COMBINATION WITH ABIRATERONE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC).

R. ZHU, L. Musib, D. Maslyar, W. Yu, H. Ma, B. Poland, R. Wada, Q. Liu, J.Y. Jin, N. Budha; Genentech, South San Francisco, CA, USA.

QUANTITATIVE PHARMACOLOGY (QP) POSTER SESSION

FRIDAY, MARCH 17, 2017

7:00 AM – 9:00 AM

EXHIBIT HALL A/B SOUTH

PII-001

POPULATION PHARMACOKINETIC MODEL OF CABOZANTINIB IN PEDIATRIC PATIENTS WITH RECCURENT OR REFRACTORY SOLID TUMORS.

R.A. Abdelrahman[1], M.K. Chuk[2], B.C. Widemann[2], E. Fox[3], C. Minard[4], B.J. Weigel[5], J.M. Reid[1]; [1]Mayo Clinic, Rochester, MN, USA, [2]Pediatric Oncology Branch, NCI, CCR, Bethesda, MD, USA, [3]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [4]Baylor College of Medicine, Houston, TX, USA, [5]University of Minnesota, Minneapolis, MN, USA.

PII-002

EFFECT OF GENETIC POLYMORPHISM IN UDP-GLUCURONOSYLTRANSFERASE (UGT) 1A1 ON PHARMACOKINETICS (PK) OF IRINOTECAN AND ITS METABOLITES, SN-38 AND SN-38 GLUCURONIDE.

R. Abdelrahman[1], M.A. Ahmed[2], M.P. Goetz[1], J.C. Buckner[1], H.C. Pitot[1], C. Erlichman[1], K.A. Jaeckle[3], J.M. Reid[1]; [1]Mayo Clinic, Rochester, MN, USA, [2]University of Minnesota, Minneapolis, MN, USA, [3]Mayo Clinic, Jacksonville, FL, USA.

PII-003

A UNIFIED MECHANISM-BASED PK/PD MODEL FOR ANTIBODY DRUG CONJUGATE INDUCED HEMATOTOXICITY.

S. AIT-OUDHIA; University of Florida, Orlando, FL, USA.

PII-004
DYNAMIC PREDICTION OF PROGRESSION FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS) IN NON-SMALL CELL LUNG CANCER (NSCLC) USING TUMOR SIZE: A LONGITUDINAL JOINT MODELING APPROACH.
N. Al-Huniti[1], D. Onishchenko[2], H. Xu[1], D. Zhou[1], E. Masson[1], G. Helmlinger[1], H. Tomkinson[3], K. Abdallah[4], J. Dunyak[1]; [1]AstraZeneca, Waltham, MA, USA, [2]AstraZeneca, Moscow, Russian Federation, [3]AstraZeneca, Cambridge, UK, [4]AstraZeneca, Gaithersburg, MD, USA.

PII-005
A COMPARATIVE EVALUATION OF THE PBPK MODELING AND ALLOMETRIC SCALING FOR PREDICTING HUMAN PHARMACOKINETICS OF TARGETED ANTI-CANCER DRUGS.
H. Ananthula[1], M.H. Werner[2], P.B. Desai[1]; [1]University of Cincinnati, Cincinnati, OH, USA, [2]Inhibikase Therapeutics, Atlanta, GA, USA.

PII-006
RELATIVE BIOAVAILABILITY, FOOD EFFECT AND INTERACTION WITH ACID REDUCING AGENTS OF FILGOTINIB TABLETS IN HEALTHY SUBJECTS.
K. Anderson, H. Zheng, M. Kotecha, B. Scott, S. Sharma, T. Tarnowski, B. Kearney, Y. Xin; Gilead Sciences, Inc, Foster City, CA, USA.

PII-007
IMPORTANCE OF ASSESSING THE EFFECT OF CLEARANCE OF ANTICANCER MONOCLONAL ANTIBODIES ON EFFICACY.
G. Bajaj, S. Agrawal, Y. Feng, A. Roy; Bristol-Myers Squibb, Princeton, NJ, USA.

PII-008
DO PHYSICIANS CHANGE TACROLIMUS DOSING AFTER 90 DAYS? AN EMR-BASED STUDY OF THERAPEUTIC DRUG MONITORING IN TRANSPLANT PATIENTS.
A.H. Balch[1], J. Constance[1], S. Kumar[1], E.K. Korgenski[2], J.R. Sherbotie[1], T. Yu[1], C.M. Sherwin[1]; [1]University of Utah, Salt Lake City, UT, USA, [2]Intermountain Health Care, Salt Lake City, UT, USA.

PII-009
DEVELOPMENT AND APPLICATION OF A PHARMACOGENETICS GUIDED PBPK MODEL FOR PREDICTION OF THE DRUG-DRUG INTERACTION (DDI) OF OXYCODONE AND CYP PERPETRATORS.
S. Basu[1], T. Samant[1], A. Trescot[2], M. Palmer[2], L. Cavallari[1], L. Lesko[1], S. Schmidt[1]; [1]University of Florida, Orlando, FL, USA, [2]Pinnacle Laboratory Services, Orlando, FL, USA.

PII-010
PHARMACOKINETICS OF ELECLAZINE, A HIGHLY SELECTIVE INHIBITOR OF CARDIAC LATE NA+ CURRENT: EVALUATION OF SINGLE AND MULTIPLE-DOSE PK, AND FOOD EFFECT, IN HEALTHY VOLUNTEERS.
R. Begley, H. Zhang, J. Hellawell, L. Wang, J. Weston, J. Ling, B.P. Kearney; Gilead Sciences, Foster City, CA, USA.

PII-011
METABOLISM AND EXCRETION OF ELECLAZINE, A HIGHLY SELECTIVE INHIBITOR OF CARDIAC LATE NA+ CURRENT, IN HUMANS.
R. Begley, H. Zhang, J. Hellawell, L. Wang, K. Grycz, T. Tarnowski, B.P. Kearney; Gilead Sciences, Foster City, CA, USA.

PII-012
AN AUTOMATED SAMPLING IMPORTANCE RESAMPLING PROCEDURE FOR ESTIMATING PARAMETER UNCERTAINTY.
A.-G. Dosne[1], **M. Bergstrand**[2], M.O. Karlsson[1]; [1]Department of Pharmaceutical Biosciences, Uppsala University, UPPSALA, Sweden, [2]Pharmetheus, UPPSALA, Sweden.

PII-013
MASS BALANCE AND ABSOLUTE BIOAVAILABILITY OF ACT-541468, A DUAL OREXIN RECEPTOR ANTAGONIST, BY ADMINISTRATION OF A MICROTRACER DOSE AND AMS ANALYSIS IN A FIRST-IN-HUMAN STUDY.
M. Boehler[1], C. Muehlan[1], P.-E. Juif[1], S. English[2], J. van Gerven[3], P. Peeters[3], J. Heuberger[3], J. Dingemanse[1]; [1]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, [2]Xceleron Inc., Germantown, MD, USA, [3]Centre for Human Drug Research, Leiden, Netherlands.

PII-014
QUANTITATIVE MODELING AND SIMULATION APPROACHES: DRIVING CRITICAL DECISIONS FROM RESEARCH THROUGH CLINICAL TRIALS.
J.M. Burke; Applied BioMath, LLC, Lincoln, MA, USA.

PII-015
MODEL-BASED UNSUPERVISED SINGLE-CELL RNASEQ ANALYSIS REVEALS CDC42 AS A DOWNSTREAM EFFECTOR IN METFORMIN INHIBITION OF TRIPLE-NEGATIVE BREAST CANCER MIGRATION.
J. Cairns[1], A. Athreya[2], K. Kalari[1], A. Gaglio[2], Q. Wills[3], N. Niu[4], R. Weinshilboum[1], R. Iyer[2], L. Wang[1]; [1]Mayo Clinic, Rochester, MN, USA, [2]University of Illinois at Urbana-Champaign, Urbana-Champaign, IL, USA, [3]University of Oxford, Oxford, UK, [4]University of Chicago, Chicago, IL, USA.

PII-016
ROLE OF CBP AND P300 IN SMOOTH MUSCLE PLASTICITY.
R. Chakraborty, J. Hwa, K. Martin; Yale University, New Haven, CT, USA.

PII-017
PHARMACOKINETIC MODELING AND SIMULATIONS OF HUMAN ANTI-C1S ANTIBODY (TNT009) IN NORMAL HUMAN VOLUNTEERS AND PATIENTS WITH COMPLEMENT-MEDIATED DISORDERS.
B. Jilma[1], J. Gilbert[2], D. Nix[2], **C. Chang**[3], M. Beliveau[3], J. Marier[3]; [1]Medical University of Vienna, Vienna, Austria, [2]True North Therapeutics, Inc., South San Francisco, CA, USA, [3]Certara Strategic Consulting, Montreal, QC, Canada.

PII-018
PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS OF HUMAN ANTI-C1S ANTIBODY (TNT009) AND CLASSICAL COMPLEMENT PATHWAY (CP) ACTIVITY.
B. Jilma[1], J. Gilbert[2], D. Nix[2], **C. Chang**[3], M. Beliveau[3], J. Marier[3]; [1]Medical University of Vienna, Vienna, Austria, [2]True North Therapeutics, Inc., South San Francisco, CA, USA, [3]Certara Strategic Consulting, Montreal, QC, Canada.

PII-019
A COMPARATIVE BIOAVAILABILITY AND DEFINITIVE FOOD EFFECT STUDY OF A NEW TABLET FORMULATION OF HT-3951, A SELECTIVE AND REVERSIBLE INHIBITOR OF MAO-B, IN HEALTHY SUBJECTS.
C.M. Charriez[1], D.J. Carpenter[1], J.J. Anderson[1], A. Youssef[2], I. Hoffmann[1], C. Mason[1], C.L. Mazzitelli[1], B. Branstetter[1], J.M. Parsons[1], J. Ruckle[3], P. Perera[1]; [1]Dart NeuroScience LLC, San Diego, CA, USA, [2]KinderPharm LLC, Exton, PA, USA, [3]Pacific Pharma Group LLC, Tacoma, WA, USA.

PII-020
ASSESSMENT OF TRANSPORTER MEDIATED DDI FOR GDC-0810 USING PBPK MODELING.
Y. Chen, R. Zhu, F. Ma, J. Mao, E. Chen, K. DeMent, E. Choo, S. Sahasranaman, L. Liu; Genentech, South San Francisco, CA, USA.

PII-021
PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING TO EVALUATE THE SYSTEMIC EXPOSURE OF GEFITINIB IN THE CYP2D6 ULTRARAPID METABOLIZERS AND EXTENSIVE METABOLIZERS.
Y. Chen, W. Zhou, W. Tang, D. Zhou, E. Masson; AstraZeneca, Waltham, MA, USA.

PII-022
PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING OF ELAGOLIX FOR PREDICTION OF DRUG-DRUG INTERACTIONS (DDIS).
M.S. Chiney, A.R. Polepally, A.M. Nader, M.B. Dufek, C.E. Klein, J.W. Ng, M. Shebley; Abbvie, North Chicago, IL, USA.

PII-023
PROPER STATISTICAL CHARACTERIZATION CAN OVERCOME COMMON FALLACIES THAT INFLATE PROBABILITY OF SUCCESS OF CLINICAL TRIALS.
Y.-L. Chiu, W. Zhao, S. Dutta, W. Awni; AbbVie Inc., North Chicago, IL, USA.

PII-024

PHARMACOKINETIC CHARACTERISTICS OF AMOXICILLIN/CLAVULANATE AND THEIR EFFECTS ON LIVER FUNCTION IN THE ELDERLY.

Y. Choi[1], J. Lee[1], J. Hwang[1], J. Sunwoo[1], S. Yoon[1], J.-Y. Cho[1], J.-Y. Chung[2]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, Republic of Korea.

PII-025

PRESENTATION OF A SIMPLIFIED METHOD FOR MODELING PROTEIN AND DRUG INTERACTIONS USING OPEN-SOURCE SOFTWARE.

B. Cicali, R. Olsen; Stockton University, Galloway, NJ, USA.

PII-026

THE APPLICATION OF A NOVEL MEDICATION RISK STRATIFICATION TOOL TO IDENTIFY HIGH RISK PATIENTS WITHIN A LARGE POPULATION.

B. Cicali, G. Badea, L. Steffen, K. Bain, E. Schwartz, C.H. Knowlton, J. Turgeon; Tabula Rasa HealthCare, Moorsetown, NJ, USA.

PII-027

CHARACTERIZATION OF CYP450 DRUG METABOLISM ENZYMES ACTIVITIES IN HUMAN SMALL INTESTINE.

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PII-028

PHARMACOKINETICS OF DUPILUMAB IN PHASE III CONFIRMATORY STUDIES IN ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS.

J.D. Davis[1], S. Rawal[1], A. Paccaly[1], M. Li[2], C.-H. Lai[1], M. Ardeleanu[1], A.T. DiCioccio[1]; [1]Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA, [2]Sanofi, Bridgewater, NJ, USA.

PII-029

PHARMACOKINETICS OF DUPILUMAB IN LONG-TERM PHASE III STUDIES IN ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS.

J.D. Davis[1], S. Rawal[1], M. Kamal[1], M. Li[2], C.-H. Lai[1], M. Ardeleanu[1], A.T. DiCioccio[1]; [1]Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA, [2]Sanofi, Bridgewater, NJ, USA.

PII-030

A CLINICAL PHARMACOKINETIC STUDY TO ASSESS BIOAVAILABILITY OF AND FOOD EFFECT ON A FIXED-DOSE COMBINATION OF THREE DIRECT-ACTING ANTIVIRAL AGENTS INDICATED FOR HEPATITIS C.

B.M. Davit[1], L. Arrington[2], X.S. Glasgow[1], J. Kuiper[1], J. Miller[1], D. Harris[1], F. Kesisoglou[1], K. Duncan[1], W. Gao[1]; [1]Merck & Co., Kenilworth, NJ, USA, [2]Merck & Co, Kenilworth, NJ, USA.

PII-031

COADMINISTRATION OF DULAGLUTIDE WITH THE DPP-IV INHIBITOR SITAGLIPTIN DOES NOT REQUIRE DOSE ADJUSTMENT.

A. de la Peña, J.S. Geiser, X. Cui, J.Y. Chien, C. Loghin; Eli Lilly and Company, Indianapolis, IN, USA.

PII-032

MECHANISTIC MODELING OF CELL DYNAMICS: CHEMOKINE MEDIATED CELL MIGRATION.

O. Demin, E. Metelkin; Institute for Systems Biology Moscow, Moscow, Russian Federation.

PII-033

MECHANISTIC MODELING OF CELL DYNAMICS: CYTOKINE DEPENDENT MATURATION OF IMMUNE CELLS.

O. Demin, E. Metelkin; Institute for Systems Biology Moscow, Moscow, Russian Federation.

PII-034

MECHANISTIC MODELING OF CELL DYNAMICS: EFFECT OF CO-STIMULATORY AND CO-INHIBITORY SURFACE MOLECULES ON PROCESSES ASSOCIATED WITH CELL-TO-CELL INTERACTIONS.

O. Demin Jr, E. Metelkin, O. Demin; Institute for Systems Biology Moscow, Moscow, Russian Federation.

PII-035

MECHANISTIC MODELING OF CELL DYNAMICS: CYTOKINE PRODUCTION BY IMMUNE CELLS.

O. Demin Jr, E. Metelkin, O. Demin; Institute for Systems Biology Moscow, Moscow, Russian Federation.

PII-036

A STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF ONS-3010 (ADALIMUMAB, ONCOBIOLOGICS, INC.) COMPARED TO HUMIRA® (EU/US, ABBVIE) IN HEALTHY SUBJECTS.

M.R. Dillingh[1], J.A. Reijers[1], M. Moerland[1], K.M. Barth[2], C. Rehrig[2], J. Burggraaf[1]; [1]Centre for Human Drug Research, Leiden, Netherlands, [2]Oncobiologics Inc, Cranbury, NJ, USA.

PII-037

CURRENT AND EMERGING APPLICATIONS OF ACCELERATOR MASS SPECTROMETRY (AMS) WITH BIOTHERAPEUTICS.

S.L. English, M. Sanghvi; Xceleron, Inc., Germantown, MD, USA.

PII-038

BIOEQUIVALENCE OF ERTUGLIFLOZIN/SITAGLIPTIN FIXED-DOSE COMBINATION TABLETS AND CO-ADMINISTRATION OF RESPECTIVE STRENGTHS OF INDIVIDUAL COMPONENTS.

D.J. Fediuk[1], K. Matschke[2], Y. Liang[1], K.B. Pelletier[1], H. Wei[3], H. Shi[1], A. Bass[4], A. Hickman[1], S.G. Terra[5], S. Zhou[6], R. Krishna[6], V. Sahasrabudhe[1]; [1]Pfizer, Inc., Groton, CT, USA, [2]Pfizer, Inc., Collegeville, PA, USA, [3]Pfizer, Inc., Shanghai, China, [4]Pfizer, Inc., Durham, NC, USA, [5]Pfizer, Inc., Andover, MA, USA, [6]Merck & Co., Inc., Kenilworth, NJ, USA.

PII-039

PHARMACOKINETICS OF MIDAZOLAM AND ITS METABOLITES IN TERMINALLY ILL PATIENTS.

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PII-040

EVALUATION OF THE RELATIONSHIP BETWEEN METHOTREXATE CO-ADMINISTRATION AND INFLIXIMAB CONCENTRATIONS IN A PEDIATRIC PATIENT POPULATION.

R.S. Funk[1], V. Shakhnovich[2], L. van Haandel[2], M.L. Becker[2]; [1]University of Kansas, Kansas City, KS, USA, [2]Children's Mercy Kansas City, Kansas City, MO, USA.

PII-041

VIRAL DYNAMICS MODELING OF ZEPATIER IN COMBINATION WITH SOFOSBUVIR IN GENOTYPE (GT) 1 AND 3 HEPATITIS C VIRUS (HCV) INFECTED PATIENTS (C-SWIFT).

W. Gao[1], K. Baron[2], M. Rizk[1], L. Wenning[1], H.-P. Feng[1], B. Haber[1]; [1]Merck & Co., West Point, PA, USA, [2]Metrum, Tariffville, CT, USA.

PII-042

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS OF A PAR4 ANTAGONIST ON THROMBUS FORMATION IN AN EX VIVO THROMBUS CHAMBER MODEL.

S. GARONZIK, T. GARIMELLA, Z. WANG, M. DESOUZA, D. SEIFFERT, F.A. ISMAT, F. LACRETA; BMS, Princeton, NJ, USA.

PII-043

QUANTITATIVE SYSTEMS PHARMACOLOGY MODELING OF DRUG-INDUCED PROXIMAL TUBULAR (PT) INJURY.

Y. Gebremichael[1], J. Lu[2], H. Shankaran[3], J. Mettetal[3], G. Helmlinger[3], M. Hallow[1]; [1]University of Georgia, Athens, GA, USA, [2]AstraZeneca Pharmaceuticals, Cambridge, UK, [3]AstraZeneca Pharmaceuticals, Waltham, MA, USA.

PII-044

EXTRAPOLATION OF DACLATASVIR DOSING RECOMMENDATIONS FROM RITONAVIR BOOSTED PROTEASE INHIBITORSTO COBICISTAT PROTEASE INHIBITORS.

Y. Gandhi, Q. Wang, W. Li, T. Eley, M. Zheng, F. LaCreta, R. Bertz, T. Garimella; Bristol-Myers Squibb, Princeton, NJ, USA.

PII-045

QSP MODELING OF LIVER AMPK ACTIVATION USING NAFLDSYM IS PREDICTED TO REDUCE STEATOSIS IN NAFLD PATIENTS.

G. Generaux[1], T.R. Rieger[2], B.A. Howell[1], R. Allen[3], C.J. Musante[2], P.B. Watkins[4], S.Q. Siler[1]; [1]DILIsym Services, Inc., Research Triangle Park, NC, USA, [2]Pfizer, Cambridge, MA, USA, [3]Pfizer, Cambridge, NC, USA, [4]University of North Carolina, Chapel Hill, NC, USA.

PII-046

MODEL-BASED APPROACH TO CHARACTERIZE THE BELL-SHAPED EXPOSURE-RESPONSE OF SENS-111, A NEW H_4R ANTAGONIST, ON VERTIGO INDUCED BY CALORIC TEST IN HEALTHY VOLUNTEERS.

R. Gomeni[1], F. Venail[2], E. Wersinger[3], S. Poli[3], F. Bressolle-Gomeni[1], P. Attali[3]; [1]Pharmacometrica, La Fouillade, France, [2]CHU Gui de Chaulliac, Montpellier, France, [3]Sensorion, Montpellier, France.

PII-047

A META-POPULATION PHARMACOKINETIC ANALYSIS OF PARITAPREVIR, OMBITASVIR, DASABUVIR, RITONAVIR AND RIBAVIRIN IN HCV-INFECTED CIRRHOTIC AND NON-CIRRHOTIC SUBJECTS.

S. Gopalakrishnan, P. Badri, S. Mensing, R.M. Menon, S. Dutta, J. Zha; AbbVie Inc., North Chicago, IL, USA.

PII-048

DOES GASTRIC BYPASS SURGERY AFFECT BIOAVAILABILITY OF ORALLY ADMINISTERED DARUNAVIR? A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING APPROACH.

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PII-049

SIMULTANEOUS ABSOLUTE PROTEIN QUANTIFICATION METHOD OF 14 CYP450 ENZYMES IN HUMAN INTESTINE BY MASS SPECTROMETRY-BASED TARGETED PROTEOMICS.

A. Grangeon[1], V. Clermont[1], A. Barama[2], F. Gaudette[3], J. Turgeon[4], V. Michaud[1]; [1]University of Montreal, CRCHUM, Montreal, QC, Canada, [2]CHUM, Montreal, QC, Canada, [3]CRCHUM, Montreal, QC, Canada, [4]University of Montreal, Montreal, QC, Canada.

PII-050

STEREOSELECTIVE INHIBITION AND INDUCTION OF BUPROPION METABOLISM BY EFAVRIENZ IN HEALTHY VOLUNTEERS.

B.T. Gufford, A.R. Masters, J.B. Lu, I.F. Metzger, D.R. Jones, Z. Desta; Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA.

PII-051

POPULATION PHARMACOKINETICS OF A MAJOR METABOLITE OF EFAVIRENZ, 8-HYDROXY-EFAVIRENZ, IN PLASMA AND PERIPHERAL BLOOD MONONUCLEAR CELLS .

A. Habtewold[1], E. Aklillu[2], E. Makonnen[3], G. Yimer[3], L. Bertilsson[2], J. Burhenne[4], J. Owen[1]; [1]Department of Pharmaceutical Sciences, School of Pharmacy, Union University, Jackson, TN, USA, [2]Division of Clinical Pharmacology, Department of Lab Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden, [3]Department of Pharmacology, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia, [4]4Department of Clinical Pharmacology & Pharmacoepidemiology, University of Heidelberg, Heidelberg, Germany.

PII-052

CURRENTLY RECOMMENDED DOSAGE REGIMENS FOR MEROPENEM IN CHILDREN WITH PSEUDOMONAS INFECTIONS MAY FAIL TO MEET SERUM CONCENTRATION TARGETS.

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PII-053

STUDY DESIGN CONSIDERATIONS FOR ALCOHOL EFFECT ON EXTENDED-RELEASE DRUG FORMULATIONS.

J. He, G. Bernstein, H. Mehta, J. Oldenhof; INC Research, Toronto, ON, Canada.

PII-054

EFFECT OF FOOD ON THE PHARMACOKINETICS OF HIP1402, A NEW FORMULATION OF TAMSULOSIN 0.4 MG, AFTER A SINGLE ORAL DOSE IN HEALTHY SUBJECTS.

J. Hwang[1], S.-I. Park[1], Y. Kim[1], S. Lee[1], J. Jung[2], Y.-I. Kim[2], S. Lee[1], H. Lee[1], K.-S. Yu[1]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea, Republic of, [2]Hanmi Pharmaceutical Co., Ltd, Seoul, Republic of Korea.

PII-055

AN ASSESSMENT OF ANALYTICAL AND NONCLINICAL PUBLISHED EVIDENCE FOR BIOSIMILARS IN ONCOLOGY AND CHRONIC INFLAMMATORY DISEASE.

I. Jacobs[1], G. Finch[2], C. Kirchhoff[3], C.-K. Ng[4], A. Ryan[2]; [1]Global Established Pharma Medicines Development Group, Pfizer Inc., New York, NY, USA, [2]Drug Safety Research and Development, Pfizer Inc., Groton, CT, USA, [3]Global Technology Services, Biotechnology and Aseptic Sciences, Pfizer Inc., Chesterfield, MO, USA, [4]Analytical Research and Development, Biotherapeutics Pharmaceutical Sciences, Pfizer Inc., Andover, MA, USA.

PII-056

PHARMACOKINETIC COMPARISON OF A SINGLE ORAL DOSE OF JLP-1207, A FIXED-DOSE COMBINATION OF SOLIFENACIN 5MG AND TAMSULOSIN 0.2MG, AND CO-ADMINISTRATION OF INDIVIDUAL TABLETS.

I. Jeon[1], S. Moon[1], Y. Choi[1], I. Hwang[1], J. Kim[2], Y. Lee[2], S. Yoon[1], J.-Y. Cho[1], K.-S. Yu[1], S. Lee[1]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Jeil Pharmaceutical Co., LTD, Seoul, Republic of Korea.

PII-057

MODEL-BASED APPROACHES FOR DDI PREDICTION AND DOSE OPTIMIZATION FOR THE COMBINATION OF ALISPORIVIR AND EDP239.

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PII-058

USE OF MIDAZOLAM (MDZ) MICRODOSING IN AN ENTRY INTO HUMAN (EIH) STUDY ALLOWS EARLY DETERMINATION OF CLINICAL DRUG INTERACTION LIABILITY THROUGH CYP3A4.

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PII-059

PHARMACOKINETICS AND TOLERABILITY PROFILE OF GEMIGLIPTIN/METFORMIN SUSTAINED RELEASE FIXED-DOSE COMBINATION COMPARAD WITH SEPARATE TABLETS IN HEALTHY SUBJECTS.

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PII-060

MULTIPLE-DOSE PHARMACOKINETIC STUDY OF PERAMPANEL, A NONCOMPETITIVE SELECTIVE AMPA RECEPTOR ANTAGONIST IN KOREAN HEALTHY SUBJECTS.

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PII-061

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) MODEL OF CW002, AN INVESTIGATIONAL INTERMEDIATE NEUROMUSCULAR BLOCKING (NMB) AGENT IN HEALTHY VOLUNTEERS.

J.D. Kaullen[1], J.S. Owen[2], K.L. Brouwer[1], P. Heerdt[3], C.A. Lien[4], J.J. Savarese[5], V.D. Schmith[6]; [1]University of North Carolina, Chapel Hill, NC, USA, [2]Union University, Jackson, TN, USA, [3]Yale School of Medicine, New Haven, CT, USA, [4]Weill Cornell Medical College, New York, NY, USA, [5]Weill Cornell University Medicine Anesthesiology, New York, NY, USA, [6]Nuventra Pharma Sciences, Durham, NC, USA.

PII-062

EVALUATION OF CYP2B6 INDUCTION AND PREDICTION OF CLINICAL DDI USING PBPK MODELING.

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PII-063

COMPARATIVE PHARMACOKINETICS AND TOLERABILITY PROFILES OF TENOFOVIR DISOPROXIL OROTATE (DA-2802) AND TENOFOVIR DISOPROXIL FUMARATE (VIREAD®) IN HEALTHY SUBJECTS.

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PII-064

AN ASSESSMENT OF THE PHARMACOKINETICS OF A LOBEGLITAZONE/METFORMIN FIXED-DOSE COMBINATION TABLET IN HEALTHY SUBJECTS.

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PII-065

PHARMACOKINETICS OF DARUNAVIR IN HCV/HIV COINFECTED ADULTS IN THE PRESENCE AND ABSENCE OF OMBITASVIR, PARITAPREVIR, RITONAVIR, DASABUVIR AND RIBAVIRIN.

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PII-066

A QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL DESCRIBES CHANGES IN PLATELETS FOLLOWING JAK MODULATION.

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PII-067

LACK OF SIGNIFICANT DRUG-DRUG INTERACTIONS BETWEEN DIRECT ACTING ANTIVIRALS GLECAPREVIR AND PIBRENTASVIR WITH CALCIUM CHANNEL BLOCKERS (FELODIPINE OR AMLODIPINE).

M.P. Kosloski, S. Dutta, W. Zhao, R. Qaqish, N. Zadeikis, F. Mensa, J. Kort, W. Liu; AbbVie, North Chicago, IL, USA.

PII-068

PHARMACOKINETICS AND SAFETY OF ABT-981 IN CHINESE, JAPANESE, AND CAUCASIAN HEALTHY SUBJECTS.

M.P. Kosloski, W. Liu, P. Jiang, M.C. Levesque, J.K. Medema, S. Dutta; AbbVie, North Chicago, IL, USA.

PII-069

POPULATION PHARMACOKINETICS OF ABT-981, DUAL VARIABLE DOMAIN-IMMUNOGLOBULIN, IN PHASE I STUDIES.

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PII-070

A PK/PD STUDY COMPARING TWICE DAILY TO ONCE DAILY DOSING OF ERTUGLIFLOZIN IN HEALTHY SUBJECTS.

V. Kumar[1], Y. Liang[1], K. Matschke[2], H. Shi[1], A. Bass[3], A. Hickman[1], S.G. Terra[4], S. Zhou[5], D. Cutler[5], V. Sahasrabudhe[1]; [1]Pfizer Inc., Groton, CT, USA, [2]Pfizer Inc., Collegeville, PA, USA, [3]Pfizer Inc., Durham, NC, USA, [4]Pfizer Inc., Andover, MA, USA, [5]Merck & Co., Kenilworth, NJ, USA.

PII-071

BIOEQUIVALENCE OF ERTUGLIFLOZIN/METFORMIN FIXED DOSE COMBINATION TABLETS AND CO-ADMINISTRATION OF RESPECTIVE STRENGTHS OF INDIVIDUAL COMPONENTS.

V. Kumar[1], Y. Liang[1], H. Wei[2], K. Pelletier[1], K. Matschke[3], H. Shi[1], A. Hickman[1], A. Bass[4], S.G. Terra[5], S. Zhou[6], R. Krishna[6], V. Sahasrabudhe[1]; [1]Pfizer Inc., Groton, CT, USA, [2]Pfizer Inc., Shanghai, China, [3]Pfizer Inc., Collegeville, PA, USA, [4]Pfizer Inc., Durham, NC, USA, [5]Pfizer Inc., Andover, MA, USA, [6]Merck & Co., Kenilworth, NJ, USA.

PII-072

MECHANISTIC MODEL OF MAST CELL LIFE CYCLE, ACTIVATION AND RELEASE OF BIOACTIVE MOLECULES DESIGNED TO SUPPORT SYSTEMS PHARMACOLOGY MODELING OF THE IMMUNE RESPONSE.

G. Lebedeva, S. Smirnov, E. Metelkin, O. Demin; Institute for Systems Biology Moscow, Moscow, Russian Federation.

PII-073

MECHANISTIC MODEL OF NEUTROPHIL CELL DYNAMICS AND ACTIVATION TO INFORM SYSTEMS PHARMACOLOGY MODELING OF THE IMMUNE RESPONSE.

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PII-074
PHARMACOKINETICS OF ORALLY INHALED FLUTICASONE, SALMETEROL AND TIOTROPIUM AFTER CO-ADMINISTRATION IN HEALTHY VOLUNTEERS.
S. Lee[1], S.-J. Rhee[1], H. Lee[1], E. Kim[1], S. Yoon[2], H. Lee[1], I.-J. Jang[1]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, Republic of Korea.

PII-075
USING SEMI-PBPK MODELING TO PREDICT THE IMPACT OF DIFFERENT ROUTES OF ADMINISTRATION (ROA) - INTRAVENOUS (IV) VS. ORAL (PO) - ON CYP3A-MEDIATED DRUG-DRUG INTERACTIONS (DDI).
M. Li, J. Venitz; Virginia Commonwealth University, Richmond, VA, USA.

PII-076
TIME DEPENDENT PK OF PEMBROLIZUMAB AND IMPLICATION IN EXPOSURE-RESPONSE (E-R) ANALYSIS
H. Li, J. Yu, C. Liu, Y. Wang; US Food and Drug Administration, Silver Spring, MD, USA.

PII-077
MOXIFLOXICIAN (MOX) SAMPLE SIZE AS PART OF PHASE I SINGLE ASCENDING DOSE (SAD) STUDIES FOR POSITIVE CONTROL (PC) TO ASSESS QT/QTC PROLONGATION WITHOUT THROUGH QT (TQT) STUDIES.
J. Li, E. Masson, J. Lu, N. Al-Huniti; AstraZeneca LP, Waltham, MA, USA.

PII-078
A DRUG-DRUG INTERACTION STUDY OF DS-1040 AND CLOPIDOGREL (CLO) IN HEALTHY SUBJECTS.
F. Pizzagalli, C. Rambaran, F. Kobayashi, J. Pav, V. Warren, A. Vandell, V. Dishy, J. Zhou, **T. Limsakun**; Daiichi Sankyo Inc., Edison, NJ, USA.

PII-079
NON-LINEAR PHARMACOKINETICS OF GLECAPREVIR, A PANGENOTYPIC PROTEASE INHIBITOR OF HEPATITIS-C VIRUS, IN HEALTHY SUBJECTS.
C.-W. Lin, A. Jones, S. Dutta, W. Liu; Abbvie, North Chicago, IL, USA.

PII-080
POPULATION PHARMACOKINETICS OF PIBRENTASVIR, A PANGENOTYPIC NS5A INHIBITOR OF HEPATITIS-C VIRUS, IN HEALTHY SUBJECTS.
C.-W. Lin, A. Jones, S. Dutta, W. Liu; Abbvie, North Chicago, IL, USA.

PII-081
BIOEQUIVALENCE OF FIXED DOSE COMBINATION (FDC) TABLETS OF EMPAGLIFLOZIN/METFORMIN EXTENDED RELEASE COMPARED WITH THE FREE COMBINATIONS IN HEALTHY VOLUNTEERS.
C. Lippert, R. Sennewald, U. Elsasser, **S. Hüttner**; Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach, Germany.

PII-082
TRANSLATIONAL MODELING AND SIMULATION IN SUPPORTING EARLY PHASE CLINICAL DEVELOPMENT OF NEW DRUG: A LEARN-RESEARCH-CONFIRM PROCESS.
D. Liu[1], Y. Zhang[2], J. Jiang[1], J. Choi[2], L. Chen[2], P. Hu[1]; [1]Peking Union Medical College Hospital, Beijing, China, [2]HuaMedicine (Shanghai) Ltd., Shanghai China, Shanghai, China.

PII-083
THE TIME DEPENDENT PHARMACOKINETICS OF NIVOLUMAB IN PATIENTS WITH SOLID TUMOR AND THE IMPLICATION IN EXPOSURE-RESPONSE ANALYSIS.
C. Liu; US Food and Drug Administration, SIlver Spring, MD, USA.

PII-084
A PHASE I, OPEN-LABEL STUDY TO EVALUATE THE EFFECT OF GDC-0810 ON THE PHARMACOKINETICS OF PRAVASTATIN IN HEALTHY FEMALE SUBJECTS OF NON-CHILDBEARING POTENTIAL.
L. Liu, S. Cheeti, M. Regalado-Dell, M. Sivasubramanian, E. Choo, E. Chen, B. Chen, M. Gates, S. Singel, R. Morley, S. Sahasranaman; Genentech, South San Francisco, CA, USA.

PII-085
MECHANISTIC MODELING AND HEPATIC BIOMARKER DATA FROM GGF2 (CIMAGLERMIN ALFA)-TREATED SUBJECTS IN PHASE I CLINICAL TRIALS SUGGEST LOW LIKELIHOOD OF PROGRESSIVE LIVER INJURY.
D.M. Longo[1], G.T. Generaux[1], B.A. Howell[1], S.Q. Siler[1], D.J. Antoine[2], D. Button[3], A. Caggiano[3], A. Eisen[3], J.F. Iaci[3], R. Stanulis[3], P.B. Watkins[4]; [1]DILIsym Services, Inc., Research Triangle Park, NC, USA, [2]MRC Centre for Drug Safety Science, Department of Molecular & Clinical Pharmacology, Liverpool University, Liverpool, UK, [3]Acorda Therapeutics Inc., Ardsley, NY, USA, [4]University of North Carolina Institute for Drug Safety Sciences, Chapel Hill, NC, USA.

PII-086
POWER OF QUADRATIC APPROXIMATION TO MODEL NONLINEAR RELATIONSHIP BETWEEN DRUG CONCENTRATION AND CHANGE FROM BASELINE IN QTC (C-ΔQTC).
J. Lu, N. Al-Huniti, J. Li; AstraZeneca, Waltham, MA, USA.

PII-087
DISCORDANCE BETWEEN DRUG TRANSPORTERS AND P450 INDUCTION: DETERMINATION OF THE EFFECT OF MULTIPLE ASCENDING DOSES OF RIFAMPIN ON P-GP, OATP, BCRP, CYP3A, CYP2C9 AND CYP1A2.
J.D. Lutz, B.J. Kirby, J. Ling, J. Weston, B.P. Kearney, A. Mathias; Gilead Sciences, Foster City, CA, USA.

PII-088
SIMULTANEOUS EVALUATION OF P-GP, OATP AND BCRP ACTIVITY USING A THREE DRUG COCKTAIL IN HEALTHY VOLUNTEERS.
J.D. Lutz, B.J. Kirby, Q. Song, B. Massetto, B.P. Kearney, A. Mathias; Gilead Sciences, Foster City, CA, USA.

PII-089
MULTI-FUNCTIONAL SCALING FOR INTEGRATED MULTI-MICROPHYSIOLOGICAL SYSTEMS (MPS).
C. Maass[1], N. Tsamandouras[1], C.L. Stokes[2], M. Cirit[1]; [1]Massachusetts Institute of Technology, Cambridge, MA, USA, [2]Stokes Consulting, Redwood City, CA, USA.

PII-090
DOSING CONSIDERATIONS FOR OBETICHOLIC ACID (OCA) IN THE TREATMENT OF PRIMARY BILIARY CHOLANGITIS (PBC).
D. Marathe, Y. Yang, E. Shang, S. Li, P. Zhao, S.-C. Lee, R. Mehta, S.O. Omokaro, L. Dimick-Santos, A. Davis-Williams, J. Meyer, A. Egan, D. Roman, E.D. Bashaw, V. Sinha, N. Mehrotra; US Food and Drug Administration, Silver Spring, MD, USA.

PII-091
PHARMACOKINETIC AND PHARMACODYNAMIC MODELING OF ARQ 087, A NOVEL PAN-FGFR INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMORS, INCLUDING INTRAHEPATIC CHOLANGIOCARCINOMA.
R. Savage[1], M. Trinh[2], M. Dupuis[2], **J.F. Marier**[2], B. Schwartz[1]; [1]ArQule, Burlington, MA, USA, [2]Certara Strategic Consulting, Montreal, QC, Canada.

PII-092
SINGLE-DOSE PHARMACOKINETICS OF ALP2011 IN SUBJECTS WITH VARIOUS DEGREES OF HEPATIC IMPAIRMENT.
J. Michaud, C. Fazio, S. Boily, **J. Massicotte**, É. Sicard, M. Lefebvre; Algorithme Pharma, Laval, QC, Canada.

PII-093
INDIVIDUALIZED DOSING OF HYDROXYUREA FOR CHILDREN WITH SICKLE CELL ANEMIA USING A PHARMACOKINETIC-BASED MODEL; THE TREAT STUDY.
P.T. McGann, M. Dong, T. Mizuno, A. Marahatta, R.E. Ware, A.A. Vinks; Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

PII-094
IMPROVING METHADONE TREATMENT OF NEONATAL ABSTINENCE SYNDROME (NAS) WITH MECHANISTIC INSIGHTS INTO THE PK VARIABILITY THROUGH PEDIATRIC PBPK MODELING.
B. McPhail[1], C. Emoto[1], T. Fukuda[1], D. Butler[1], J. Wiles[2], H. Akinbi[1], A.A. Vinks[1]; [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]St Mary's Medical Center, Evansville, IN, USA.

PII-095
EXPOSURE RESPONSE OF VELIPARIB TO INFORM PHASE 2 TRIAL DESIGN IN REFRACTORY OR RELAPSED PATIENTS WITH HEMATOLOGICAL MALIGNANCIES.
S. Mehrotra[1], M. Gopalakrishnan[1], J. Gobburu[1], J.M. Greer[2], R. Piekarz[3], J.E. Karp[2], K. Pratz[2], M.A. Rudek[2]; [1]Center for Translational Medicine, University of Maryland, Baltimore, MD, USA, [2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA, [3]National Cancer Institute, Rockville, MD, USA.

PII-096
SAFETY, TOLERABILITY AND PHARMACOKINETICS (PK) OF DS-1040 IV INFUSION COADMINISTERED WITH ENOXAPARIN 1 MG/KG SC IN HEALTHY SUBJECTS.
J. Mendell[1], V. Dishy[1], J. Kochan[1], J. Pav[1], C. Zamora[2], J. Zhou[1]; [1]Daiichi Sankyo Pharma Development, Edison, NJ, USA, [2]Worldwide Clinical Trials, San Antonio, TX, USA.

PII-097
MECHANISTIC MODELING OF CELL DYNAMICS: NEUTROPHILS SURVIVAL IN THE PRESENCE OF PRO-INFLAMMATORY CYTOKINES.
E. Metelkin; Institute for Systems Biology (Moscow), Moscow, Russian Federation.

PII-098
POPULATION PHARMACOKINETICS OF ABT-494 IN HEALTHY SUBJECTS AND IN SUBJECTS WITH RHEUMATOID ARTHRITIS: COMBINED ANALYSIS OF PHASE I AND II TRIALS.
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PII-099
POPULATION PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS OF BUPRENORPHINE FOR THE TREATMENT OF NEONATAL ABSTINENCE SYNDROME.
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PII-100
MECHANISTIC UNDERSTANDING OF NONLINEAR PK OF AZD1775: A PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) APPROACH.
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PII-101
PREDICTING TISSUE PENETRATION OF BGB-3111 BASED ON A TRANSLATIONAL PK/PD MODEL.
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PII-102

FIRST-IN-HUMAN STUDY OF ACT-541468, A NOVEL DUAL OREXIN RECEPTOR ANTAGONIST: CHARACTERIZATION OF ITS PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND TOLERABILITY.

C. Muehlan[1], P.-E. Juif[1], J. van Gerven[2], J. Heuberger[2], J. Dingemanse[1]; [1]Actelion Pharmaceuticals Ltd., Allschwil, Switzerland, [2]Centre for Human Drug Research, Leiden, Netherlands.

PII-103

PHARMACOKINETICS, METABOLISM, AND EXCRETION OF GS-4997 IN HEALTHY SUBJECTS.

C.H. Nelson, T. Tarnowski, L. Wang, M.M. Vimal, R. Aoyama, T. O'Riordan, Y. Xin; Gilead Sciences, Inc., Foster City, CA, USA.

PII-104

EVALUATION OF TRANSPORTER AND CYTOCHROME P450-MEDIATED DRUG-DRUG INTERACTIONS BETWEEN GS-4059 AND THE PHENOTYPIC PROBE DRUG RIFAMPIN.

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PII-105

INFLUENCE OF IMMUNOGENICITY ON THE PHARMACOKINETICS OF JNJ-63823539, A NOVEL TUMOR NECROSIS FACTOR ALPHA AND INTERLEUKIN-17A BISPECIFIC ANTIBODY, IN HEALTHY SUBJECTS.

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PII-106

EFFECT OF CARDIOPULMONARY BYPASS SURGERY ON UNBOUND FRACTION OF CEFAZOLIN IN PLASMA.

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PII-107

DEVELOPMENT OF A SEMI-MECHANISTIC PK/PD MODEL OF AN ORAL FIXED DOSE COMBINATION OF CDA INHIBITOR E7727 WITH DECITABINE (ASTX727) IN SUBJECTS WITH MYELODYSPLASTIC SYNDROMES.

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PII-108

EVALUATION OF PHARMACOKINETICS AND TOLERABILITY OF TAUROURSODEOXYCHOLIC ACID (T-UDCA) AND ITS METABOLITES AFTER A MULTIPLE ORAL ADMINISTRATION IN HEALTHY SUBJECTS.

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PII-109

PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) PREDICTIONS FOR ENTRY INTO HUMAN. AN ANALYSIS OF SMALL MOLECULE DEVELOPMENT CANDIDATES AT HOFFMANN LAROCHE, 2003-2015.

N. Parrott[1], M. Delporte[1], T. Lave[1], R. Peck[2], B. Ricci[2]; [1]Roche, BASEL, Switzerland, [2]Roche, Basel, Switzerland.

PII-110

CLINICAL BIOPHARMACEUTIC ASSESSMENTS OF THE SOURCES OF ABSORPTION VARIABILITY FOR THE ANTICANCER AGENT TAK-117, AN INHIBITOR OF PHOSPHOINOSITIDE 3-KINASE-α (PI3K α).

C. Patel[1], S. Sankoh[2], Y. Shou[3], C. Griffin[4], K. Venkatakrishnan[1]; [1]Quantitative Clinical Pharmacology, Takeda Pharmaceuticals International Co., Cambridge, MA, USA, [2]Biostatistics, Takeda Pharmaceuticals International Co., Cambridge, MA, USA, [3]Oncology Clinical Research, Takeda Pharmaceuticals International Co., Cambridge, MA, USA, [4]Oncology Medical Safety, Takeda Pharmaceuticals International Co., Cambridge, MA, USA.

PII-111

QUALIFICATION AND APPLICATION OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING AND SIMULATION (MANDS) TO PREDICT DRUG-DRUG INTERACTIONS FOR ALISERTIB.

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PII-112

THE EFFECT OF SYM-1219 ON HERG POTASSIUM CHANNELS *IN VITRO* AND ITS IMPLICATIONS ON CARDIAC FUNCTION *IN VIVO*.

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PII-113

DIFFERENCES IN 24-H AMBULATORY BLOOD PRESSURE MONITORING (ABPM) WHEN PATIENTS SWITCHED BETWEEN DIFFERING 30-MG NIFEDIPINE FORMULATIONS.

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PII-114

METABOLISM, PHARMACOKINETICS AND EXCRETION OF A SELECTIVE, POTENT INHIBITOR OF THE ISOCITRATE DEHYDROGENASE-1 MUTANT PROTEIN, AG-120, IN HEALTHY MALE VOLUNTEERS.

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PII-115

PHARMACODYNAMIC SYSTEMS MODEL OF BORTEZOMIB SIGNALING IN U266 MULTIPLE MYELOMA CELLS.

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PII-116

RELATIVE BIOAVAILABILITY OF A SINGLE SUBCUTANEOUS (SC) DOSE OF TREVOGRUMAB (REGN1033) PRODUCED FROM TWO DIFFERENT CELL LINES IN HEALTHY SUBJECTS.

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PII-117

POPULATION PHARMACOKINETICS (PPK) OF APIXABAN IN PEDIATRIC SUBJECTS AT RISK FOR A VENOUS OR ARTERIAL THROMBOSIS.

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PII-118

SYSTEMATIC REVIEW AND META-ANALYSIS OF DRUG-DRUG INTERACTION EFFECT SIZE BETWEEN COMMONLY-USED CYP INDEX SUBSTRATES AND PERPETRATORS.

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PII-119

QSP MODELING OF LIVER DGAT INHIBITION USING NAFLDSYM IS PREDICTED TO REDUCE STEATOSIS BUT MAY NOT RELIEVE LIPOTOXICITY IN NAFLD PATIENTS.

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DEVELOPMENT OF A QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL OF INFLAMMATORY BOWEL DISEASES.

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PHARMACOKINETICS AND SAFETY OF OLAPARIB IN PATIENTS WITH ADVANCED SOLID TUMORS AND HEPATIC OR RENAL IMPAIRMENT.

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PII-122

DELINEATING THE ROLE OF VARIOUS FACTORS IN RENAL DISPOSITION OF DIGOXIN THROUGH APPLICATION OF PHYSIOLOGICALLY BASED KIDNEY MODEL TO RENAL IMPAIRMENT POPULATIONS.

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PII-123

EFFECT OF FOOD ON THE PHARMACOKINETICS OF ERTUGLIFLOZIN AND ITS FIXED DOSE COMBINATIONS: ERTUGLIFLOZIN/SITAGLIPTIN AND ERTUGLIFLOZIN/METFORMIN.

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PII-124

DEVELOPMENT OF AN ADULT PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL OF SOLITHROMYCIN IN PLASMA AND EPITHELIAL LINING FLUID.

S. Salerno[1], A. Edginton[2], M. Cohen-Wolkowiez[3], C.P. Hornik[3], B.D. Jamieson[4], P. Fernandes[4], D. Gonzalez[1]; [1]University of North Carolina, Chapel Hill, NC, USA, [2]University of Waterloo, Kitchener, ON, Canada, [3]Duke University Medical Center, Durham, NC, USA, [4]Cempra Inc., Chapel Hill, NC, USA.

PII-125

VALIDATED LC-MS/MS METHOD FOR THE ABSOLUTE DETERMINATION OF CETUXIMAB IN HUMAN SERUM AND ITS CLINICAL APPLICATION.

K. Shibata, T. Naito, H. Shida, J. Kawakami; Hamamatsu University School of Medicine, Hamamatsu, Japan.

PII-126

LOW-DOSE TOLVAPTAN PK/PD: COMPARISON OF SUBJECTS WITH HYPONATREMIA DUE TO SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH) TO HEALTHY ADULTS.

S.E. Shoaf[1], P. Bricmont[1], A. Dandurand[2]; [1]Otsuka Pharmaceutical Development & Commercialization, Inc, Rockville, MD, USA, [2]Otsuka Pharmaceutical Development & Commercialization, Inc, Princeton, NJ, USA.

PII-127

POPULATION PHARMACOKINETICS OF OMBITASVIR, PARITAPREVIR, RITONAVIR AND DASABUVIR IN HCV-INFECTED SUBJECTS WITH CHRONIC KIDNEY DISEASE STAGE 4 OR STAGE 5.

D.L. Shuster[1], D. Eckert[2], S. Mensing[2], S. Dutta[1], R. Menon[1], J. Zha[1]; [1]AbbVie, North Chicago, IL, USA, [2]AbbVie, Ludwigshafen, Germany.

PII-128

USING SYSTEMS PHARMACOLOGY MODELING TO UNDERSTAND THE PATHOPHYSIOLOGY OF NAFLD AND RESPONSE TO DIETARY INTERVENTION IN A SIMULATED POPULATION.

S.Q. Siler[1], T.R. Rieger[2], G. Generaux[1], B.A. Howell[1], R. Allen[2], C.J. Musante[2], P.B. Watkins[3]; [1]DILIsym Services, Inc., Research Triangle Park, NC, USA, [2]Pfizer, Cambridge, MA, USA, [3]University of North Carolina, Chapel Hill, NC, USA.

PII-129

THE T0901317-TREATED MOUSE: A RAPID AND COST-EFFECTIVE ANIMAL MODEL FOR STUDYING THE EFFECTS OF HEPATIC STEATOSIS ON CYP450-MEDIATED DRUG METABOLISM.

S. Pilote, C. Thibault, E. Jubinville, J. Routhier, B. Drolet, M.C. Morissette, **C. Simard**; Institut universitaire de cardiologie et de pneumologie de Quebec, Quebec, QC, Canada.

PII-130

HEPATIC DISPOSITION OF ^{99M}TECHNETIUM-MEBROFENIN IS ALTERED IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS.

J. Slizgi, J. Kaullen, I. Ali, P. Stewart, A. Barritt, K. Brouwer; University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

PII-131

MECHANISTIC MODELING OF CELL DYNAMICS: MATHEMATICAL DESCRIPTION OF MULTIPLE EFFECTS OF REGULATORY MOLECULES.

S. Smirnov, E. Metelkin, G. Lebedeva, O. Demin; Institute for Systems Biology, Moscow, Moscow, Russian Federation.

PII-132

PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING PREDICTION OF EFFECT OF ITRACONAZOLE ON PHARMACOKINETICS OF OLANZAPINE AND SAMIDORPHAN GIVEN IN COMBINATION AS ALKS 3831.

L. Sun, L. von Moltke, K.R. Yeo; Alkermes, Inc., Waltham, MA, USA.

PII-133

EFFECT OF FOOD ON THE PHARMACOKINETICS OF LCB01-0371; AN APPLICATION OF PBPK MODEL.

J. Sunwoo[1], S.-J. Rhee[1], Y. Kim[1], H. Lee[1], I.-J. Jang[1], S. Yoon[2], Y. Kim[3], Y. Cho[3], H. Nam[3], J.-Y. Chung[2]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, Republic of Korea, [3]LegoChem Biosciences, Inc., Daejeon, Republic of Korea.

PII-134

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PH1 STUDY TO EVALUATE SAFETY AND PHARMACOKINETICS OF AMG203 (NAMILUMAB) IN HEALTHY ADULT JAPANESE/CAUCASIAN MALE SUBJECTS.

S. Tanaka, S. Harada, N. Hiramatsu, R. Nakaya, M. Kawamura; Takeda Pharmaceutical Company Ltd, Osaka, Japan.

PII-135

A TARGET-MEDIATED DRUG DISPOSITION MODEL TO CHARACTERIZE THE PK-PD OF BMS-986089 IN HEALTHY ADULTS AND ITS APPLICATION TO PEDIATRIC DOSE SELECTION.

G.S. Tirucherai[1], L.K. Jacobsen[2], L. Hamuro[1], M. Ahlijanian[2], C. Bechtold[1], M. AbuTarif[1]; [1]Bristol-Myers Squibb, Lawrenceville, NJ, USA, [2]Bristol-Myers Squibb, Wallingford, CT, USA.

PII-136

PHARMACOKINETICS AND SAFETY OF A NOVEL APOLIPOPROTEIN A-I THERAPY, CSL112, IN ADULTS WITH MODERATE RENAL IMPAIRMENT (RI) AND NORMAL RENAL FUNCTION.

M.A. Tortorici, D. Duffy, M. Zhou, R. Evans, J. Feaster, D. D'Andrea; CSL Behring, King of Prussia, PA, USA.

PII-137

CLINICALLY-WEIGHTED CARDIOMYOCYTE TRANSCRIPTOMIC SIGNATURES FOR KINASE INHIBITOR ASSOCIATED CARDIOTOXICITY.

J.G. van Hasselt, J. Hansen, Y. Xiong, E.A. Sobie, M.R. Birtwistle, E.U. Azeloglu, R. Iyengar; Icahn School of Medicine at Mount Sinai, Department of Pharmacology and Systems Therapeutics, New York, NY, USA.

PII-138

ETROLIZUMAB POPULATION PK-PD MODELING: TREATMENT-INDUCED SERUM SMADCAM-1 REDUCTION PREDICTS B7 RECEPTOR OCCUPANCY IN PATIENTS WITH ULCERATIVE COLITIS.

L. Gibiansky[1], **Y. Wang**[2], F. Fuh[2], N.X. Wang[2], A. Quartino[2], R. Erickson[2], T. Ramirez-Montagut[2], M.T. Tang[2]; [1]QuantPharm LLC, North Potomac, MD, USA, [2]Genentech, Inc, South San Francisco, CA, USA.

PII-139

PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF FUNCTIONAL COMPLEMENT 1 ESTERASE INHIBITOR AND COMPLEMENT 4 FOR PREVENTION AND TREATMENT OF HEREDITARY ANGIOEDEMA ATTACKS.

J. Marier[1], G. Vasilinin[1], S. Jennifer[2], P. Martin[2], **Y. Wang**[2]; [1]Certara Strategic Consulting, Montreal, QC, Canada, [2]Shire Human Genetic Therapies, Inc., Lexington, MA, USA.

PII-140

POPULATION PHARMACOKINETIC MODELING OF TEDUGLUTIDE TO SUPPORT DOSING IN PEDIATRIC PATIENTS WITH SHORT BOWEL SYNDROME.

J. Marier[1], N. Kassir[1], P. Martin[2], **Y. Wang**[2]; [1]Certara Strategic Consulting, Montreal, QC, Canada, [2]Shire Human Genetic Therapies, Inc., Lexington, MA, USA.

PII-141

EFFECT OF MULTIPLE DOSES OF IDALOPIRDINE ON SINGLE-DOSE PHARMACOKINETICS OF MEMANTINE AND ESCITALOPRAM IN HEALTHY SUBJECTS.

Y. Wang[1], A. Raoufinia[2], E. Schmidt[3], J. Amatniek[1]; [1]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA, [2]Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD, USA, [3]H. Lundbeck A/S, Valby, Denmark.

PII-142

IMPACT OF POPULATION PHARMACOKINETIC ANALYSES ON LABELING: A REVIEW OF NEW MOLECULAR ENTITIES LABELS APPROVED BETWEEN 2011 AND 2015.

Y.S. Wu[1], A. Bhattaram[2], J. Earp[2], J. Florian[2], J. Grillo[2], K. Krudys[2], J. Lee[2], F. Li[2], H. Li[2], C. Liu[2], J. Liu[2], L. Ma[2], A. Marathe[2], D. Marathe[2], Y. Mulugeta[2], D. Rekic[2], X. Wang[2], Y. Wang[2], Y. Xu[2], Y. Yang[2], I. Younis[2], J. Yu[2], P. Zhao[2], N. Zheng[2], L. Zhuang[2], V. Sinha[3], N. Mehrotra[2]; [1]University of Pittsburgh, School of Pharmacy, Pittsburgh, PA, USA, [2]Office of Clinical Pharmacology, US Food and Drug Administration, Silver Spring, MD, USA, [3]Merck & Co., Inc., North Wales, PA, USA.

PII-143

TRANSLATIONAL DRUG INTERACTION EVIDENCE GAP DISCOVERY USING TEXT MINING.

H.-Y. Wu[1], S. Zhang[1], Z. Desta[2], S. Quinney[2], L. Li[1]; [1]Center for Computational Biology and Bioinformatics, School of Medicine, Indiana University, Indianapolis, IN, USA, [2]Indiana University School of Medicine, Indianapolis, IN, USA.

PII-144

POPULATION PHARMACOKINETICS (PK) OF RUCAPARIB (CO-338) IN PATIENTS WITH ADVANCED OVARIAN CANCER (AOC) OR OTHER SOLID TUMORS.

J.J. Xiao[1], M. Green[2], S. Ma[2], S. Goble[1], H. Giordano[1], L. Maloney[1], T. Harding[1]; [1]Clovis Oncology, Inc., Boulder, CO, USA, [2]Quantitive Solutions - A Certara Company, Menlo Park, CA, USA.

PII-145

POPULATION PHARMACOKINETIC (PK) AND EXPOSURE - HAEMOGLOBIN RESPONSE ANALYSIS FOR OLAPARIB TABLET FORMULATION.

H. Xu[1], J. Li[1], M. Learoyd[2], K. Bui[1], H. Tomkinson[2], N. Al-Huniti[1]; [1]AstraZeneca, Waltham, MA, USA, [2]AstraZeneca, Cambridge, UK.

PII-146

IMPACT OF FLAVIN-CONTAINING MONOOXYGENASE 3 GENETIC VARIANTS ON PLASMA DISPOSITION OF VORICONAZOLE IN JAPANESE PATIENTS.

T. Yamada, Y. Mino, T. Naito, J. Kawakami; Hamamatsu University School of Medicine, Hamamatsu, Japan.

PII-147

IMPACT OF ORGAN SPECIFIC INDUCTION ON PREDICTING THE EFFECT OF EFAVIRENZ AS A MODERATE CYP3A INDUCER USING PBPK: ANALYSIS OF MODELS SUBMITTED TO THE US FOOD AND DRUG ADMINISTRATION.

Y. Yang[1], D. Rekic[1], A. Galetin[2], P. Zhao[1]; [1]US Food and Drug Administration, Silver Spring, MD, USA, [2]2Centre for Applied Pharmacokinetic Research, University of Manchester, Manchester, UK.

PII-148

EFFECT OF FOOD ON THE PHARMACOKINETICS OF JLP-1207, A COMBINATION TABLET OF TAMSULOSIN AND SOLIFENACIN FOLLOWING ORAL ADMINISTRATION IN HEALTHY MALE VOLUNTEERS.

H. Yoo[1], S. Moon[1], S. Lee[1], S. Lee[1], J. Kim[2], Y. Lee[2], S. Yoon[1], J.-Y. Jo[1], K.-S. Yu[1], S. Lee[1]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Jeil Pharmaceutical Co., LTD, Seoul, Republic of Korea.

PII-149

TOLERABILITY, PHARMACOKINETICS AND FOOD EFFECT STUDY OF SA001 AND ITS METABOLITE, REBAMIPIDE IN HEALTHY MALE SUBJECTS.

S. Yoon, A. Kim, S. Jung, I. Jeon, S. Lee, I.-J. Jang, K.-S. Yu; Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea.

PII-150

ASSESSMENT OF UNINTENDED INTERPERSONAL TRANSFERABILITY OF TOPICAL TESTOSTERONE PRODUCTS AND MITIGATION STRATEGIES.

M.A. Akbar, S.-A. Park, M.-J. Kim, J. Shon, L. Lee, M. Ahn, L. Li, **C. Yu**; US Food and Drug Administration, Silver Spring, MD, USA.

PII-151

DRUG-DRUG INTERACTIONS OF SIROLIMUS OR EVEROLIMUS WITH THE HCV DIRECT ACTING ANTIVIRAL (DAA) COMBINATION OF OMBITASVIR, PARITAPREVIR/R AND DASABUVIR.

J. Zha, P. Badri, D.L. Shuster, Q. Jiang, B. Yao, D.E. Cohen, S. Dutta, R.M. Menon; AbbVie Inc., North Chicago, IL, USA.

PII-152

GLOBAL SENSITIVITY ANALYSIS AS A TOOL TO IDENTIFY KEY PARAMETERS FOR CHARACTERIZING PHARMACOKINETIC DISPOSITION OF HIGH-POTENCY ANTIBODY DRUG CONJUGATES: A CASE STUDY.

X. Zhang, M.M. Cotreau; ImmunoGen, Waltham, MA, USA.

PII-153

PREDICTING THE WEIGHT-LOSING EFFECT OF OXYNTOMODULIN IN HUMAN FROM MOUSE DATA USING PHARMACOKINETIC/PHARMACODYNAMIC MODELING.

S. Zheng, W. Wang; Janssen R&D, Spring House, PA, USA.

PII-154

PREDICTIVE PERFORMANCE OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING OF SUFENTANIL IN CHILDREN.

W. Zhou[1], T. Johnson[2], K. Bui[1], A. Cheung[3], J. Li[1], H. Xu[1], N. Al-Huniti[1], **D. Zhou**[1]; [1]AstraZeneca, Waltham, MA, USA, [2]Certara, Sheffield, UK, [3]AstraZeneca, Cambridge, UK.

PII-155

APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING TO PREDICT ONDANSETRON PHARMACOKINETICS IN CHILDREN.

W. Zhou[1], T. Johnson[2], K. Bui[1], A. Cheung[3], J. Li[1], H. Xu[1], N. Al-Huniti[1], **D. Zhou**[1]; [1]AstraZeneca, Waltham, MA, USA, [2]Certara, Sheffield, UK, [3]AstraZeneca, Cambridge, UK.

PII-156

THE ROLE OF ALDH1A1 IN THE VASCULAR EFFECTS OF NITROGLYCERIN.

K. Zhou, H. Shih, Z. Yang, J. Parker; University of Toronto, Toronto, ON, Canada.

PII-157

POPULATION PHARMACOKINETICS (PK) OF LEBRIKIZUMAB AND EXPOSURE-RESPONSE (ER) ANALYSES OF PHASE III STUDIES IN SEVERE ASTHMA PATIENTS.

R. ZHU, N.L. Dirks, S. Vadhavkar, J.Y. Jin, C. Holweg, J. Olsson, J. Matthews, W. Putnam; Genentech, South San Francisco, CA, USA.

POSTER WALKS

ENDOGENOUS/EXOGENOUS PREDICTORS OF DRUG RESPONSE ONCOLOGY

WEDNESDAY, MARCH 15, 2017

5:15 PM – 6:00 PM

CHAIRS:

Mark Dresser, PhD, Denali Therapeutics, South San Francisco, CA

Kari Morrissey, PhD, Genentech, Inc. South San Francisco, CA

PWI-001

TCL1A IDENTIFICATION AS A NOVEL TRANSCRIPTION FACTOR AND A PHARMACOGENOMIC LINK TO AROMATASE INHIBITOR-INDUCED MUSCULOSKELETAL ADVERSE EVENTS.

M.-F. Ho[1], E. Lummertz da Rocha[1], T. Bongartz[2], J. Ingle[1], P. Goss[3], T. Mushiroda[4], M. Kubo[4], L. Shepherd[5], H. Li[1], L. Wang[1], R. Weinshilboum[1]; [1]Mayo Clinic, Rochester, MN, USA, [2]Vanderbilt University Medical Center, Nashville, TN, USA, [3]Massachusetts General Hospital Cancer Center, Boston, MA, USA, [4]RIKEN Center for Integrative Medical Sciences, Yokohama City, Japan, [5]NCIC Clinical Trials Group, Kingston, ON, Canada.

PWI-002

MAN1A2 IS A NOVEL PREDICTIVE MARKER OF REFRACTORY RESPONSE TO R-CHOP THERAPY IN DIFFUSE LARGE B-CELL LYMPHOMA.

M.K. Breitenstein[1], J. Cairns[1], S.M. Ansell[1], D.G. Cox[2], R. Delarue[3], U. Farooq[4], A.L. Feldman[1], H. Ghesquieres[5], T.M. Habermann[1], C. Haioun[6], F. Jardin[3], B. Link[4], M.J. Maurer[1], T. Molina[7], G.S. Nowakowski[1], C.L. Olswold[1], G. Salles[5], S.L. Slager[1], C.A. Thompson[1], H. Tilly[3], T.E. Witzig[1], A.J. Novak[1], R.M. Weinshilboum[1], L. Wang[1], J.R. Cerhan[1]; [1]Mayo Clinic, Rochester, MN, USA, [2]Mayo ClinicCancer Research Center of Lyon, Lyon, France, [3]Centre Henri Becquerel, Rouen, France, [4]University of Iowa, Iowa, IA, USA, [5]Université Claude Bernard, Lyon, France, [6]Hospital Henri Mondor, Créteil, France, [7]Universite Paris Descartes, Paris, France.

PWI-003

PHARMACOGENETICS OF CHEMOTHERAPY RESPONSE IN OSTEOSARCOMA: A GENETIC VARIANT IN *SLC7A8* IS ASSOCIATED WITH PROGRESSIVE DISEASE.

M.J. Coenen[1], H.I. Vos[1], J.M. Groothuismink[1], W.T. van der Graaf[1], U. Flucke[1], B.H. Schreuder[1], M.M. Hagleitner[1], H. Gelderblom[2], T. van der Straaten[2], E.S. de Bont[3], L.C. Kremer[4], J. Bras[5], H.N. Caron[5], R. Windsor[6], J.S. Whelan[6], A. Patiño-García[7], A. González-Neira[8], G. McCowage[9], S. Nagabushan[9], D. Catchpoole[10], F.N. van Leeuwen[1], H.-J. Guchelaar[2], M.D. te Loo[1]; [1]Radboudumc, Nijmegen, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [4]Emma Childrens' Hospital, Academic Medical Center, Amsterdam, Netherlands, [5]Academic Medical Center, Amsterdam, Netherlands, [6]University College London Hospitals, London, UK, [7]Clinica Universidad de Navarra, Pamplona, Spain, [8]Spanish National Cancer Centre, Madrid, Spain, [9]Children's Hospital at Westmead, Westmead, Australia, [10]Children's Hospital at Westmead, Westmead, Australia.

PWI-004

PRECISION MEDICINE BY MODELING PHARMACOKINETIC AND BIOMARKER DRIVERS OF TUMOR KINETICS: ASSESSING EFFECTS OF ALISERTIB EXPOSURE AND TARGET SNP STATUS ON ANTITUMOR ACTIVITY.

K. Williams, H. Niu, X. Zhou, A. Chakravarty, J. Jung, M. Bargfrede, K. Venkatakrishnan, **D. Bottino**; Takeda Pharmaceuticals International Co., Cambridge, MA, USA.

PWI-005

TSPYL GENE FAMILY REGULATES *CYP17A1* AND *CYP3A4* EXPRESSION: POTENTIAL MECHANISM CONTRIBUTING TO ABIRATERONE RESPONSE IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS.

S. Qin, D. Liu, M. Kohli, L. Wang, P. Vedell, N. Niu, J. Yu, R.M. Weinshilboum, L. Wang; Mayo Clinic, Rochester, MN, USA.

APPLICATIONS OF NOVEL TECHNOLOGY

THURSDAY, MARCH 16, 2017

4:45 PM – 5:30 PM

CHAIRS:

Richard Peck, MD, F. Hoffmann La Roche Ltd., Switzerland

Mohamed H. Shahin, BPharm, MS, PhD, University of Florida, Gainesville, FL

PWII-001

A NOVEL HIGH-THROUGHPUT BIOASSAY TO FUNCTIONALLY TEST GENETIC VARIANTS IN MICRO-RNA BINDING SITES.

J. Ipe[1], K.S. Burgess[1], Y. Hao[1], H. Gao[1], M. Swart[1], Z. Desta[1], A. Gaedigk[2], Y. Liu[1], T.C. Skaar[1]; [1]Indiana University School of Medicine, Indianapolis, IN, USA, [2]Children's Mercy Hospital, Kansas City, MO, USA.

PWII-002

IMAGING ANTIRETROVIRAL DISTRIBUTION WITHIN GASTROINTESTINAL TISSUES ACROSS PRE-CLINICAL SPECIES: IMPLICATIONS FOR HIV ERADICATION.

C. Thompson[1], E.P. Rosen[1], M. Mathews[1], N. White[1], C. Sykes[1], Y. Fedoriw[1], P. Charlins[2], L. Mulder[2], M. Kovarova[1], L. Adamson[3], D.C. Muddiman[4], R. Akkina[2], V. Garcia[1], P. Luciw[3], A.D. Kashuba[1]; [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Colorado State University, Fort Collins, CO, USA, [3]University of California Davis, Davis, CA, USA, [4]North Carolina State University, Raleigh, NC, USA.

PWII-003

ZEBRAFISH: A NEW SCREENING TOOL TO EVALUATE ORGANIC CATION TRANSPORTERS.

A.F. Leblanc, K. Hong, S. Hu, N. Pabla, A.A. Gibson, A. Sparreboom; The Ohio State University, Columbus, OH, USA.

PWII-004

MICRODOSING PREVENTS THE KNOWN PHARMACOKINETIC DRUG INTERACTION BETWEEN CHLORZOXAZONE AND MIDAZOLAM.

N. Hohmann, J. Burhenne, G. Mikus, W.E. Haefeli; Department of Clinical Pharmacology, University Hospital Heidelberg, Heidelberg, Germany.

PWII-005

DATA-DRIVEN LEARNING ANALYSIS IDENTIFIES GENDER DIFFERENCES IN METABOLIC TREATMENT RESPONSE OF CITALOPRAM/ESCITALOPRAM IN MAJOR DEPRESSIVE DISORDER.

A.P. Athreya[1], D. Neavin[2], W.V. Bobo[2], M.A. Frye[2], M. Skime[2], R. Kaddurah-Daouk[3], A.J. Rush[3], W. Matson[4], R.K. Iyer[1], L. Wang[2], R.M. Weinshilboum[2]; [1]University of Illinois at Urbana-Champaign, Urbana, IL, USA, [2]Mayo Clinic, Rochester, MN, USA, [3]Duke University School of Medicine, Durham, NC, USA, [4]Bedford VA Medical Center, Bedford, MA, USA.

ENDOGENOUS/EXOGENOUS PREDICTORS OF DRUG EXPOSURE

THURSDAY, MARCH 16, 2017

5:30 PM – 6:15 PM

CHAIRS:

Stacy Shord, US Food and Drug Administration, Silver Spring, MD

Larissa A. Wenning, PhD, Merck & Co., Inc., North Wales, PA

PWIII-001

CLINICAL APPLICATION OF PBPK MODELING: MECHANISTIC INSIGHTS INTO VARIABILITY IN MORPHINE CLEARANCE AMONG PEDIATRIC AND ADULT PATIENTS.

C. Emoto[1], T. Fukuda[1], T.N. Johnson[2], S. Neuhoff[2], S. Sadhasivam[3], A.A. Vinks[1]; [1]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]Simcyp Limited (a Certara company), Sheffield, UK, [3]Department of Anesthesia, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

PWIII-002

TACROLIMUS POPULATION PHARMACOKINETICS AND CYP3A5 GENOTYPES IN AFRICAN AMERICAN AND CAUCASIAN RENAL TRANSPLANT RECIPIENTS.

O. Campagne[1], D.E. Mager[1], D. Brazeau[2], R.C. Venuto[3], K.M. Tornatore[4]; [1]Department of Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, NY, USA, [2]Department of Pharmaceutical Sciences, College of Pharmacy, University of New England, Portland, ME, USA, [3]Erie County Medical Center, Division of Nephrology; Department of Medicine, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA, [4]Department of Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Immunosuppressive Pharmacology Research Program, Translational Pharmacology Research Core, NYS Center of Excellence in Bioinformatics and Life Sciences, University at Buffal, Buffalo, NY, USA.

PWIII-003

INTACT NEPHRON THEORY MAY NOT FULLY EXPLAIN THE EFFECT OF SEVERE RENAL IMPAIRMENT FOR DRUGS ACTIVELY SECRETED VIA RENAL ORGANIC ANION TRANSPORTERS.

C.-H. Hsueh[1], P. Zhao[2], W. Hsu[2], L. Zhang[2], K. Giacomini[3], S. Huang[2]; [1]US Food and Drug Administration/University of California San Francisco, San Francisco, CA, USA, [2]US Food and Drug Administration, Silver Spring, MD, USA, [3]University of California San Francisco, San Francisco, CA, USA.

PWIII-004

UGT1A9 RS3832043 INFLUENCES ACETAMINOPHEN GLUCURONIDATION IN NEONATES.

M.W. Linakis[1], X. Liu[1], S.F. Cook[2], S. Kumar[1], D.G. Wilkins[1], R. Gaedigk[3], A. Gaedigk[3], C.M. Sherwin[1], J.N. van den Anker[4]; [1]University of Utah, Salt Lake City, UT, USA, [2]University at Buffalo, Buffalo, NY, USA, [3]Children's Mercy Hospital, Kansas City, MO, USA, [4]Children's National Medical Center, Washington, DC, DC, USA.

PWIII-005

APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING FOR PREDICTION OF BUPRENORPHINE EXPOSURE IN SUBJECTS WITH HEPATIC IMPAIRMENT (HI).

K. Rowland-Yeo, T. Johnson; Simcyp (part of Certara), Sheffield, UK.

ENDOGENOUS/EXOGENOUS PREDICTORS OF DRUG RESPONSE CARDIAC/ METABOLIC

FRIDAY, MARCH 17, 2017

7:15 AM – 8:00 AM

CHAIRS:

Larissa Cavallari, PharmD, University of Florida, Gainesville, FL

Sony Tuteja, PharmD, University of Pennsylvania School of Medicine, Philadelphia, PA

PWIV-001

RNA-SEQ ANALYSES IDENTIFY MOLECULAR MARKERS OF BLOOD PRESSURE (BP) RESPONSE TO THIAZIDE DIURETICS (TD).

A. Costa Sa[1], A. Webb[2], Y. Gong[1], C.W. McDonough[1], M.H. Shahin[1], S. Datta[3], T.Y. Langaee[1], S.T. Turner[4], A.L. Beitelshees[5], A.B. Chapman[6], E. Boerwinkle[7], J.G. Gums[8], S.E. Scherer[9], R.M. Cooper-DeHoff[10], W. Sadee[11], J.A. Johnson[10]; [1]Center for Pharmacogenomics and Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, FL, USA, [2]Department of Biomedical Informatics, College of Medicine, The Ohio State University, Columbus, OH, USA, [3]Department of Biostatistics, University of Florida, Gainesville, FL, USA, [4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA, [5]Division of Endocrinology, Diabetes and Nutrition, University of Maryland, Baltimore, MD, USA, [6]Department of Medicine, University of Chicago, Chicago, IL, USA, [7]Division of Epidemiology, University of Texas at Houston, Houston, TX, USA, [8]Department

of Pharmacotherapy and Translational Research and Department of Community Health and Family Medicine, University of Florida, Gainesville, FL, USA, [9]Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA, [10]Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research and Division of Cardiovascular Medicine, Department of Medicine, University of Florida, Gainesville, FL, USA, [11]Center for Pharmacogenomics, Department of Cancer Biology and Genetics, College of Medicine, Ohio State University, Columbus, OH, USA.

PWIV-002

DISCOVERY OF SUBSTRATES FOR GLUT2, A TRANSPORTER IMPLICATED IN METFORMIN RESPONSE.

O.J. Enogieru, S. Yee, J. Chien, K. Giacomini; University of California San Francisco, San Francisco, CA, USA.

PWIV-003

COMMON GENETIC VARIANTS IN NEUROBEACHIN (*NBEA*) ARE ASSOCIATED WITH METFORMIN DRUG RESPONSE IN INDIVIDUALS WITH TYPE 2 DIABETES IN THE ACCORD CLINICAL TRIAL.

D.M. Rotroff[1], S.W. Marvel[1], J.R. Jack[1], T.M. Havener[2], A. Doria[3], H.S. Shah[3], J.C. Mychaleckyi[4], H.L. McLeod[5], J.B. Buse[6], M.J. Wagner[2], A.A. Motsinger-Reif[1], the ACCORD/ACCORDion Investigators; [1]Bioinformatics Research Center, North Carolina State University, Raleigh, NC, USA, [2]Center for Pharmacogenomics and Individualized Therapy, University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [3]Joslin Diabetes Center and Harvard Medical School, Boston, MA, USA, [4]Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA, [5]Moffitt Cancer Center, Tampa, FL, USA, [6]Division of Endocrinology, University of North Carolina School of Medicine, Chapel Hill, NC, USA.

PWIV-004

A GENETIC VARIANT OF ABCG2 CONFERS RISK FOR POOR RESPONSE TO ALLOPURINOL INDEPENDENT OF ITS EFFECT ON GOUT SEVERITY.

D. Brackman[1], E. Jorgenson[2], C. Wen[1], T. Hoffmann[1], C. Schaefer[2], N. Risch[1], K. Giacomini[1]; [1]University of California San Francisco, San Francisco, CA, USA, [2]Kaiser Permanente, Oakland, CA, USA.

PWIV-005

GENOME-WIDE COPY NUMBER VARIATION AND WARFARIN DOSE RESPONSE IN AFRICAN AMERICANS.

W. Hernandez[1], E.R. Gamazon[2], A.I. Konkashbaev[2], L.H. Cavallari[3], B. Stranger[1], M.A. Perera[4], International Warfarin Pharmacogenetics Consortium; [1]The University of Chicago, Department of Medicine, Section of Genetic Medicine, Chicago, IL, USA, [2]Vanderbilt University, Department of Medicine, Division of Genetic Medicine, Nashville, TN, USA, [3]University of Florida, College of Pharmacy, Department of Pharmacotherapy and Translational Research, Center for Pharmacogenomics, Gainesville, FL, USA, [4]Northwestern University, Department of Pharmacology, Chicago, IL, USA.

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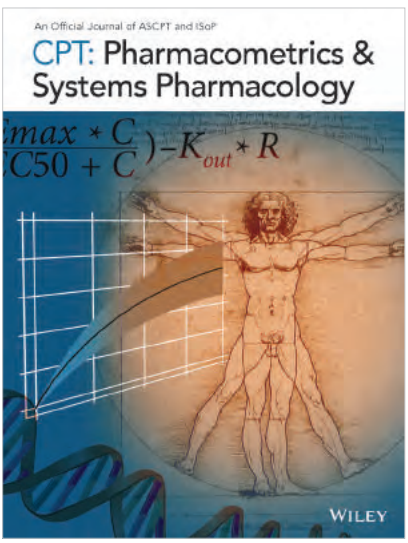

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