

An Overview of Drug Transporters in ADME & Safety

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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

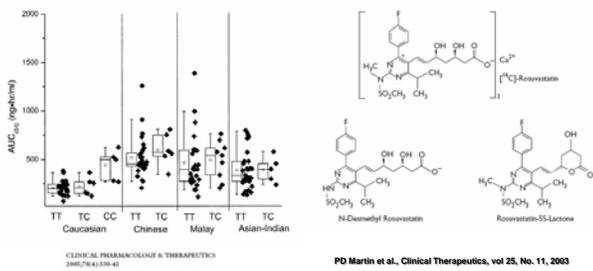
- Impact of Drug Transport on ADME
 - Oral absorption of drug
 - Complex metabolism interaction(s)
 - Drug Distribution and elimination
 - Organ-selective delivery of drugs and prodrugs
- Impact of Drug Transport on Response and Toxicology
 - Emerging Role in Toxicology*
 - Over expression of drug transporter may be a major factor in tumor, bacterial, and fungal multi-drug resistance (MDR).
- Drug Transporters as Targets
 - LY335979, Zosuquidar

Rosuvastatin Calcium (Crestor) Pharmacokinetics and Prescribing Information

Rosuvastatin Calcium (marketed as Crestor) Information
FDA ALERT [03/2005]
Rhabdomyolysis (serious muscle damage) has been reported in patients taking Crestor as well as other statin drugs. To date, it does not appear that the risk is greater with Crestor than with other marketed statins. However, the labeling for Crestor is being revised to highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. The labeling will also be revised to reflect the results of a large pharmacokinetic study involving a diverse population of Asian patients compared with a Caucasian control group that found drug levels to be elevated approximately 2-fold. Kidney failure of various types

Impact: Start patients of Asian descent at lowest dose of Rosuvastatin (5 mg)

Influence of *SLCO1B1* T521>C Genotype on Rosuvastatin AUC



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 ADME
 - Absorption
 - Distribution
 - Metabolism and Transporter Interplay
 - Elimination (kidney and liver)
- Provide examples of drug-drug and drug-transporter interactions
- Inter-Individual variability as a determinant of drug transport
- Examples of when drug transport is a primary determinant of drug-induced toxicity.

P-glycoprotein Substrates

- | | |
|---|--|
| <ul style="list-style-type: none"> ⚡ Cancer Chemotherapy <ul style="list-style-type: none"> - Doxorubicin - Daunorubicin - Vinblastine - Vincristine - Paclitaxel - Teniposide - Etoposide ⚡ Immunosuppressive Drugs <ul style="list-style-type: none"> - Cyclosporine A - FK506 ⚡ Antihistamine <ul style="list-style-type: none"> - Terfenadine ⚡ Steroid-like <ul style="list-style-type: none"> - Aldosterone - Hydrocortisone et al. | <ul style="list-style-type: none"> ⚡ HIV Protease Inhibitors <ul style="list-style-type: none"> - Amprenavir - Indinavir - Ritonavir - Saquinavir ⚡ Cardiac Drugs <ul style="list-style-type: none"> - Digoxin - Quinidine - Posicor - Most statins ⚡ Anti-helminthics <ul style="list-style-type: none"> - Ivermectin - Abamectin ⚡ Miscellaneous <ul style="list-style-type: none"> - Loperamide - Colchicine - Ondansetron - Erythromycin |
|---|--|

Ivermectin Toxicity in the Collie

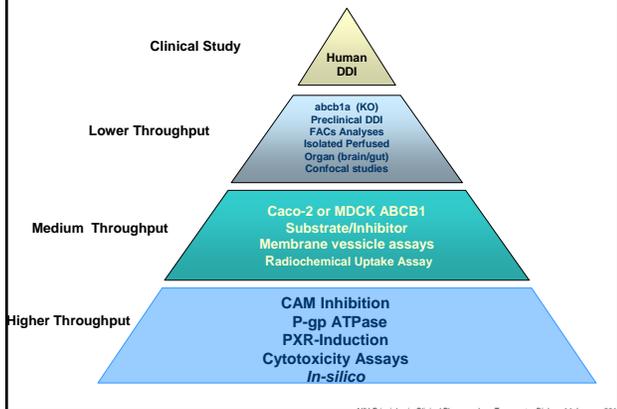


<http://www.awca.net/drug.htm>

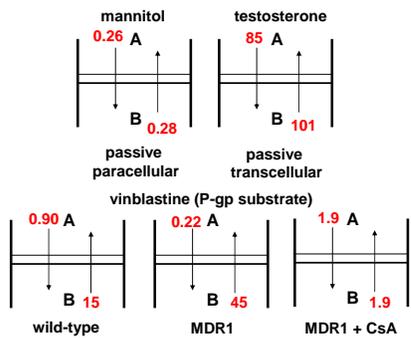
- 50% of Collies display CNS toxicity when treated with normal doses of IVM (>60 µg/kg).
- Ivm-sensitive Collies lack functional P-gp at the blood brain barrier.
- ABCB1 cDNA sequencing
 - Sensitive Collies (7/7)
 - 4-base pair deletion
 - homozygous
 - Non-sensitive Collies (6/6)
 - heterozygous (mutant/normal)
 - Other breeds (4/4)
 - normal/normal

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

P-glycoprotein (ABCB1) Cluster Evaluation



In Vitro Permeabilities



Caco-2 and MDCK cell comparison

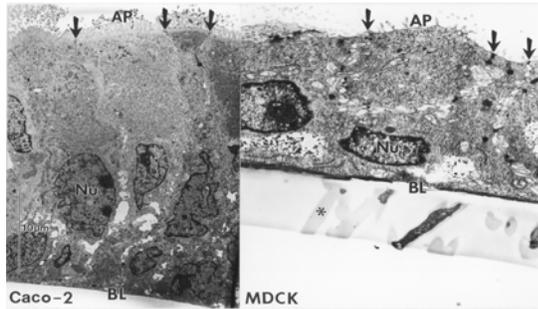
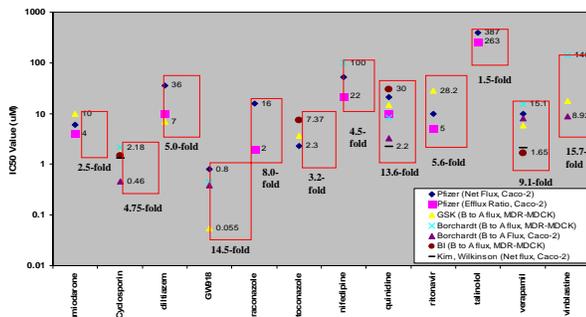


Figure courtesy from Phil Burton/Allen Hilgers/ Thomas Raub

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

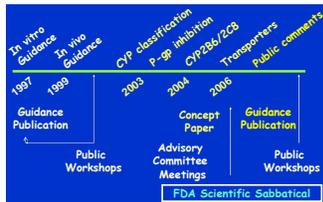


Slide courtesy of M. Troutman/C. Lee Pfizer

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

2006 FDA Draft Guidance

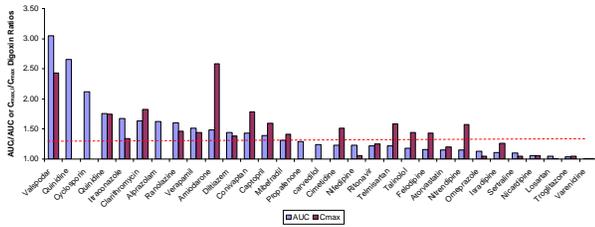
- Knowledge of NME metabolic pathways, interactions, and influence of active transport on drug disposition with respect to DDJ potential is key to benefit/risk assessment.
- Integrated approach may reduce number of unnecessary studies and optimize clinical pharmacology studies.
- Classification of CYP inhibitors and substrates can aid in study design and labeling.
 - Substrate (25% metabolism)
 - Inhibitor (I₁/K_i > 0.1)
 - Inducer (40% control)



Slide adapted from Shiew-Mei Huang, Ph.D., FDA

International Transport Consortium

Digoxin: Safety Concerns



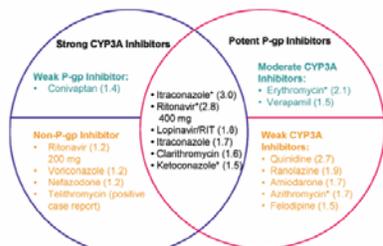
- Therapeutic conc ~ 1.5 ng/mL
- 33% change in Digoxin Exposure (C_{max}) ~ 2.0 ng/mL → Safety concerns
- 25% change in exposure might be clinically relevant

Clinical Pharmacology & Therapeutics (2009); 85, 173–181

P-gp Mediated Digoxin DDIs

- <2-fold change in digoxin C_{max} or exposure were observed in the majority of published cases
 - $1/IC_{50} > 0.1$ is predictive of positive clinical digoxin DDI related to P-gp
 - $12/IC_{50} < 10$ 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 $1/IC_{50}$ or false (+)'s with $12/IC_{50}$

Drug Metabolizing Enzyme - Drug Transporter Interplay



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.
- 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. 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 a concern
- Overlap in CYP3A4 and P-gp inhibition may produce 'worse case scenario' for some drugs that are substrates for CYP3A4 and P-gp

ABC Substrate/Inhibitor Overlap

Distinct but Overlapping Substrate Specificities

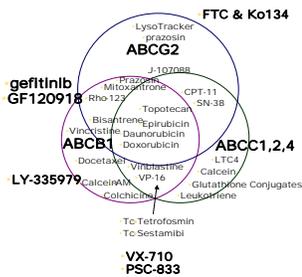


Figure adapted from Thomas Litman

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 camptothecin 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)

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

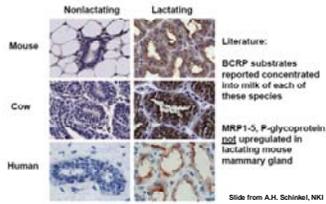
The breast cancer resistance protein protects against a major chlorophyll-derived dietary phototoxin and protoporphyria.

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

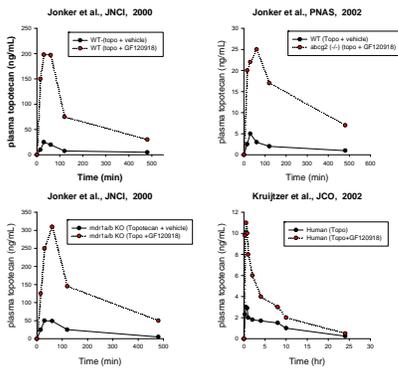
Bcrp -/- ADME Phenotype

- Mice displayed diet-dependent phototoxicity
- Protoporphyrin
- Enhanced oral absorption of topotecan
- ABCG2 is expressed in bone marrow stem cells.
- Milk secretion of drugs and xenotoxins *Nat. Med.* 2005 Feb;11(2):127-9

Expression BCRP in mammary gland across species



Of mice and men: Topotecan:BCRP interaction



Absorption, metabolism, and excretion of salicylazosulfapyridine in man

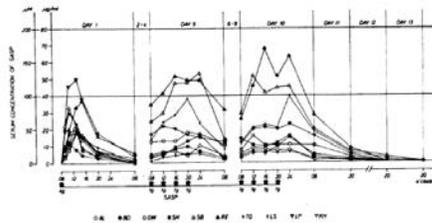
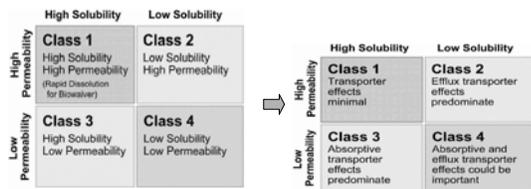


Fig. 2. Serum concentrations of SASP after ingestion of a single 4 Co. dose of SASP on Day 1 (10 subjects) and 4 x 1 Co. of SASP on Days 2 to 10 (9 subjects).

Hosse 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



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.

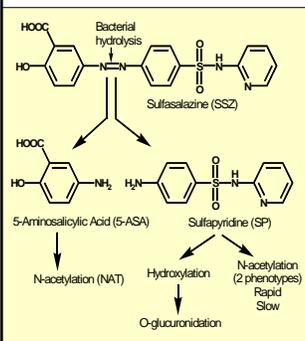
ABCG2 Polymorphisms and Ethnic Distribution of SNPs.

- 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.

Allelic variant	Caucasians	African-Americans	Asians	Hispanics	Africans	Middle Easterns
V12M	2	4	20-45	40		5
Q141K	11-14	2.3-5.0	15-35	10	1.0	13
I206L	0	0	0	10		0
N590Y	1					

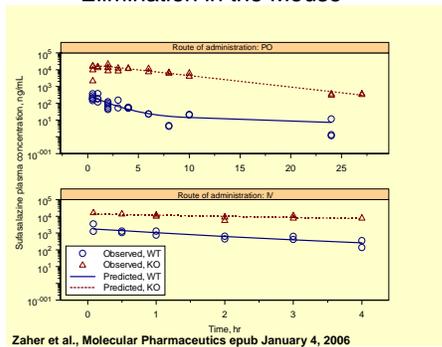
Figg et al., Anticancer Drugs. 2007

Sulfasalazine (SASP) Disposition



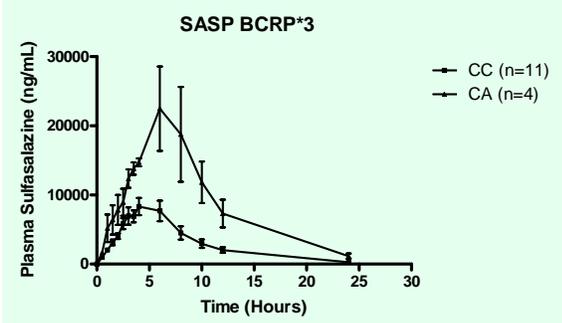
- Indications: Rheumatoid arthritis (RA), Long term therapy of ulcerative colitis, and Crohn's disease
- Bioavailability (F) of SASP in humans is low (F < 15%) and highly variable
- Low %F primarily attributed to SASP's low permeability and poor solubility (thus, poor absorption)
- Azo-reduction is the 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



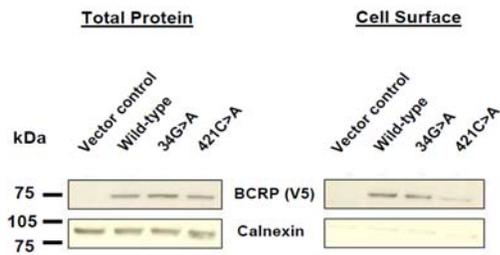
Zaher et al., Molecular Pharmaceutics epub January 4, 2006

Altered SASP Exposure in Q141K Subjects



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

421C>A SNP Changes Surface ABCG2 Expression



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

SASP Disposition in Healthy Japanese Volunteers

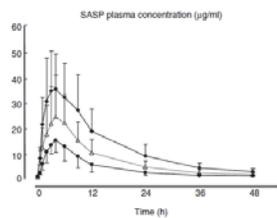


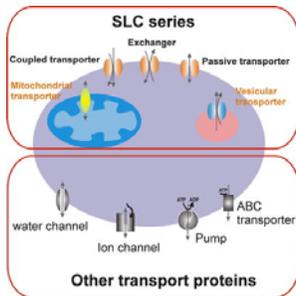
Figure 2 Effect of ABCG2 genotype on pharmacokinetics of sulfasalazine (SASP). Plasma concentration-time profiles of SASP after oral administration of a 2,000 mg conventional SASP tablet to 421C/C subjects (closed circles, n = 12), 421C/A subjects (open triangles, n = 16), and 421A/A subjects (closed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

Yamasaki et al., CPT January 2, 2008

ABCG2 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.

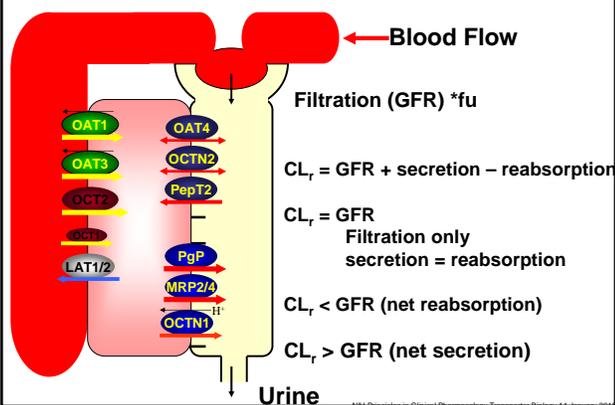
The SLC Superfamily



- Solute Carrier (SLC) superfamily contains
 - 43 families
 - 298 genes
- HUGO database (see <http://www.gene.ucl.ac.uk/nomenclature/>)
 - SLC root symbol
 - Followed by numeral (family)
 - Followed by letter
 - Followed by numeral (ie SLC22A1)
 - Further elaborated in the SLC21/SLCO

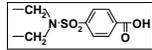
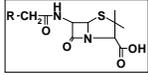
References: Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA. Introduction. *Pharmacol Arch*. 2004 Feb;447(5):465-8.

Major Renal Transporters



Renally-Mediated DDIs

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



⚡ 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

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 preclinical data support that compound is a prototypical transport substrate?

Package Inserts: Clinical Studies and DDI Potential

Drug (CL_R)	Results (Bedside)
Mirapex (400 mL/min) + cimetidine + probenecid	N=12 subjects/treatment arm. 50% ↑ in AUC; 40% ↑ in T 1/2 No effect on PK
Tikosyn (420 mL/min) + cimetidine + probenecid	Narrow TDI 40% ↑ in AUC; CL_R ↓ 33%; QTc ↑17-19 ms No effect
Oseltamivir +cimetidine +probenecid	N=12-18/treatment (see Hill et al.) No change on PK 2.5-fold AUC of Ro64-0802 (active metab)
Axid (500 mL/min)	Not currently defined, however TDI very high

Transporter Nomenclature

SLC Family

- **Basolateral**
 - OCT2 = SLC22A2
 - OAT1 = SLC22A6
 - OAT3 = SLC22A8
 - System L = SCL7A5/8
- **Apical**
 - PepT2 = SLC15A2
 - OCTN1 = SLC22A4
 - OCTN2 = SLC22A5
 - OAT4 = SLC22A11

ABC Family

- **Apical**
 - MDR1 = ABCB1
 - MRP2 = ABCC2
 - MRP4 = ABCC4
 - BCRP = ABCG2

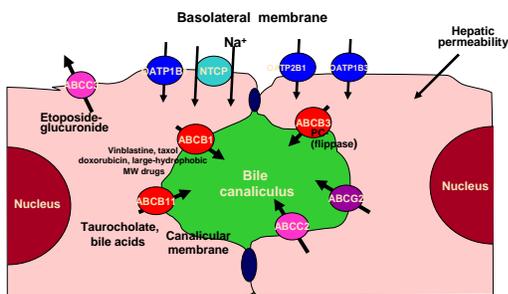
Hepatic Transporters

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

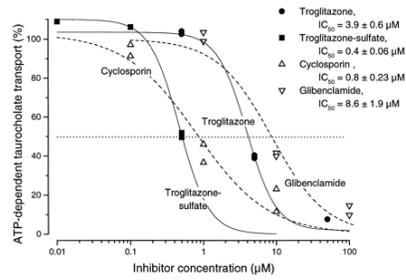
Question 2. Is it possible to predict the DDI potential mediated through hepatic uptake or efflux or are we only able to define potential mechanisms of a PK observation?

Question 3. Toxicological significance of bile acid uptake, synthesis, or efflux inhibition

Hepatic Uptake/Efflux Transporters



Hepatic Transport and Liver Injury



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

OATP Substrates

OATP1B1 (OATP-C, LST-1, OATP2)	OATP1B3 (OATP8, LST-2)
Endogenous Substrates: Estrone Sulfate, PGE ₂ , Bilirubin, thyroid hormone (T ₃ , T ₄) Bilirubin-glucuronides Estradiol 17β-d-glucuronide, bile acids	Endogenous Substrates: CCK-8, PGE ₂ , Thyroid hormone (T ₃ , T ₄) Estradiol 17 β -d-glucuronide, Bile acids, Deltaphin, DPDPE,
Drug Substrates: Atorvastatin, Cerivastatin, Pravastatin Rosuvastatin, Pitavastatin, Caspofungin, Troglitazone-sulfate, Rifampin, Arsenic, Atrasentan, Valsartan, Olmesartan, Enalapril, MTX, Temocaprilat, SN-38	Drug Substrates: Pravastatin, Pitavastatin, Rosuvastatin, Fexofenadine, BQ-123, Oubain,, Digoxin, Doxotaxel, Paclitaxel,, Rifampin, MTX, Bilirubin, Repaglinide, Telmisartan, Valsartan, Olmesartan, Enalapril, Temocaprilat, SN-38
Toxins: Phalloidin, Microcystin-LR	Toxins: Phalloidin, Microcystin-LR

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The NEW ENGLAND JOURNAL of MEDICINE

SLCO1B1 Variants and Statin-Induced Myopathy — A Genome-Wide Study

ABSTRACT

BACKGROUND: Learning how genetic differences affect drug response may help address individual differences in side-effect risks and drug efficacy. We used genome-wide association study (GWAS) to identify genetic variants associated with statin-induced myopathy in 44 subjects with moderate to severe myopathy and 44 controls. All subjects were taking 40 mg of simvastatin daily for a total of 12,000 patient-years. Myopathy was noted in a total of 44 of 12,000 patient-years (0.37%).

RESULTS: The association of simvastatin with myopathy was significantly associated with the SLCO1B1 gene (P = 1.1 × 10⁻¹⁰). The SLCO1B1 gene encodes a protein that transports drugs and bile acids. The association of simvastatin with myopathy was replicated in the total of 44 of 12,000 patient-years, which also showed an association between simvastatin and the chromosome 12q24 region. The association of simvastatin with myopathy was replicated in the total of 44 of 12,000 patient-years, which also showed an association between simvastatin and the chromosome 12q24 region.

CONCLUSIONS: We have identified common variants in SLCO1B1 that are strongly associated with an increased risk of severe statin-induced myopathy. Genotyping these variants may help to reduce the frequency of severe statin-induced myopathy and other adverse effects. (ClinicalTrials.gov number, NCT00724105.)

Ongoing work with *Oatp1b2* KO

- Understand the physiologic role of *Oatp1b2*
- Further characterize translatability of murine *Oatp*'s to human ADME and disease

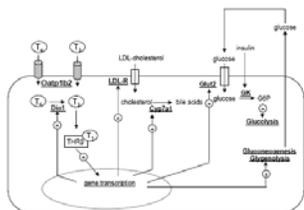


Figure from Henriette E. Meyer zu Schwabedissen

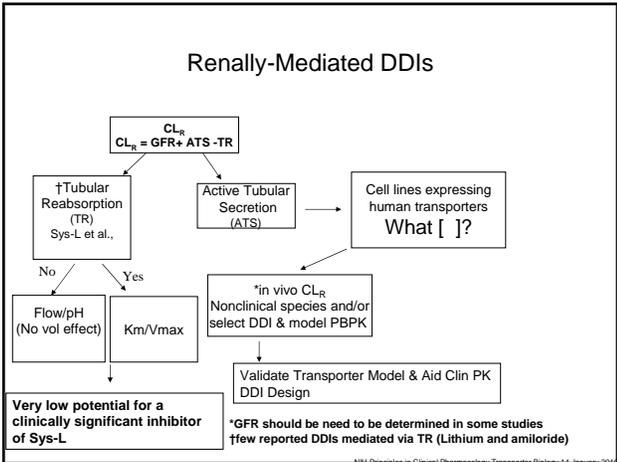
Future Direction of Drug Transport in Preclinical Development and Clinical Pharmacology

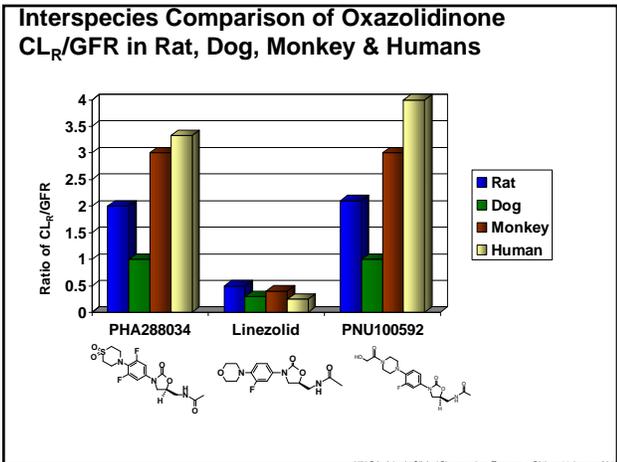
- DDIs mediated through drug transporter(s) have received increased attention, however, at present one can define the likelihood of a DDI for well characterized transporters only qualitatively (Likely, Possible, and Not Likely).
- Significant overlap exists between drug metabolizing enzymes and drug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

Acknowledgment(s) and Contributors

- /// Genentech Development Sciences Clinical Pharmacology, ED-PK/PD, SA, and DMPK
- /// Collaborators: Richard Kim, Yuichi Sugiyama, Tim Tracy, Thomas Litman & Suresh Ambudkar and Hani Zaher
- /// Timothy Brayman, Bob Conradi, Alla Karnovsky, Anis Khan, Joe Palandra, James P. Sams, and Kathy Sampson. Groton: Scott Campbell, Scott Obach, and Neil Duncan. La Jolla: Caroline Lee, Bill Smith and Eric Reyner. Cambridge: Muhammid Hashim.
- /// PHA Legacy Collaborators: AZO: Tom Raub, Phil Burton, Larry Schaaf, Mark Grillo, Wade Adams, Jeff Stevens, Jim Bourdage, John Easter, Brad Maxwell, and Greg Winterrowd. Nerviano Medical Sciences (Congregazione dei Figli dell'Immacolata Concezione, CFIC): Pietro Grossi, Mario Monshouwer, Marina Ciomei, Erminia Fontana, Chris James, and Cinzia Pellizzoni
- /// Legacy Pfizer PDMLT: Suri Surendran, Steven Michael, Simon Ball, Terry Smolarek, Madhu Cherukury, Phil Worboys, Cathy Knupp, Rob

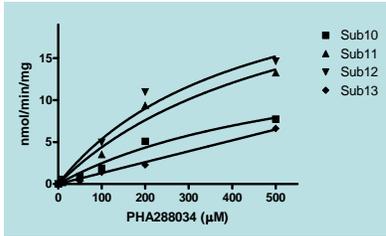






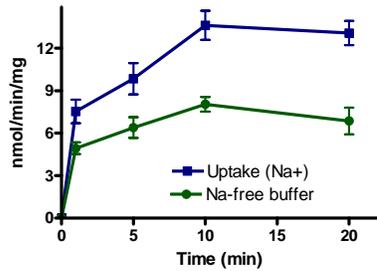
In Vitro Uptake Models

- Transport of PHA-288034 in human proximal tubules.
 - Drug uptake in cell suspension of hPTs.
 - Determine kinetics, substrate specificity, energy & ion dependence
 - Preliminary study suggested no metabolism in hPTs

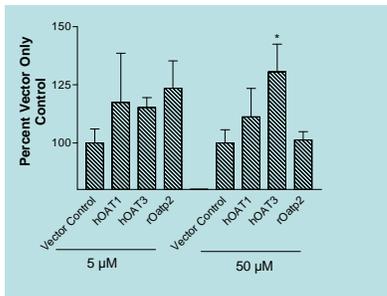


Na⁺-dependent Uptake of PHA288034

Human Proximal Tubule Studies

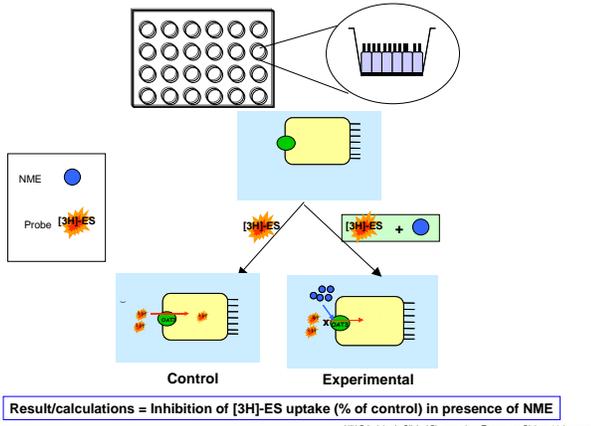


PHA-288034 Uptake in HeLa cells Transfected with Transporter cDNAs

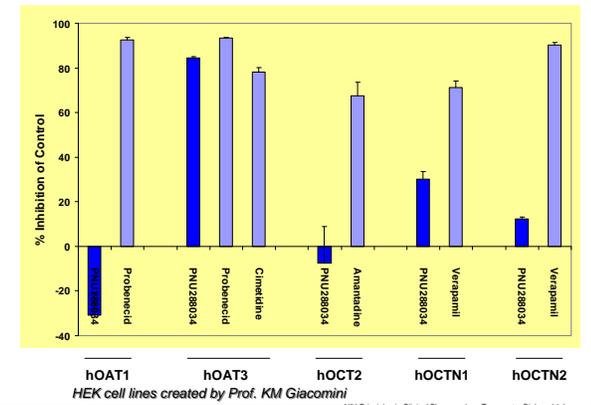


Richard Kim and Brenda Leake

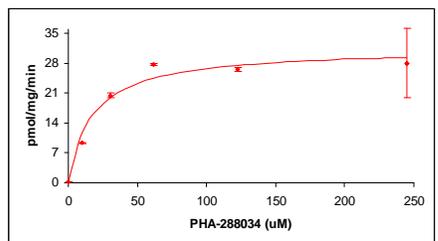
Experimental Protocol: Interaction Assay in Stable Transfectants



PHA-288034 Interaction with hOAT1-HEK, hOAT3-HEK, hOCT2-HEK, hOCTN1-HEK and hOCTN2-HEK Cells.



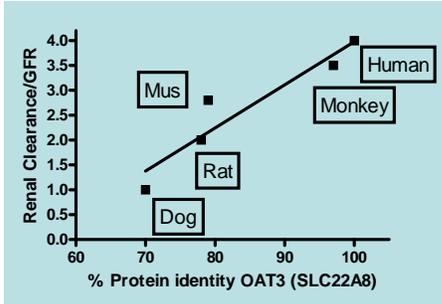
PHA-288034 uptake in hOAT3 cells



Michaelis-Menten Model fitted to individual responses using OLS

	Estimate	Standard Error	95% Confidence Interval
Km (uM)	18	6.9	7.42
Vmax (pmol/mg/min)	31.5	2.90	25.1 38.0

Cross-species Homology of OAT3 (SLC22A8) vs PHA288034 CL_R



Summary of PHA288034 Studies

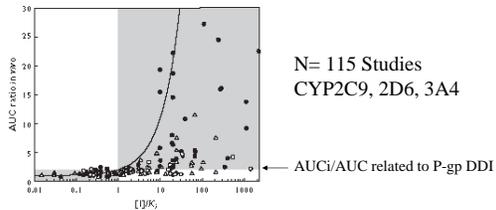
Multi-tier approach appears to best way to identify substrates/inhibitors of uptake/efflux drug transporters.

Active Tubular Secretion

- PHA-288034 appears to be a substrate and an inhibitor of hOAT3 (SLC22A8).
- PHA-288034 does not appear to be a substrate for hOAT1, OCT2, OCTN1, or OCTN2.
- Additional work is needed to fully appreciate OAT3 cross-species differences.
- Cimetidine inhibits OAT3-mediated transport as well as OCT-2 mediated transport.

Drug Interactions: CYP Mediated

- Significant CYP mediated drug interactions based on AUC ratio



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
