An Overview of Drug Transporters in ADME & Drug Action

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Principles of Clinical Pharmacology
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Implications of Drug Transport in Drug Discovery and Development

Graphic illustration of drug transport in drug discovery and development.

Impact of Drug Transport on ADME
  - Oral absorption of drug
  - Drug Distribution and elimination
  - Drug-Drug Interaction
  - Influence of Pharmacogenomics (PGx on Drug Transport)

Impact of Drug Transport on Response and Toxicology
  - *Emerging Role in Toxicology*
  - Over expression of drug transporter may be a major factor in tumor, bacterial, and fungal multi-drug resistance (MDR).
The rate-determining process

“To understand transporter-mediated drug-drug interactions, we have to know the rate-determining process of a substrate in the overall clearance.”
uptake, basolateral efflux, apical excretion, and metabolism

Professor Sugiyama, Keynote address AAPS, November 2007
Lecture Objectives

At the end of this lecture and workshop, the student will be able to:

- List the 7 transporters currently identified by the International Transporter Consortium (ITC) as clinically important in drug absorption and disposition
- Explain why transporters can be major determinants of the pharmacokinetic, efficacy, and safety profiles of drugs
- Describe the process of transport induction, its time course, and how induction influences pharmacokinetic variability
- Describe the process of transport inhibition, its time course, and how induction influences pharmacokinetic variability
- Given a target drug(s), predict the effects on F, CL, exposure (AUC, Cmax) when a second agent (drug, natural product, etc) is administered that is an:
  - Inducer of transporters of the target drug
  - Inhibitor of transporters of the target drug
When Is an Interaction Clinically Significant?

Wide Therapeutic Range

Chart

Narrow Therapeutic Range chart

Adapted from S-M. Huang/FDA

‘Membrane Transporters in Drug Development’
The International Transporter Consortium (ITC): Academia, FDA, Industry

Key Issues Addressed:

• Which transporters are clinically important and should be considered for evaluation during drug development for induction and/or inhibition studies?
• Which methods for studying transporters should be used?
• When are evaluations recommended (decision trees)?
Transporters covered
Efflux: P-gp, BCRP
Renal: OAT/OCT

a Intestinal epithelia
Image showing effects in the blood and intestines

b Hepatocytes
Image showing effects in the blood

c Kidney proximal tubules
Image of effects in the blood and urine

d Blood-brain barrier
Image of effects in the brain and Basolateral
Drug Transporters of Interest from Second ITC Meeting

a Intestinal epithelia
Image showing effects in the blood and intestines

b Hepatocytes
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c Kidney proximal tubules
Image of effects in the blood and urine

d Blood-brain barrier
Image of effects in the brain and Basolateral
Transporters in Drug Absorption

*Intestinal Epithelial Transporters*
Transporters in the Intestinal Epithelia

Images

Efflux (efflux into lumen): P-gp (MDR1), BCRP

PK consequences of induction/inhibition of intestinal transporters
• Inhibition of intestinal uptake transporters or induction of efflux transporters may decrease intestinal absorption of drugs
• Inhibition of intestinal efflux transporters may increase the oral bioavailability of drugs
### P-glycoprotein Substrates

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<th>Cancer Chemotherapy</th>
<th>HIV Protease Inhibitors</th>
<th>Cardiac Drugs</th>
<th>Immunosuppressive Drugs</th>
<th>Anti-thelmints</th>
<th>Steroid-like</th>
<th>Miscellaneous</th>
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<td>– Doxorubicin</td>
<td>Amprenavir</td>
<td>Digoxin</td>
<td>– Cyclosporine A</td>
<td>Ivermectin</td>
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Drug Metabolizing Enzyme - Drug Transporter Interplay

Comparison chart of Strong CYP3A Inhibitors and Potet P-gp Inhibitors

Substrate overlap with multiple CYPs and Drug Transporters complicates in vitro to in vivo predictions

However, if your drug is a substrate of CYP3A4 and P-gp, Ketoconazole or itraconazole represents the worse case scenario for a Clinical DDI study

Mol. Pharmaceutics, 2009, 6 (6), pp 1766–1774
Consequences of Inducing Intestinal Efflux Transporters

Chart
Expression of P-gp in Human Duodenal Biopsy

Microscope images

P-gp expression before rifampin administration.

P-gp expression after rifampin administration.

Consequences of Inhibiting Intestinal Efflux Transporters

Image
Effect of P-gp Inhibitors on Plasma Digoxin Concentrations

Chart

Mean digoxin plasma concentration time curves in 28 patients before (closed circles) and at least 14 days after the start (open circles) of an antiretroviral therapy containing 400 mg lopinavir + 100 mg ritonavir twice daily. The patients received 0.5 mg digoxin orally at both occasions. Error bars indicate standard deviations.

Clinical Pharmacology & Therapeutics (2008); 84, 1, 75–82
Digoxin: Label Information

Drug Interactions

PGP Inducers/Inhibitors: drugs that induce or inhibit PGP have the potential to alter digoxin pharmacokinetics (7.1)

There are numerous drug interactions associated with digoxin. The potential for drug-drug interactions must be considered prior to and during drug therapy. See full prescribing information for a complete listing of pharmacokinetic (7.2) (12.3) and pharmacodynamic interactions (7.3)
Digoxin: Label Information

Picture of the Digoxin label
Digoxin: Safety Concerns

Bar chart showing AUC/AUC or $C_{\text{MAX,J}}$ Digoxin Ratios over
Valspodar
Quinidine
Cyclosporin
Quinidine
Itraconazole
Clarithromycin
Alprazolam
Ranolazine
Verapamil
Amiodarone
Diltiazem
Conivaptan
Captopril
Mibefradil
Propafenone
Carvedilol
Cimetidine
Nifedipine
Ritonavir
Telmisartan
Talinolol
Felodipine
Atorvastatin
Nitrendipine
Omeprazole
Isradipine
Sertraline
Nicardipine
Losartan
Troglitazone
Varenicline

Therapeutic conc ~ 1.5 ng/mL

33% change in Digoxin Exposure (Cmax) ~ 2.0 ng/mL Safety concerns

25% change in exposure might be clinically relevant
P-gp Mediated Digoxin DDIs

<2-fold change in digoxin Cmax or exposure were observed in the majority of published cases

- $I/IC50 > 0.1$ is predictive of positive clinical digoxin DDI related to P-gp
- $I2/IC50 < 10$ is predictive of no clinical digoxin DDI

For Digoxin or NMEs that have a narrow T.I. (similar to digoxin), P-gp may be an important determinant of PK and response.

Additional work is needed to fully understand the mechanism of false (-)'s observed with $I/IC50$ or false (+)'s with $I2/IC50$
Role of mdr1a in the Blood-Brain Barrier and the Placenta (murine studies)

Chart showing Ivermectin dose (mg/kg) and % survival of exposed mice.

Mdr1a/b (-/-) were found to be:
   Viable
   Fertile
   Without observable phenotype until pharmacological challenge with IVM.
   mdr1a -/- LD50 = 0.7 mg/kg
   mdr1a +/- LD50 = 60 mg/kg

CF-1 mice were found to be spontaneously mutant in mdr1a by MSD Scientists. The degree of chemical exposure of fetuses within each litter was inversely related to expression of placental P-gp and cleft palate susceptibility
   mdr1a -/- 100% cleft palate
   mdr1a +/- 50% cleft palate
   mdr1a +/- 0%
Ivermectin Toxicity in the Collie

Photo of a group of five collies with the following web address beneath it: http://www.awca.net/drug.htm.

50% of Collies display CNS toxicity when treated with normal doses of IVM (>60 microgram/kg).

Ivm-sensitive Collies lack functional P-gp at the blood brain barrier.

ABCB1 cDNA sequencing
- Sensitive Collies (7/7)
  4-base pair deletion
  homozygous
- Non-sensitive Collies (6/6)
  heterozygous (mutant/normal)
- Other breeds (4/4)
  normal/normal

ABCG2 (*alias* BCRP, MXR, ABCP, BMDP)

- Expressed endogenously in the intestine (small & large), liver, kidney, placenta, skeletal muscle, brain, and in hematopoietic stem cells
- In-vitro role in tumor drug resistance for Topo-1 and Topo-2 inhibitors (MXR, SN-38, Topotecan, J-107088)
- Emerging role in drug absorption of camptothecan analogues (Irinotecan and Topotecan).

  ABC subfamily 7 (G); member 2 (related to Drosophila White proteins)
  655 amino acid protein
  - ABCP isolated from human placenta R482 WT (Allikmets, 1996)
  - BCRP breast cancer resistance protein R482 T (Doyle et al., 1998)
  - MXR: Mitoxantrone resistance protein R482G (Bates et al., 1999)
  - BMDP: Brain multidrug resistance protein (Eisenblatter et al., 2003)

Phylogram with distances
### Substrates & Inhibitors of ABCG2

#### Drugs/NMEs
- Topotecan
- CPT-11/SN-38
- J-107088
- Mitoxantrone
- Flavoperidol
- Diflomotecan
- Methotrexate
- Sulfasalazine
- Prazosin
- Benzoylphenylurea
- Cimetidine
- Imatinib

#### Xenobiotics
- PhIP
- Pheophorbide A
- Estrogen SO4
- lysotracker (green)
- H33342
- Rhodamine 123
- Bodipy-prazosin
- Riboflavin (vitamin B2)

#### Endobiotics

#### Inhibitors
- FTC
- Ko134, 143
- Tryprostatin A
- GF120918
- Lapatinib
- Erlotinib
- Gefitinib
- CI-1033
- Novobiocin
- Imatinib
- Ritonavir
The breast cancer resistance protein protects against a major chlorophyll-derived dietary phototoxin and protoporphyria.


**Bcrp -/- ADME Phenotype**
- Diet-dependent phototoxicity
- Protoporphyria
- Enhanced oral absorption of topotecan
- Milk secretion of drugs and xenotoxins
- ABCG2 is expressed in bone marrow stem cells.

Electron microscopy

Charts
Of mice and men: Topotecan:BCRP interaction

Four separate line charts indicating the following:

- Plasma topotecan (ng/mL) over time (Jonker et al., JNCI, 2000)
- Plasma topotecan (ng/mL) over time (min) (Jonker et al., PNAS, 2002)
- Plasma topotecan (ng/mL) over time (min) (Jonker et al., JNCI, 2000)
- Plasma topotecan (ng/mL) over time (hr) in humans (Kruijtzer et al., JCO, 2002)
Absorption, metabolism, and excretion of Salicylazosulfapyridine in man

Chart

Serum concentrations of SASP after ingestion of a single 4Gm. Dose of SASP on Day 11 (10 subjects) and 4 x 1 Cm. of SASP on Days 2 to 10 (9 subjects).

Hasse Schröder and Dag E. S. Campbell  Uppsala, Sweden
Department of Zoophysiology, University of Uppsala, Pharmacia AB, Box 604, 751 25
Sulfasalazine (SASP) Disposition

Chemical structure of SASP and metabolites (5-ASA and sulfapyridine).

Indications: Rheumatoid arthritis (RA), Long term therapy of ulcerative colitis, and Crohn’s disease

Bioavailability (F) of SASP in humans is low (F< 15%) and highly variable

Low %F primarily attributed to SASP’s low permeability and poor solubility (thus, poor absorption)

Azo-reduction is the primary route of metabolic clearance

Metabolism occurs in distal small intestine and large intestine via bacterial flora

Studies in T-cells (CEM) demonstrate SASP is an ABCG2 (BCRP) substrate
Sulfasalazine (SASP) Resistance *in-vitro* Regulated by BCRP (ABCG2)

*Image*

van der Heijden et al., *Ann Rheum Dis.* 2004
Sulfasalazine (SASP) Hypothesis

Inter-individual differences in intestinal expression and function of ABCG2 (BCRP) contribute to variability in drug bioavailability, exposure and pharmacological response to SASP.
Abcg2 is Major Determinant of SASP Absorption and Elimination in the Mouse

Charts showing comparison between WT and KO mice.

Route of administration: PO over time, hr

Route of administration: IV over time, hr

Sufasalazine plasma concentration, ng/mL

Zaher et al., Molecular Pharmaceutics epub January 4, 2006
Abcb1 (mdr1a) does not contribute to SASP Bioavailability or Clearance in the Mouse

Two charts showing Sulfasalazine plasma concentration, ng/mL, comparing the route of administration, PO, with the route of administration, IV, over time in WT and KO mice.

Zaher et al., Molecular Pharmaceutics epub January 4, 2006
Altered SASP PK in ABCG2 (BCRP) Q141K
North American Healthy Volunteers

SASP BCRP*3

Chart

Plasma Sulfasalazine (ng/mL) over time (hours).

SASP PK Disposition in Healthy Japanese Volunteers

Chart showing SASP plasma concentration (μg/ml) over time.

Figure 2  Effect of ABCG2 genotype on pharmacokinetics of sulfasalazine (SASP). Plasma concentration-time profiles of SASP after oral administration of a 2,000 mg conventional SASP tablet to 421C/C subjects (closed circles, n = 12), 421C/A subjects (open triangles, n = 16), and 421A/A subjects (closed diamonds, n = 9).

Yamasaki et al., CPT January 2, 2008
421C>A SNP Changes Surface ABCG2 Expression

Chart comparing total protein with Cell surface

ABCG2 Polymorphisms and Ethnic Distribution of SNPs.

The ABCG2 Q141K genotype significantly affected the pharmacokinetics of diflomotecan (Clin Pharmacol Ther. 2004)

Gefitinib-induced diarrhea correlates with Q141K (J Natl Cancer Inst. 2006).

ABCG2 expression correlates with flavopiridol-induced myelotoxicity.

Figg et al., Anticancer Drugs. 2007
Role of Intestinal Efflux Transporter BCRP/ABCG2 Uric Acid excretion and Gout

- Gout is a common disease with a genetic predisposition
- In Japanese subjects, GWAS showed that serum uric acid levels relate to ABCG2/BCRP gene, which locates in a gout-susceptibility locus revealed by a genome-wide linkage study. Risk was observed in those with ≤1/4 function (OR, 25.8; 95% CI, 10.3-64.6; p = 3.39 × 10^{-21}). (Nucleosides Nucleotides Nucleic Acids. 2011 and Science Translation 2009)
- In addition to renal secretion of UA, intestinal efflux is an important determinant of UA clearance. Efflux is mediated by BCRP (ABCG2)
Gefitinib (Iressa)-enhanced SASP Bioavailability

Chart

Chemical structure of Gefitinib (Iressa)

Plasma concentrations versus time curve after oral administration of SASP (20 mg/kg) alone or combined with gefitinib (50 mg/kg) gavage 2 hrs prior to SASP administration in wt-type mice.
Curcumin (Tumeric)

Curcumin: from ancient medicine to current clinical trials

• Many ongoing clinical investigations including:
  – 89 trials listed in Clinicaltrials.gov
  – anti-inflammatory, antioxidant, age-associated Cognitive impairment, chemopreventive and chemotherapeutic activity

Curcumin increases SASP Bioavailability in Mouse

One chart showing SASP (ng/mL) over time.

Another chart (a bar chart) showing SASP (ng/mL) over
  FYB WT
  FVB WT = Curcumin
  abcg2 KO
  abcg2 KO + Curcumin
  abcb1aKO
  abcb1a KO + Curcumin

Suneet Shukla et al. Pharm Res. 2008 Oct 9
Clinical SASP/Curcumin Interaction

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SASP absorption enhanced with curcumin
Greater curcumin interaction after higher dose of SASP likely
the impact of intestinal update and SASP efflux

Kusuhara et al., Br J Pharmacol. 2012 Jul;166(6):1793-803
Sulfasalazine BCRP (ABCG2)

• SAPS may be a useful probe to investigate the impact of ABCG2 PGx on human PK
  – SAPS dose and formulation are important determinants of ABCG2’s impact on drug absorption.
  – SAPS still used in various inflammatory diseases (RA and IBD). Can knowledge of SAPS PK provide insight into how inflammation impacts SAPS PK/PD?
• The abcg2 KO mouse in combination with ABCG2 (BCRP) assay cluster may be best way to define ABCG2 substrates and inhibitors.
  – abcg2 KO mouse prediction significantly over-predicted clinical impact of ABCG2 variants
  – ABCG2-transfected LLC-PK1 or MDCK cells may be useful to evaluate the interaction of this transporter with NCEs or Drugs, however, many BCRP (ABCG2) substrates require a basolateral uptake transporter.
Oncology Drug Development Challenges

• **Despite significant progress in the understanding of genetic determinants of cancer, only 1 in 10 oncology molecules that entered phase III drug trials from 2004-2009 were approved by the FDA.**

• **The therapeutic index for many molecular-targeted agents is quite narrow.**
  – MTD approach to determine dose and schedule versus exposure-driven cancer biological response.
  – A ‘personalized’ approach is needed to define optimal dose and schedule to achieve maximal efficacy with an acceptable safety profile.

• **Each Cancer patient represents a ‘special population’**.
  – Cancer patients may take up to 20 concomitant medications + multiple complimentary alternative medicines.
  – Some cancer patients develop liver metastasis or have had significant gastric surgery.
Intrinsic and Extrinsic Factors Impacting Drug Absorption and Pharmacokinetics

**Intrinsic (Host Dependent)**
- Disease
- Age, Gender, Ethnicity
- Special populations and PGx
- *H. pylori* is known to cause hypochlorhydria
- Ethnic differences in hypochlorhydria (Japanese ~ 60%, European ~ 10%)

**Physicochemical and CMC Properties**
Biopharmaceutical
- Solubility, permeability, pKa
- Tablet compression, coating and matrix
- Excipients
- Particle size

**Extrinsic Factors**
Environment
- Drug-Drug Interaction (DDI)
  - *pH-dependent absorption*
  - Drug Metabolism and Drug Transport
- Food-effect

Chart
Influence of pH-dependent Solubility on Maximum Absorbable Dose (MAD) of a Weakly Basic Drug or NME

Graph of the maximum absorbable Dose
Many Molecular Targeted Agents Display pH-dependent Solubility

- Approximately 50-70% of recently approved orally administered targeted cancer therapies display pH-dependent solubility.
- We hypothesize that a decrease in the overall exposure of an orally administered cancer therapy may occur due to concomitant ARA use and this could lead to compromised efficacy and overall patient outcomes.

Budha et al., CPT Aug, 2012
Proton Pump Inhibitor (PPI) Pharmacology (*aka* “Nexium Nation”)
Prevalence of Acid-Reducing Agent Use in Different Cancer Populations - Results
Part 2: Dasatinib PK (control, plus PPI, plus PPI/betaine-HCl reacidification)
Rabeprazole Significantly Decreases Dasatinib Exposure in Healthy Volunteers
Betaine-HCl Increases Dasatinib Exposure in Subjects with Pharmacologically-induced Hypochlorydria
Dasatinib-Rabeprazole-BHCl provides Clinical PoC:
Translation of Single dose HV to Chronic Administration is Needed
Points to Consider to Evaluate Impact of pH-dependent Solubility on PK/PD
The SLC Superfamily

Solute Carrier (SLC) superfamily contains
43 families
298 genes
HUGO database
  SLC root symbol
  Followed by numeral (family)
  Followed by letter
  Followed by numeral (ie SLC22A1)
  Further elaborated in the SLC21/SLCO

Graphic illustration

Evaluation of OCT or OAT inhibitors requires determination of an IC50 in an *in vitro* study

Nature Reviews Drug Discovery 9, 215-236 (March 2010)
Major Renal Transporters

Graphic illustration of a nephron unit.

Blood flow

Filtration (GFR) *fu

\[ \text{CL}_{r} = \text{GFR} + \text{secretion} - \text{reabsorption} \]

\[ \text{CL}_{r} = \text{GFR} \]

Filtration only

\[ \text{secretion} = \text{reabsorption} \]

\[ \text{CL}_{r} < \text{GFR} \text{ (net reabsorption)} \]

\[ \text{CL}_{r} > \text{GFR} \text{ (net secretion)} \]

Urine
When is it Important to Study Renal Transporters?

Does scientific evidence suggest that it is necessary to investigate renal transport DDI potential for NMEs?

Toxicologic significance
Primary determinant of systemic CL
NME inhibits the CL\textsubscript{R} of compound with narrow TDI

What is the optimal in vitro and in vivo strategy that will bridge preclinical to Clinical Development Plan?

Is there a need to perform both probenecid and cimetidine studies in healthy volunteers if in vitro and preclinical data support that compound is a prototypical transport substrate?
Renally-Mediated DDIs

Penicillin/Probenecid one of the earliest examples of ATS (Active Tubular Secretion) inhibition.

Chemical structure

Drugs that have labeling precautions relating to renally-mediated drug transport:
- Dofetilide (Tikosyn™)
  - Concomitant administration OCT inhibitors *increase* potential for cardiac toxicity
- Cidofovir (Vistide™)
  - Concomitant administration of OAT inhibitors *decrease* potential for nephrotoxicity
Package Inserts: Clinical Studies and DDI Potential

Chart showing drugs ($\text{CL}_R$) with Results (Bedside) for Mirapex, Tikosyn, Oseltamivir and Avid and their interaction with cimetidine and probenecid.
Metformin – 1st line therapy for newly diagnosed Type II Diabetics (T2D)
Metformin is Predominately Eliminated in the Proximal Tubule of the Kidney
Consequences of Blocking Organic Cation Elimination
Consequences of Blocking Organic Cation Elimination
Impact of Cimetidine on the PK of Metformin Depends on OCT2 Genotype
OCT1 transports metformin into the liver, the major site of its hypoglycemic activity
Hepatic Uptake/Efflux Transporters

Graphic illustration of hepatic cell transporters at the basolateral and canalicular membrane.
Hepatic Transporters
Hepatic Transporters

Question 1. Is uptake transport the rate-Limiting Step of total clearance (assume low/no metabolism).

Question 2. Is it possible to predict the DDI potential mediated through hepatic uptake or efflux or are we only able to define potential mechanisms of a PK observation?

Question 3. Toxicological significance of bile acid uptake, synthesis, or efflux inhibition
An abstract from The New England Journal of Medicine entitled

SLC01B1 Variants and Statin-Induced Myopathy – A genomewide Study.
7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see Clinical Pharmacology (12.3)]. In cases where co-administration of LIPITOR with cyclosporine is necessary, the dose of LIPITOR should not exceed 10 mg [see Warnings and Precautions, Skeletal Muscle (5.1)].
Rosuvastatin Calcium (Crestor) Pharmacokinetics and Prescribing Information

Image of Rosuvastatin Calcium (marked as Crestor) Information
FDA Alert 03/2005

Impact: Start patients of Asian descent at lowest dose of Rosuvastatin (5 mg)
Influence of \textit{SLCO1B1} T521>C Genotype on Rosuvastatin AUC

Graph of its affects in Caucasians, Chinese, Malay and Asian-Indian
Source: Clinical Pharmacology & Therapeutics 2006; 78(4) 330-41

Chemical structure of Rosuvastatin, n-Desmethyl Rosuvastatin and Rosuvatatin 5S-Lactone
Source: PD Martin et al., Clinical Therapeutics, vol 25, No. 11, 2003

CYP2C9 responsible for formation of N-desmethyl rosuvastatin (10%)
Rosuvastatin also substrate for BCRP (ABCG2)
Effect of Gemfibrozil on the PK of Rosuvastatin via uptake transporter OATP1B1 inhibition
When Should You Look and at What!
Summary and Conclusions

Transporters are membrane proteins that move substrates (including) drugs into or out of cells

The ITC has currently identified 7 transporters that are currently considered to be clinically important in PK and response:
- **Efflux:** P-gp, BCRP
- **Uptake:** OATP1B1, OATP1B3, OCT2, OAT1, OAT3

Transporter mediated drug-drug interactions (caused by induction and inhibition) have the potential to influence pharmacokinetics and pharmacodynamics (efficacy and toxicity) of many drugs.

Transporter mediated drug-drug interactions are now routinely taken into account in drug development and drug labeling now usually includes information about transporter DDIs.

PGx-dependent impact of drug transporter function is an important consideration for OATP1B1 and BCRP (ABCG2).

The transporter field is a dynamic area of research and new data continues to emerge at a rapid pace. It is important to keep up to date with reviews in the literature and transporter information in drug labels.
# Acknowledgment(s) and Contributors

Genentech Research and Early Development, Development Sciences, Clinical Pharmacology, ED-PK/PD, SA, and DMPK
ITC Collaborators

## Academia:

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## Industry:

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## Regulatory:

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<td>Lei Zhang</td>
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Transporter mediated drug uptake and efflux
Clinical Pharmacology & Therapeutics (2011) 89 6, 798–805
Clinical Pharmacology & Therapeutics (2012) 92 5,

Transporter-mediated drug-drug interactions

Membrane transporters in drug development

UCSF-FDA Drug Transporter Portal (website)
http://bts.ucsf.edu/fdatransportal/

Transporter Mediated Drug-Drug Interactions (DDIs)
Presentation slides by Lei Zhang, PhD (OCP, FDA)
Clinical Pharmacology Advisory Committee (March 2010)
Thank you!!
Examples of Mechanisms Underlying Adverse Drug Reactions
Due to Modifications in Transport Processes

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Transporter Nomenclature

SLC Family

**Basolateral**
- OCT2 = SLC22A2
- OAT1 = SLC22A6
- OAT3 = SLC22A8
- System L = SCL7A5/8

**Apical**
- PepT2 = SLC15A2
- OCTTN1 = SLC22A4
- OCTN2 = SLC22A5
- OAT4 = SLC22A11

**ABC Family**

**Apical**
- MDR1 = ABCB1
- MRP2 = ABCC2
- MRP4 = ABCC4
- BCRP = ABCG2
Drug Interactions: CYP Mediated

Significant CYP mediated drug interactions based on AUC ratio

Chart showing AUC ratio in vivo for CYP2C9, 2D6 and 3A4 substrates

CYP Summary

CYP interactions were complex when first recognized

Largest CYP-mediated DDIs
  Increase AUC 20X, $C_{\text{max}}$ 12X

Mechanism of CYP inhibition
  Competitive or non-competitive
  Potent inhibitors in sub-nanomolar range

Many CYP liabilities are thought to be ‘screened’ out at an early stage of preclinical development, however, what liabilities are we selecting for?
ABC Substrate/Inhibitor Overlap

Distinct but Overlapping Substrate Specificities

Graphic illustration

Figure adapted from Thomas Litman
Pravastatin Css Disposition in WT vs Slco1b2\textsuperscript{-/-} Mice

6 charts showing plasma and liver concentrations.

*Zaher et al., Mol Pharmacol 74: 320-329, 2008*
Pgp/BCRP Substrate Decision Tree

Step by step guide to substrate decision
Pgp/BCRP Inhibitor Decision Tree

False Positives (unnecessary clinical studies)
Alert for $\frac{[I]}{IC_{50}} \geq 0.1$ or $\frac{[I]}{IC_{50}} \geq 10$,

$[I]$ is steady-state total Cmax at the highest clinical dose
$[I]$ is the GI concentration calculated as dose (mg)/250 mL

$\frac{[I]}{IC_{50}} > 10$ will be exceeded at a dose of ~12 mg for a drug with
an inhibition potency of ~10 µM in vitro (MW ~ 500).

False Negatives (safety concerns for NTI drugs like digoxin and topotecan)
OATP Inhibitor Decision Tree

Flow chart of steps for hepatic uptake

Nature Reviews Drug Discovery 9, 215-236 (March 2010)