An Overview of Drug Transporters in ADME & Drug Action

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Principles of Clinical Pharmacology
Joseph A. Ware, Ph.D.
Sr. Scientist, Clinical Pharmacology
Genentech, Inc.
ware.joseph@gene.com

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
- Complex metabolism interaction(s)
- Drug Distribution and elimination
- Organ-selective delivery of drugs and prodrugs

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).

Transporters as Targets

- Zosuquidar and Tariquidar
- SGLT2 Na-Glucose contransporter

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 *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)

Presentation Objectives

Provide an Integrated approach to transporter biology

Review when drug transport is the rate-limiting step of
- **A**bsorption
- **D**istribution
- **M**etabolism and Transporter Interplay
- **E**limination (kidney and liver)

Examples of when drug transport is a primary determinant of drug action and drug-induced toxicity.

Provide examples of drug-drug and drug-transporter interactions

Functional consequences of genetic variations in transporter genes

2006 FDA Draft Guidance, International Transport Consortium and FDA Critical Path Workshop

2006 FDA Draft Guidance

- Knowledge of NME metabolic pathways, interactions, and influence of active transport on drug disposition with respect to DDI potential is key to benefit/risk assessment.
- Integrated approach may reduce number of unnecessary studies and optimize clinical pharmacology studies.
- Classification of CYP inhibitors and substrates can aid in study design and labeling.
  - Substrate (25% metabolism)
  - Inhibitor ([I]/Ki > 0.1)
  - Inducer (40% control)

New Molecular Entity (NME)
International Transport Consortium (ITC)

Image of a graph
Slide adapted from Shiew-Mei Huang, Ph.D., FDA

Drug Transporter White Paper

Nature Reviews Drug Discovery 9, 215 - 236, (2010)
'Membrane Transporters in Drug Development'
The International Transporter Consortium.
Corresponding Authors:
Kathy.Giacomini@ucsf.edu
ShiewMei.Huang@fda.hhs.gov
Donald.tweedie@boehringer-ingelheim.com

Article on Transporters in drug development: advancing on the Critical Path

The ITC considers this report as a work in progress, and is highly interested in obtaining feedback, including areas that have not been included in the report but should be considered in the next version as well as controversial concepts. Please send any comments to the corresponding authors.

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

P-glycoprotein Substrates

Cancer Chemotherapy
- **Doxorubicin**
- **Daunorubicin**
- **Vinblastine**
- **Vincristine**
- **Paclitaxel**
- **Teniposide**
- **Etoposide**

Immunosuppressive Drugs
- **Cyclosporine A**
- **FK506**

Antihistamine
- **Terfenadine**

Steroid-like
- **Aldosterone**
-
- **Hydrocortisone et al.**

HIV Protease Inhibitors
- **Amprenavir**
- **Indinavir**
- **Ritonavir**
- **Saquinavir**

Cardiac Drugs
- **Digoxin**
- **Quinidine**
- **Posicor**
- **Most statins**

Anti-thelmintics
- **Ivermectin**
- **Abamectin**

Miscellaneous
- Loperamide
- Colchicine
- Ondansetron
- Erythromycin

Clinical Translation of P-gp Inhibition at the BBB

N=12 subjects [11C]verapamil +/- CsA.

Mean 88% increase in BBB exposure (range 62-148%).

Clinical observation significantly less than mouse prediction.

MRI images

Three charts showing [^{11}C]verapamil levels in blood, plasma and brain before and after cyclosporine A.

Clinical Pharmacology & Therapeutics (2005) 77, 503–514

Role of mdr1a in the Blood-Brain Barrier and the Placenta

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 -/- LD_{50}= 0.7 mg/kg**
  - **mdr1a +/+ LD_{50}= 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%**

P-gp at the Blood-Brain Barrier

Graphic illustration of in vivo BBB P app x 10^{-6} cm/sec by clog $D_{pH\ 7.4}$

Many Examples of Drugs whereby BBB Entry is Not Desirable
- Ivermectin
- Digoxin
- Non-sedating antihistamines
  - Fexofenadine
  - Loratadine
  - Cetirizine

TJ Raub Mol. Pharmaceutics, 3 (1), 3 -25, 2006

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

From Mealy et al. Pharmacogenetics. 2001 Nov;11(8):727-33.

P-glycoprotein (ABCB1) Cluster Evaluation

Graphic illustration of a pyramid showing from top

(narrow part) – Clinical Study of drug-drug interactions in humans.
Followed by Lower,
Medium and
(wide part of pyramid at bottom) Higher Throughput pre-clinical screening assays.

In Vitro Permeabilities

Graphic illustration for mannitol, (passive paracellular), testosterone, (passive transcellular), and vinblastine (P-gp substrate).

Caco-2 and MDCK cell comparison

Electron microscopy

Figure courtesy from Phil Burton/Allen Hilgers/ Thomas Raub

In Vitro P-gp IC50 for Inhibition of Digoxin Efflux Data from Multiple Labs / Techniques

Graphic illustration

IC50Value (uM)

Amiodarone
Cyclosporin
Diltiazem
GW918
Itraconazole
Ketoconazole
Nifedipine
Quinidine
Ritonavir
Talinolol
Verapamil
Vinblastine

Digoxin: Safety Concerns

Bar chart showing AUC_i/AUC or $C_{MAX,J}$ 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

Drug Metabolizing Enzyme - Drug Transporter Interplay

Comparison chart

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

P-gp Summary

For some compounds, P-gp may hinder drug absorption, moderately change AUC/Cmax and be moderate to major determinant of CNS exposure.

No Single in-vitro assay appears to be durable enough to perform within diverse chemical libraries and yield consistent ‘predictable’ in-vivo performance.
Multi-tiered Assay Cluster Approach used to define NCE/Drug- P-gp interaction.

Use of mdr1a KO mouse appears to be the most sensitive method to define P-gp substrates, however, cross-species differences in P-gp remains an area of debate (JPharmacol Toxicol Methods. 2006 Mar 15 and Feng et al., DMD 2008)

P-gp may be a target for Drug-Drug Interactions, optimal in-vitro to in-vivo or in-vivo to in-vitro strategy is needed in a case by case basis.

Pgp/BCRP Substrate Decision Tree

Step by step guide to substrate decision

Pgp/BCRP Inhibitor Decision Tree

False Positives (unnecessary clinical studies)

Alert for $[I]_1/IC_{50} \geq 0.1$ **or** $[I]_2/IC_{50} \geq 10$,

$[I]_1$ is steady-state total Cmax at the highest clinical dose

$[I]_2$ is the GI concentration calculated as dose (mg)/250 mL

$[I]_2/IC_{50} > 10$ 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)

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
Endobiotics

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

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.

Jonker et al., *Proc Natl Acad Sci* U S A 2002 Nov 26;99(24):15649-54

Bcrp -/- ADME Phenotype

Diet-dependent phototoxicity
Protoporphyria
Enhanced oral absorption of topotecan
Milk secretion of drugs and xenotoxins Nat. Med. 2005 Feb;11(2):127-9
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

Permeability is an important determinant of In vitro-in vivo extrapolation for both Metabolism and Transport

Chart showing permeability and solubility of Class 1, 2, 3. and 4 drugs

Amidon et al., Pharm. Res. 12:413 (1995)
Wu and Benet, Pharm. Res. 22:11 (2005)

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.

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

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

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

Chart showing that exposure to SASP is in Bcrp1 KO mice.

SASP C_{max} and exposure (AUC) in Bcrp1 (abcg2) and mdr1a (WT and KO) mice following intravenous (IV) and oral (PO) administration.

Zaher et al., Molecular Pharmaceutics epub January 4, 2006

SASP Disposition in North American Healthy Volunteers

Chart showing Plasma Sulfasalazine (μg/mL) over time (Hours) in subjects with variant genotypes.

Brad Urquhart et al., Pharmacogenet Genomics. 2008 May;18(5):439-48.

Altered SASP Exposure in Q141K Subjects

SASP BCRP*3

Chart

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

Urquhart et al., Pharmacogenet Genomics. 2008 May;18(5):439-48.

421C>A SNP Changes Surface ABCG2 Expression

Chart comparing total protein with Cell surface

Pharmacogenet Genomics. 2008 May;18(5):439-48.

SASP 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

ABCG2 Pharmacogenomic Studies

DRUG	REFERENCE
Sulfasalazine	Yamasaki et al (2008) Clin Pharmacol Ther, ePub
Sulfasalazine	Urquhart et al (2008) Pharmacogen & Genomics, ePub
Sulfasalazine	Adkison et al (2008) ASCPT mtg poster
Gefitinib (IRESSA)	Cusatis et al (2007) JNCI 98(23:1739
Topotecan	Sparreboom et al (2005) Canc Biol Ther 4:650
Rosuvastatin	Zhang et al (2006) Clin Chim Acta 373:99
Diflomotecan	Sparreboom et al (2004) Clin Pharmacol Ther 76:38
Imatinib (GLEEVEC)	Gardner et al (2006) Clin Pharmacol Ther 80:192
Pitavastatin	Ieiri et al (2007) Clin Pharmacol Ther. 82:541

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

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 increases SASP Bioavailability

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

ABCG2 Summary

ABCG2 (BCRP/ABCP) has a role in the absorption and the elimination of a growing list of drugs, endobiotics, and xenobiotics.

Additional probe substrates and inhibitors are needed to investigate cross-species to human comparisons and to improve *in-vitro* to *in-vivo* predictions.
SASP **dose** and **formulation** are important determinants of ABCG2's influence on F.

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.

The abcg2 KO mouse in combination with ABCG2 (BCRP) assay cluster may be best way to define ABCG2 substrates and inhibitors.

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

References: Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA. Introduction. Pflugers Arch. 2004 Feb;447(5):465-8

Chart from Nature Magazine
Nature Reviews Drug Discovery 9, 215-236 (March 2010

Transporter Interaction Redundancy:

Drugs that are shown to interact with one transporter typically interact with multiple transporters.

Thus, multiple pathways for clearance are possible for transporter substrates.

Major Renal Transporters

Graphic illustration of a nephron unit.

Blood flow

Filtration (GFR) *fu

CLr = GFR + secretion – reabsorption

CLr = GFR
Filtration only
secretion = reabsorption

CLr < GFR (net reabsorption)

CLr > GFR (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_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 preclinicial 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 (CL_R) with Results (Bedside) for Mirapex, Tikosyn, Oseltamivir and Axid and their interaction with cimetidine and probenecid.

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)

Hepatic Uptake/Efflux Transporters

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

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

Hepatic Transport and Liver Injury

Chart showing ATP-dependent taurocholate transport (%) over inhibitor concentration (μM) for troglitazone, troglitazone-sulfate, cyclosporine, and glibenclamide.

Funk et al., Mol. Pharm. Vol. 59, Issue 3, 627-635, March 2001

An abstract from The New England Journal of Medicine entitled

SLC01B1 Variants and Statin-Induced Myopathy – A genomewide Study.

SLCO1B1 Variants and Statin-Induced Myopathy

Chart - Figure 1. Results of tests for a trend in the association between myopathy and each SNP measured in the Genome-wide Association Study.

N Engl J Med. 2008 Aug 21;359(8):789-99

Rifampicin

Antibiotic used in treatment of tuberculosis

Known for its ability to induce drug metabolizing enzymes and transporters through activation of pregnant X receptor (PXR)

Recently identified as an inhibitor of OATPs and entry into human hepatocytes mediated by OATP1B1

Bar graph of rifampicin uptake.

Tirona et al, J.Pharmacol.Exp. Ther 304:223-228, 2003

Rifampicin Inhibits Atorvastatin through OATP

Two charts showing atorvastatin acid and lactone concentrations versus time.

600 mg rifampacin IV increases atorvastatin acid AUC 7-fold.

Acutely, single dose rifampacin may inhibit OATP1B3, CYP3A4, and CYP2C8.

(Lau YY et al., Clin Pharmacol Ther, 81, 194-204 (2007), slide courtesy of Dr. L.Z. Benet)

Rifampacin Disposition in WT vs *Slco1b2*$^{-/-}$ KO Mice

Four charts illustrating plasma and liver concentrations

Zaher et al., Mol Pharmacol 74: 320-329, 2008

Rifampacin PKPD, Disease and PGx

Graphs

In multivariate analyses, the rifampin AUC0-24 was significantly affected by rifampin dosage (in mg/kg),
SLCO1B1 c.463C>A polymorphism, and presence of tuberculosis by the region of enrollment

Weiner, M. et al. 2010. Antimicrob. Agents Chemother. 54(10):4192-4200

Hepatic Uptake Substrate Decision Tree

Flow chart of steps for hepatic uptake

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

OATP Inhibitor Decision Tree

Flow chart of steps for hepatic uptake

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

Future Direction of Drug Transport in Preclinical Development and Clinical Pharmacology

DDIs mediated through drug transporter(s) have received increased attention, however, at present one can define the likelihood of a DDI for well characterized transporters only qualitatively (Likely, Possible, and Not Likely).

Significant overlap exists between drug metabolizing enzymes and drug transporters.

Evaluation of *in-vitro* screens to predict *in-vivo* drug-drug interactions is an area of increased regulatory awareness. Therefore, the accuracy of the predicted DDI is dependent on the ***Quality*** of the *in-vitro* assay.

Greater emphasis on Clinical Translation with respect to PK/PD of select transport probes is needed.

Preclinical and clinical differences in transporter expression may be a determinant of drug-induced toxicity and a developing area of research for drug-induced diseases.

- Additional KO and Tg mice to investigate the *in-vivo* contribution of drug transporters are needed.

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Thank you!!

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**

Hepatic Drug-Drug and Drug Transporter Interaction Potential

Is NME eliminated unchanged in the bile and is a substrate of uptake transporter or transporters?

- Permeability
- Multiplicity
- Affinity and Capacity
  - Relative abundance of OATP1B1, OATP1B3, OAT2B1, NTCP
  - Selective vs pan-inhibitors (ie CsA)

Is NME a substrate of uptake and efflux transporters

- Multiplicity (ABCB1, ABCC2, and ABCG2)

Uptake/efflux synergy

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

Brown et al., Br J Clin Pharmacol 60:508 (2005)

CYP Summary

CYP interactions were complex when first recognized

Largest CYP-mediated DDIs
- Increase AUC 20X, C_{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?

The rate determining process

"To understand the transporter-mediated drug-drug interaction, we have to know the rate determining process of a substrate in the overall clearance."

uptake, basolateral efflux, apical excretion, metabolism

Professor Sugiyama, Keynote address AAPS, November 2007

ABC Substrate/Inhibitor Overlap

Distinct but Overlapping Substrate Specificities

Graphic illustration

Figure adapted from Thomas Litman

Pravastatin Css Dispositon in WT vs Slco1b2$^{-/-}$ Mice

6 charts showing plasma and liver concentrations.

Zaher et al., Mol Pharmacol 74: 320-329, 2008