Introductory remarks

Peter Krajcsi

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The Meet the Experts (MEEX) series

Meeting	Region	Place / Year
MEEX	Europe	Budapest / 2014
MEEX	North America	San Francisco / 2014
MEEX	Asia	Tokyo / 2015
MEEX	North America	Boston / 2015
MEEX	Europe	Budapest / 2016
MEEX	**North America**	**San Francisco / 2017**
MEEX	Asia	Tokyo / 2017
MEEX	Europe	Budapest / 2018
MEEX	**North America**	**Cambridge / 2019**
MEEX	Asia	Seoul / 2019

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10+ Years of Regulatory Change

2006: FDA Draft Guidance (P-gp)

2007: Formation of International Transporter Consortium (ITC)

2010: ITC Transporter White Paper (P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3)

2010: EMA Draft Guidance (P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, BSEP, OCT1)

2012: Revised FDA Draft Guidance (P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, BSEP, MATEs, MRPs)

2013: Seven ITC Whitepapers Published

2013: Final EMA Guidance (more detailed)

2014: PMDA Guidance published

2017: EMA Concept Paper on Guidance Update Released

2017: Revised FDA Draft Guidance Released

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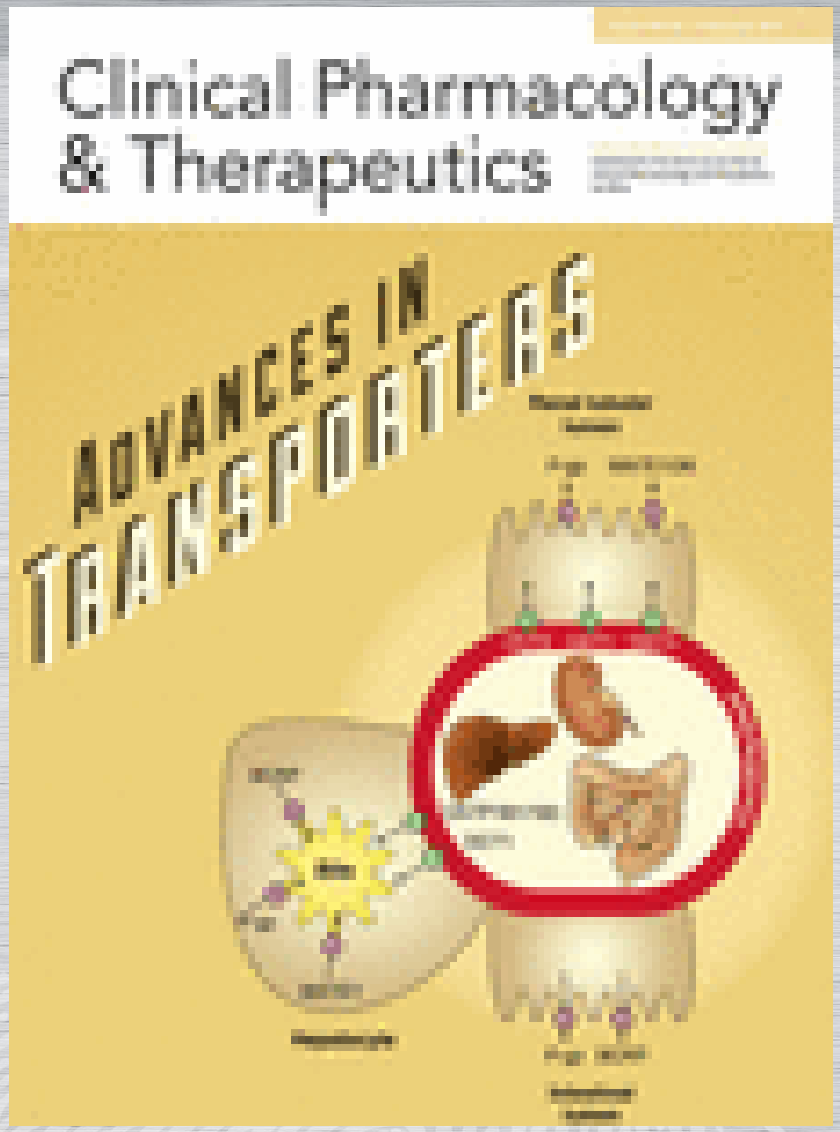

The past few years have ushered in an increased understanding of the role of transporters in the pharmacokinetics and pharmacodynamics of drugs, including transporter-mediated drug-drug interactions, nutrient-drug interactions, and in drug efficacy and safety…..

Although great advancements have been made in our understanding of factors affecting transporter function and clinical relevance, challenges remain, and the knowledge gaps must be addressed via collaborative efforts such as the International Transporter Consortium.

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Transporters as drug targets

Target class	Category	Tclin	Tchem	Tbio	Tdark
G-protein coupled receptors (non-olfactory)	GPCR	96	142	120	50
Olfactory G-protein coupled receptors	GPCR			8	413
Ion channels	Ion channel	126	85	106	24
ATP-binding cassette transporters	Transporter	3	7	32	5
SLC transporters	Transporter	15	65	218	89
Transcription factors	TF		36	926	476
Nuclear hormone receptors	TF	18	19	11	
Kinases	Enzyme	52	373	178	31

Oprea 2019
Mammalian Genome

T_{clin} Linked to approved drug by MoA
T_{chem} Potently bind small molecules, no MoA
T_{biol} Confirmed Mendelian dis phenotype (OMIM)
T_{biol} Do not meet above criteria

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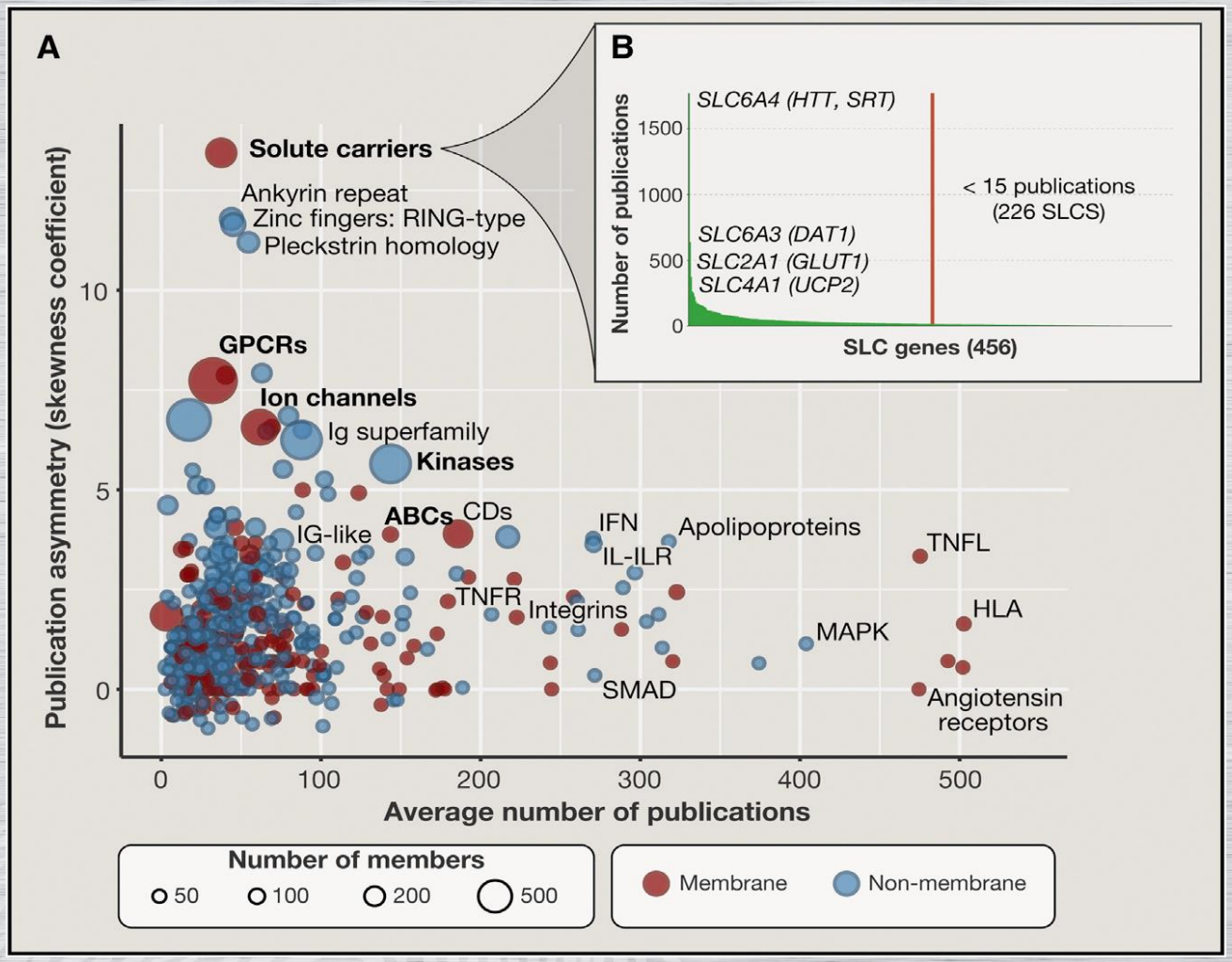
Deorphanizing SLCs



Cezar-Razquin 2015 Cell

Average publ/gene: 35
Overall average: 66

-SLCs 75% druggable
-12 transporter classes targeted and 6 further were at Phase II clinical or beyond

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Theme issues

- **DMD -** Special Section on Transporters in Drug Disposition and Pharmacokinetic Prediction (2018)
- **BBA Biomembranes -** Beyond the Structure-Function Horizon of Membrane Proteins (2018)
- **Pharmaceutics** – ABC transporter - mediated drug disposition (2018)
- **International J Molecular Sciences** – Physiological and pathological roles of ABC transporters 2.0 (2017) Plasma-Membrane Transport (2018)
- **Sci Reports -** Structure and mechanism of membrane transporters (2019);
- **FEMS Microbiol Lett -** Metabolite Transport and its Impact on Metabolic Engineering Approaches (2019)

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Technologies and applications

Biology, physiology, pathophysiology	Pharmacology, toxicology
Structural biology (cryo-EM, XFEL, NMR, etc.)	• Virtual screening • Molecular simulations
Functional genomics (haploid cells, CRISPR-cas9, etc.)	• Pathway mapping • Disease association • Target identification • Toxicity
Physiology (quantitative confocal microscopy, proteomics, microbiota, metabolomics, etc.)	• Organellar sequestration • Biomarkers • Simulation • Toxicity

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Solvo Publications 2018 - 2019

2018

- Sáfár Z. (2018) J Pharm Sci.
- Szerémy P. (2018) Cytometry B Clin Cytom.
- Tóth B. (2018) Toxicol In Vitro.
- Ishida K. (2018) Drug Metab Dispos.
- Mihály D. (2018) Exp Biol Med (Maywood).
- Kalapos-Kovács B. (2018) Phytother Res. 2018
- Moldován N. (2018) Sci Rep.
- Cenacchi V. (2018) Eur J Pharm Sci.
- Jani M. (2018) Toxicol In Vitro.
- Ishida K. (2018) Drug Metab Dispos.

2019

- Tupova L. (2019) Drug Metab Dispos.
- Erdő F. (2019) Front Aging Neurosci.
- Tátrai P. (2019) Drug Metab Dispos.
- Li CY. (2019) J Steroid Biochem Mol Biol.
- Vaskó B. (2019) Xenobiotica.
- Cusato J. (2019) Diagn Microbiol Infect Dis.
- Safar Z. (2019) Expert Opin Drug Metab Toxicol.
- Longo DM. (2019)bToxicol Sci.
- Doki K. (2019) Biol Pharm Bull.

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https://www.ncbi.nlm.nih.gov/pubmed

Collaborations yielding publications 2018-

Industry

- Novartis, Basel, CHE
- Takeda, Cambridge, MA
- Sigma, St Louis, MO
- DILISym, RTP, NC
- Cyprotex, Macclesfield, UK
- Chiesi, Parma, ITA
- Nerviano, Milano, ITA
- GSK, Ware, UK
- Amgen, Cambridge, MA
- Servier, Suresnes Fedex, FRA
- MDQuest, Szeged, HUN

Academia

- U Washington, Seattle, WA
- UNC, Chapel Hill, NC
- U Tsukuba, Tsukuba, Jpn
- U Turin, Turin, ITA
- U Barcelona, Barcelona, ESP
- U Liverpool, Liverpool, UK
- Charles University, Prague, CZE
- Hun Acad Sci, Budapest, HUN
- U Debrecen, Debrecen, HUN
- Semmelweis U, Budapest, HUN
- Peter Pazmany Catholic University, Budapest, HUN

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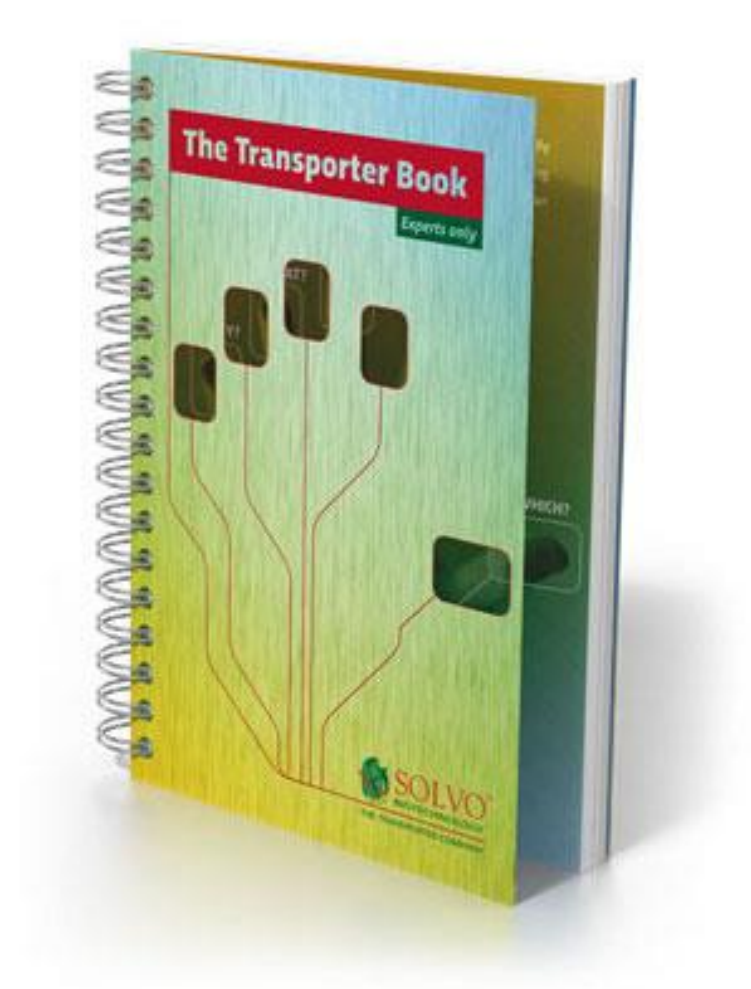
EXPERTS ONLY Transporter Book - 3rd Edition



- 294 pages: All about transporters
- 50 transporter monographs
- Transporter-mediated drug interactions
- Pros and cons of different assay types
- The Extended Clearance Classification System
- Regulatory requirements
- Case studies

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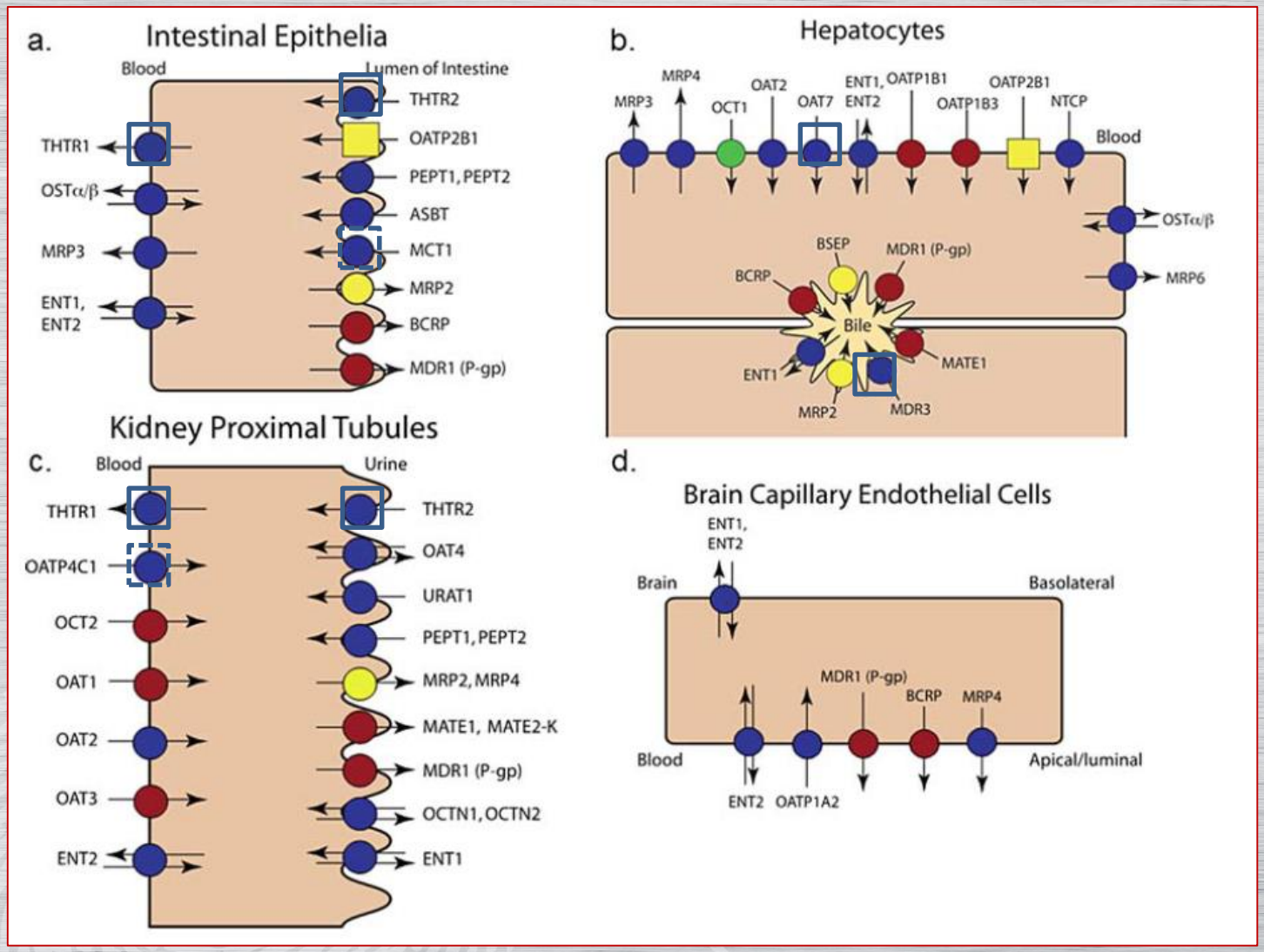
Clinically Relevant Transporters SOLVO portfolio



Modified from Zamek-Gliszczynski 2018 CPT

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About SOLVO

1999
- SOLVO, the first transporter assay provider

2012
- Boston Office opened

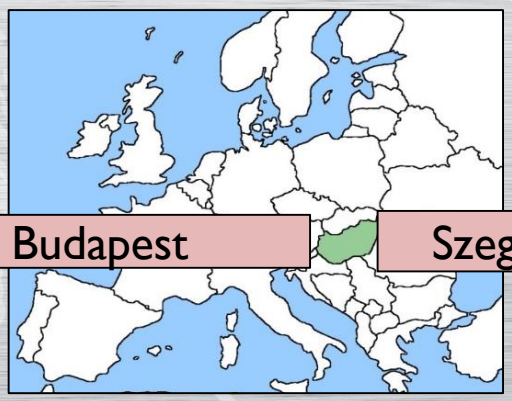
2015
- Seattle Office opened

2017
- San Francisco Office opened

2018
- Joined Citoxlab Group

2019
- Joined Charles River

- *>90 employees, 60 scientists - 20 in R&D*
- Worldwide presence: *500 clients in 40 countries*



DAY 1 (4 September)			
TIMING	**DURATION (min)**	**TOPIC**	**SPEAKER**
9:30-10:20		**Registration and coffee with snack**	
10:20-10:35	20	Introductory Remarks	Péter Krajcsi, PhD, Chief Scientific Officer, SOLVO Biotechnology, Hungary
		Session 1: Oral Exposure, DDI	
10:35-11:05	30	Variability in Oral Exposure – Formulation Investigations and Mitigating Approaches	Laurent Salphati, PhD, Principal Scientist, Drug Metabolism and Pharmacokinetics, Genentech, South San Francisco, CA, US
11:05-11:35	30	The Gut-Brain-Microbiome Axis: Epacadostat Transport and Metabolism on Brain Serotonin Concentration	Yan Zhang, Ph.D., Associate Director, Incyte Corporation, Drug Metabolism Pharmacokinetics & Clinical Pharmacology, Wilmington, DE, US
11:35-12:05	30	Selection of an Optimal In Vitro Assay and Clinical Probe Substrate to Assess P-gp Inhibition: Challenges and Path Forward	Xiaoyan Chu, PhD, Senior Investigator, Merck, New York, NY, US
12:05-13:05	**60**	**Lunch Break**	
		Session 2: Hepatic, Renal DDI and Toxicity	
13:05-13:45	40	Keynote: ADME Biomarkers: VIsion and Update	Dave Rodrigues,PhD, Senior Scientific Director, Pharmacokinetics, Dynamics & Metabolism Department, Pfizer, Groton, CT, US
13:45-14:15	30	Emerging *In Vitro* Kidney Models to Study Drug Elimination and Nephrotoxicity	Piyush Bajaj, PhD, Scientist II – Investigative Toxicology, Drug Safety Research and Evaluation, Takeda Pharmaceuticals, Cambridge, MA, US
14:15-14:45	30	*In-vitro* and *In-vivo* Models to Study Drug Inflicted Changes on Bile Acids/salt Homeostasis	Yutai Li, PhD, Principal Scientist, Safety Assessment, Merck, West Point, PA, US
14:45-15:00	15	Poster presentation: Mechanistic basis of cabotegravir-glucuronide disposition in humans	Mitesh Patel, PKDM Scientist, Amgen, Cambridge, MA, US
15:00-15:30		**Coffee Break**	
		Session 3: CNS Disposition	
15:30-16:00	30	Blood-Brain Barrier Transporters in Ischemic Stroke: Focus on Oatps	Patrick T. Ronaldson, Ph.D, Associate Professor, Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, US
16:00-16:30	30	Organoid Platform for Modeling the Blood-Brain-Barrier	Choi-Fong Cho, PhD, Affiliate in Dept. of Chemistry, Massachusetts Institute of Technology; Associated Scientist | Broad Institute of Harvard and MIT, Boston, MA, US
16:30-17:00	30	Translating Transporter Activity into Quantitative Brain Penetration Predictions	Jennifer Liras, PhD, Vice President, Pharmacokinetics, Dynamics and Metabolism Department Pfizer Inc. Cambridge, MA
17:00-19:00		**RECEPTION WITH POSTER SESSION**	

17:00-19:00		**RECEPTION WITH POSTER SESSION**	
DAY 2 (5 September)			
TIMING	**DURATION (min)**	**TOPIC**	**SPEAKER**
Session 4: Protein Binding, Metabolism and Transport			
8:00-8:40	40	Keynote: Transporter-Enzyme Interplay in Hepatic Clearance...More Common than We Th	Manthena V. Varma, Ph.D, Associate Research Fellow, Pfizer Inc., Groton, CT, US
8:40-9:10	30	Clinical Significance and Regulatory Framework for the Evaluation of Organic Anion Transporting Polypeptide 1B-Based Drug-Drug Interactions	Savannah McFeely, PhD, Research Scientist, UW Drug Interaction Solutions, University of Washington School of Pharmacy, Seattle, WA, US
9:10-9:40	30	Protein Binding Methodologies and Relevance for DDI - an Industry Perspective	Li Di, PhD, Research Fellow, Pharmacokinetics, Dynamics Metabolism Department, Pfizer, Groton, CT, US
9:40-9:55	15	Poster presentation: Can We Improve Drug Design by Illuminating Druggable Targets with BDDCS?	Giovanni Bocci, Translational Informatics Division, University of New Mexico School of Medicine, Albuquerque NM, US
9:55-10:25	**30**	**Coffee Break**	
Session 5: Physiology, Oathophysiology and Therapy			
10:25-10:55	30	A Role for ABC Transporters and Porphyrin Metabolism Leukemia?	John Schuetz, PhD, Vice-Chair, Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, US
10:55-11:25	30	Structure-based Ligand Discovery for Human Nutrient Transporters	Avner Schlessinger, PhD, Assistant Professor, Department of Pharmacological Sciences, Associate Director, Center for Therapeutics Discovery, Icahn School of Medicine at Mount Sinai, New York, NY, US
11:25-11:55	30	Improvement of Nanoparticle Drug Delivery by Surface Conjugation with L-carnitine: Role of OCTN2/SLC22A5 and ATB0,+ (SLC6A14)	Vadivel Ganapathy, PhD Department of Cell Biology and Biochemistry, Texas Tech University, Lubbock, TX, US
11:55-12:10	15	Poster presentation: Novel Mechanisms and a Potential Therapy for Manganese Excess due to Inherited SLC30A10 Deficiency	Courtney Mercadante, Postdoc, Medical and Population Genetics, Brown University, Millville, US
12:10-13:10	**60**	**Lunch**	
Session 6: Methods and Models			
13:10-13:40	30	Validating and Optimizing In Vitro Assays for Improved DDI Prediction – assay calibration and time-dependent inhibition	Péter Tátrai, PhD, Senior Scientist, SOLVO Biotechnology, Hungary
13:40-14:10	30	Utilizing DILIsym, a QST Platform, to Extract More from Your Data to Support Decisions	Brett A. Howell, PhD, President, DILIsym Services Inc., a Simulations Plus Company, Research Tringle Park, NC, US
14:10-14:40	30	Approaches and Lessons Learned in Establishing HT-ADME Assays	Adrian Sheldon, PhD, Director, In Vitro ADME, Charles River Laboratories, Worcester, MA, US
14:40-14:55	**15**	**Closing Remarks by Péter Krajcsi**	

Topic	Title	Authors	Primary affiliation
I	Human precision-cut intestinal slices as an ex vivo model for ABCB1 transporter Induction	Martinec O, et al.	Department of Pharmacology and Toxicology, Faculty of Pharmacy in Hradec Kralove, Charles University, Czech Republic
I	P-glycoprotein efflux activity is inhibited by Anti-HIV and anti-HCV drugs in Caco-2 cells and precision-cut rat and human intestinal slices	Vokral I, et al.	Department of Pharmacology and Toxicology, Charles University, Faculty of Pharmacy in Hradec Kralove, Hradec Kralove, Czech Republic.
I, L	**Novel Mechanisms and a Potential Therapy for Manganese Excess due to Inherited SLC30A10 Deficiency**	**Mercadante C, et al.**	**Brown University, Providence, RI**
L	Characterization of GCDC transport by human hepatic uptake transporters for in vitro testing purposes	Tóth B, et al.	SOLVO Biotechnology, Budapest, Hungary
L, K	**Mechanistic basis of cabotegravir-glucuronide disposition in humans**	**Patel M, et al.**	**PKDM, Amgen, Cambridge, MA**
B	Optimization and validation of rodent chemical knock out model for P-glycoprotein using the selective inhibitor, Valspodar, and application to internal cut-off values and calibration of MDCK-MDR1 cell line	Kapadnis S. et al.	Biogen, DMPK, Cambridge, USA
B	Applying a Bayesian multi-level model to in vitro screening data to improve decision making in drug discovery	Ferber K, et al.	Biogen, Cambridge, MA
T	**Can we improve drug design by illuminating druggable targets with BDDCS?**	**Bocci G, et al.**	**Translational Informatics Division, University of New Mexico School of Medicine, Albuquerque NM 87131, USA**

Topic	Title	Authors	Primary affiliation
DDI	Assay calibration to refine prediction of P-gp mediated DDI based on in vitro vesicular transport assay data	Nerada Zs, Et al.	SOLVO Biotechnology, Budapest, Hungary
DDI	Assay calibration to refine prediction of OATP1B1/1B3 mediated drug-drug interactions (DDI) based on in vitro uptake transport assay data	Kovács P, et al.	SOLVO Biotechnology, Budapest, Hungary
DDI	Predictive value of coproporphyrin I compared to E217bG for OATP1B1-mediated drug-drug interactions	Kovács P, et al.	SOLVO Biotechnology, Budapest, Hungary
Assay	Correlation of BCRP kinetic transport and inhibitory potential parameters for different probe substrates in vesicular transport experiments using different expression systems	Sáfár Zs, et al.	SOLVO Biotechnology, Hungary
Assay	Validation and Optimization of a MDCK-BCRP Cell Line	Rowbottom C, et al.	Biogen, Cambridge MA
Assay	P-glycoprotein Expression Differences in the In Vitro Models and the Impact on Substrate Assessment	Badrinarayanan A. et al.	Department of Pharmacokinetics and Drug Metabolism, Amgen Research, Amgen Inc. Cambridge, MA 02142
PK	Optimization of the sample collection procedures for selective BCRP inhibitor, KO143, in rodents	Pietrasiewicz A, et al.	Biogen, Cambridge, MA, USA

DILIsym Services

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SLC drug targets

Drug Status	SLC	Common Protein Name	Examples
Approved	SLC5A2	SGLT2	canagliflozin; dapagliflozin
	SLC6A1	GAT1	tiagabine
	SLC6A2	NET	atomoxetine
	SLC6A3	DAT	methylphenidate
	SLC6A4	SERT	fluoxetine; sertraline; citalopram (SSRIs)
	SLC12A1/2	NKCC1/2	furosemide (loop diuretics)
	SLC12A3	NCC	hydrochlorothiazide (thiazide diuretics)
	SLC18A1/2	VMAT1/2	reserpine
	SLC18A2	VMAT2	tetrabenazine
	SLC22 family	OATs	probenecid
	SLC25A4/5/6	ANT1/2/3	clodronate
	SLC29A1	ENT1	dipyridamole
Phase II+ Clinical Trial	SLC5A1 (and SLC5A2)	SGLT1 (and SGLT2)	sotagliflozin
	SLC6A9	GlyT1	bitopertin
	SLC9A3	NHE3	tenapanor
	SLC10A2	IBAT	elobixibat
	SLC22A12	URAT1	lesinurad
	SLC40A1	Ferroportin-1	LY2928057

Cezar-Razquin 2015 Cell

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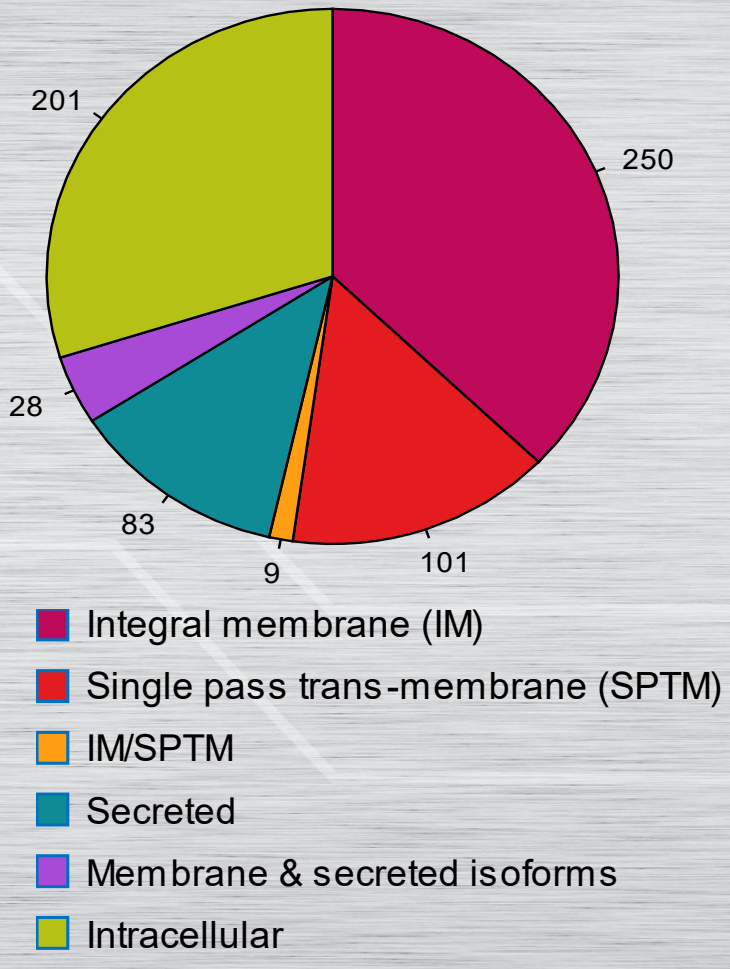
Protein classes – drug targets

Function	Protein class	Number of genes
	Enzymes	260
	Transporters	149
	Voltage-gated ion channels	49
	G-protein coupled receptors	98
	Nuclear receptors	24
	CD markers	71



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