

Drug Transporters: Report from the International Transporter Consortium; Decisions, Impact and Future Directions

New England Drug Metabolism Discussion Group
March 3rd, 2010

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‘Membrane Transporters in Drug Development’

The International Transporter Consortium.

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

- International Transporter Consortium (ITC)
 - Genesis
 - Goals
 - White paper
 - How we got there
 - What it is
 - What it is not
 - Examples, MDR1, OATP, decisions tree(s)
 - Current Issues, Challenges, and Actions
 - Future Activities
- Conclusions
- Acknowledgements

■ PhRMA Pharmaceutical and Research Manufacturers of America

- Advocacy forum for the industry to influence the FDA (PhRMA – America)
- Drug Metabolism Technical Group (DMTG)
 - Subgroup responsible for DMPK issues
 - (MIST, DDI, pharmacogenomics, time-dependent inhibition)¹
 - Nov 2007, transporters identified as a key topic
- Academic group headed by Kathy Giacomini and Toshi Ishikawa were considering initiating a global committee to generate a white paper providing preferred approaches to conduct transporter studies

¹Baillie et al. (2002) Drug **metabolites in safety testing** Toxicol. Appl. Pharmacol. **182**, 188-96

Bjornsson et al. (2004) The Conduct of *In Vitro* and *In Vivo* **Drug-Drug Interaction** Studies: A Pharmaceutical Research and Manufacturers of America (PhRMA) Perspective. Drug Metabolism and Disposition **31**, 815-832 and Journal of Clinical Pharmacology **43**, 443-469.

Williams et al. (2008) PhRMA white paper on **pharmacogenomics** J Clin Pharmacol. **48**(7), 849-89

Grimm SW et al. (2009) The conduct of *in vitro* studies to address **time-dependent inhibition** of drug-metabolizing enzymes: a perspective of the pharmaceutical research and manufacturers of America. Drug Metabolism and Disposition **37**(7):1355-1370

■ Key goals for the ITC

- Provide an update on current thinking on transporters.
- For in vitro studies, provide a focus on studies that can have a viable clinical interpretation (avoid raising red flags with in vitro studies that cannot be addressed in vivo in the clinic).
- Explore gaps and suggest ways forward.
- Provide a coordinated approach (Academia, Industry and Regulatory).
- Help to move the science forward.
 - Decision trees to assist drug development and regulatory
 - Consensus on current scientific status

Workshop Bethesda North Marriott October 2nd and 3rd, 2008

- Sponsored by FDA Critical Path
- Workshop organized by Drug Information Association (DIA)
- Co-sponsorship by AAPS, ISSX, PhRMA
- Provide a focus to initiate a White Paper for completion in 2009

Academia:

Kim Brouwer	UNC
Kathy Giacomini	UCSF
Toshi Ishikawa	OSC,
Tokyo	
Dietrich Keppler	Heidelberg
Richard Kim	W. Ontario
Peter Swann	Maryland

Industry:

Raymond Evers	Merck
Volker Fischer	
Abbott	
Kate Hillgren	Lilly
Joe Polli	GSK
Donald Tweedie	BI
Joe Ware	Genentech

Regulatory:

Shiew Mei Huang	FDA
Lei Zhang	FDA

Academia:

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Kim Brouwer	UNC
Amber Dahlin	UCSF
Kathy Giacomini	UCSF
Toshi Ishikawa	OSC, Tokyo
Dietrich Keppler	Heidelberg
Richard Kim	W. Ontario
Mikko Niemi	Helsinki
Yuichi Sugiyama	Tokyo
Peter Swann	Maryland
Steve Wright	Arizona
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Kate Hillgren	Lilly
Keith A. Hoffmaster	Novartis
Caroline Lee	Pfizer
Joe Polli	GSK
Donald Tweedie	BI
Joe Ware	Genentech
Maciej Zamek- Gliszczynski	Lilly

Regulatory:

Shiew Mei Huang	FDA
Lei Zhang	FDA

Drug Transporters in Drug Development

The International Transporter Consortium, ITC

1. Basic Introduction and Summary of Transporters
 - Highlights what we know

2. Methods for Studying Transporters
 - Current solutions and future prospects

3. Drug Development Issues
 - Decision trees

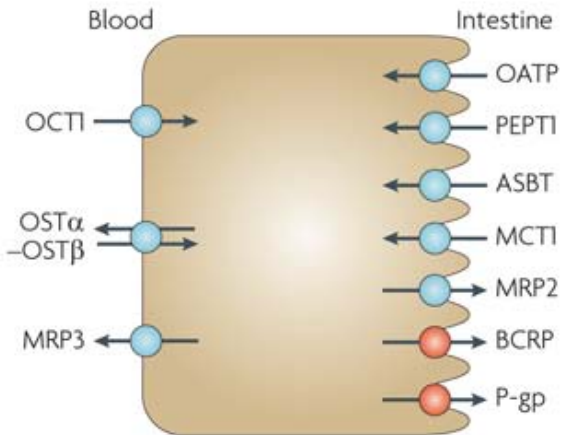
■ Transporters covered

- Efflux: P-gp, BCRP
- Renal: OAT/OCT
- Hepatic uptake: OATP

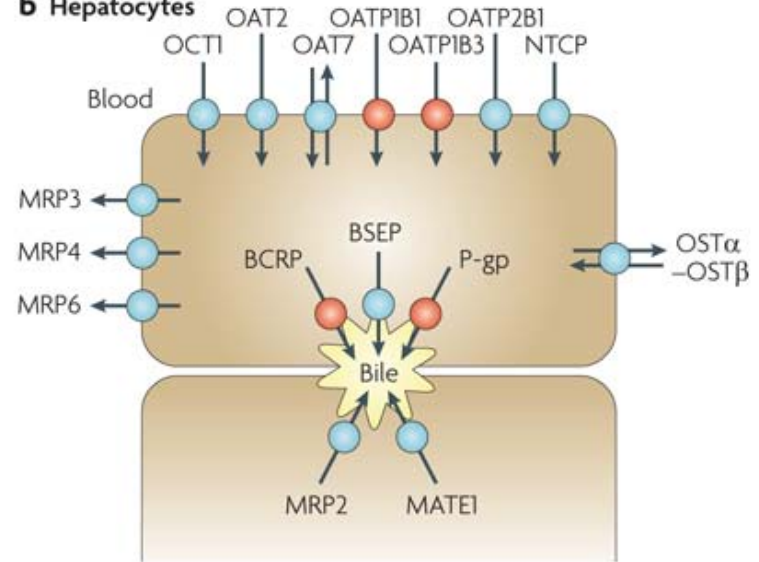
■ Other transporters not discussed in detail

- MRPs
- MATEs
- Considered less critical in the overall view
- But could be important for specific drugs?

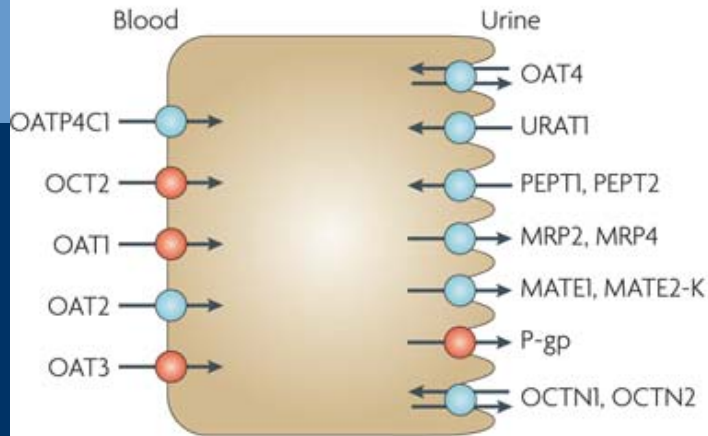
a Intestinal epithelia



b Hepatocytes



c Kidney proximal tubules



d Blood-brain barrier

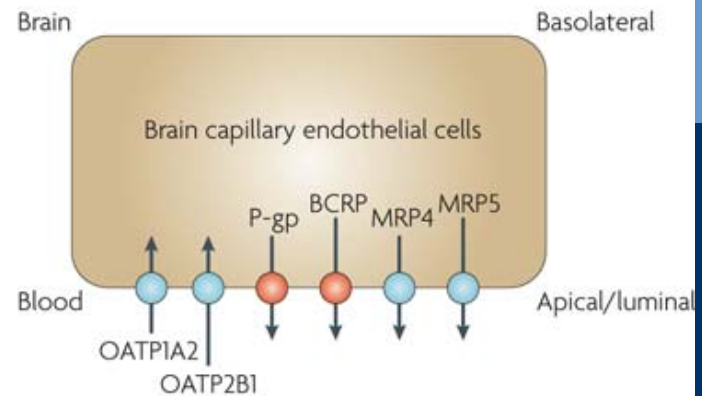


Table 1 | **Solute carrier transporters of emerging clinical importance in the disposition of drugs**

Transporter/alias (Gene)	Selected substrates	Selected inhibitors	Organs/cells	Comments
OATP1B1/OATP-C, OATP2, LST-1 (SLCO1B1)	Bromosulphophthalein, oestrone-3-sulphate, oestradiol-17 β -glucuronide, statins*, repaglinide*, valsartan, olmesartan*, bilirubin glucuronide, bilirubin, bile acids	Saquinavir, ritonavir*, lopinavir*, rifampicin*, cyclosporine*	Hepatocytes (sinusoidal)	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has clinically relevant polymorphisms • Has known clinical drug–drug interactions at the transporter level
OATP1B3/OATP-8 (SLCO1B3)	Bromosulphophthalein, cholecystokinin 8, statins*, digoxin, fexofenadine, telmisartan glucuronide, telmisartan*, valsartan, olmesartan, oestradiol-17- β -glucuronide, bile acids	Rifampicin*, cyclosporine*, ritonavir, lopinavir*	Hepatocytes (sinusoidal)	<ul style="list-style-type: none"> • Has a role in disposition and excretion
OAT1 (SLC22A6)	Para-aminohippurate, adefovir, cidofovir, zidovudine*, lamivudine*, zalcitabine*, acyclovir*, tenofovir*, ciprofloxacin*, methotrexate*	Probenecid*, novobiocin	Kidney proximal tubule, placenta	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has known clinical drug–drug interactions at the transporter level
OAT3 (SLC22A8)	Oestrone-3-sulphate, non-steroidal anti-inflammatory drugs, cefaclor, ceftizoxime, furosemide*, bumetanide*	Probenecid*, novobiocin	Kidney proximal tubule, choroid plexus, blood–brain barrier	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has known clinical drug–drug interactions at the transporter level

A. Cell and Membrane Models

B. Intact Organ/*In Vivo* Models

C. Methods to Measure the Contribution of Transporters to Tissue Distribution and Excretion

D. Interplay of Efflux Transporters and Enzymes

E. Coordination of Influx and Efflux Transporters and Enzymes in the Clearance of Drugs

F. Computational Models

Box 2. Decision trees for P-gp or BCRP substrate interactions

Box 3. Decision trees for P-gp or BCRP inhibitor interactions

Box 4. Decision trees for OCT or OAT substrate interactions

Box 5. Decision trees for OCT or OAT inhibitor interactions

Box 6. Decision trees for OATP interactions

Box 7. OATP1B1 Decision Analysis: Case Studies

Summary and Conclusions

In bi-directional transporter assays, for example, in Caco-2 or P-gp-overexpressing polarized epithelial cell lines, is the net flux ratio of NME ≥ 2 ?

a Net flux ratio ≥ 2

Net flux ratio < 2

b Is efflux significantly inhibited by 1 or more P-gp inhibitors?

Poor or non-P-gp substrate

Yes

No

c Probably P-gp substrate

d Other efflux transporters are responsible for observed data

Complete an assessment of preclinical and clinical information to determine whether an *in vivo* DDI study is warranted

Decision Trees

■ Pros

- evolution of concepts
- highlight discussion points
- offers flexibility

■ Cons

- rigid interpretation – prescriptive and overly cautious
- insufficient knowledge to populate the decision points
- lack of selective substrates and inhibitors

■ ‘The evolution and appropriate application of these decision trees will require constant monitoring. How can this be achieved with an assured and encompassing measure of success?’

- 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 C_{max} 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)















- A consensus view on the current thinking on drug transporters
 - What are the current realities
- The known knowns
 - What do we know about the relative importance of all transporters?
 - Where do you put your effort?
- The known unknowns
 - What facts are known to be untrue (dispelling myths)?
 - Where are our gaps in knowledge (so where should we focus short and long term to increase our knowledge)?
- A guideline (not a guidance) towards what we should focus on currently
 - What are we capable of addressing?

- A complete literature review.
- A prescriptive guidance on what to do and how to do it, with a clear description of what it will mean.
- A consensus document that everyone agrees to.
- A description of all of the exceptions.
- Your experience is important to you and we would certainly appreciate you sharing that with the scientific community to educate us all.
- The decision trees are clearly not definitive.
- Included to help move the science forward by acting as templates for discussion
- P-gp most mature but not perfect

The issues presented by transporters are significantly more complex than for DMEs

- Involved in absorption, distribution and excretion, so multiple processes of concern
- Broad tissue distribution; different effects at different sites, e.g. P-gp at intestine and BBB
- Redundancy; different transporters (P-gp and BCRP) and different subfamilies (OATP1B1 and 1B3)
- Uptake and efflux transporters (need to consider both to assess the overall effect)
- Applicability of kinetic parameters and their interpretation

Table 1. Substrates (clinically relevant drugs) [11,13,20,24,32].

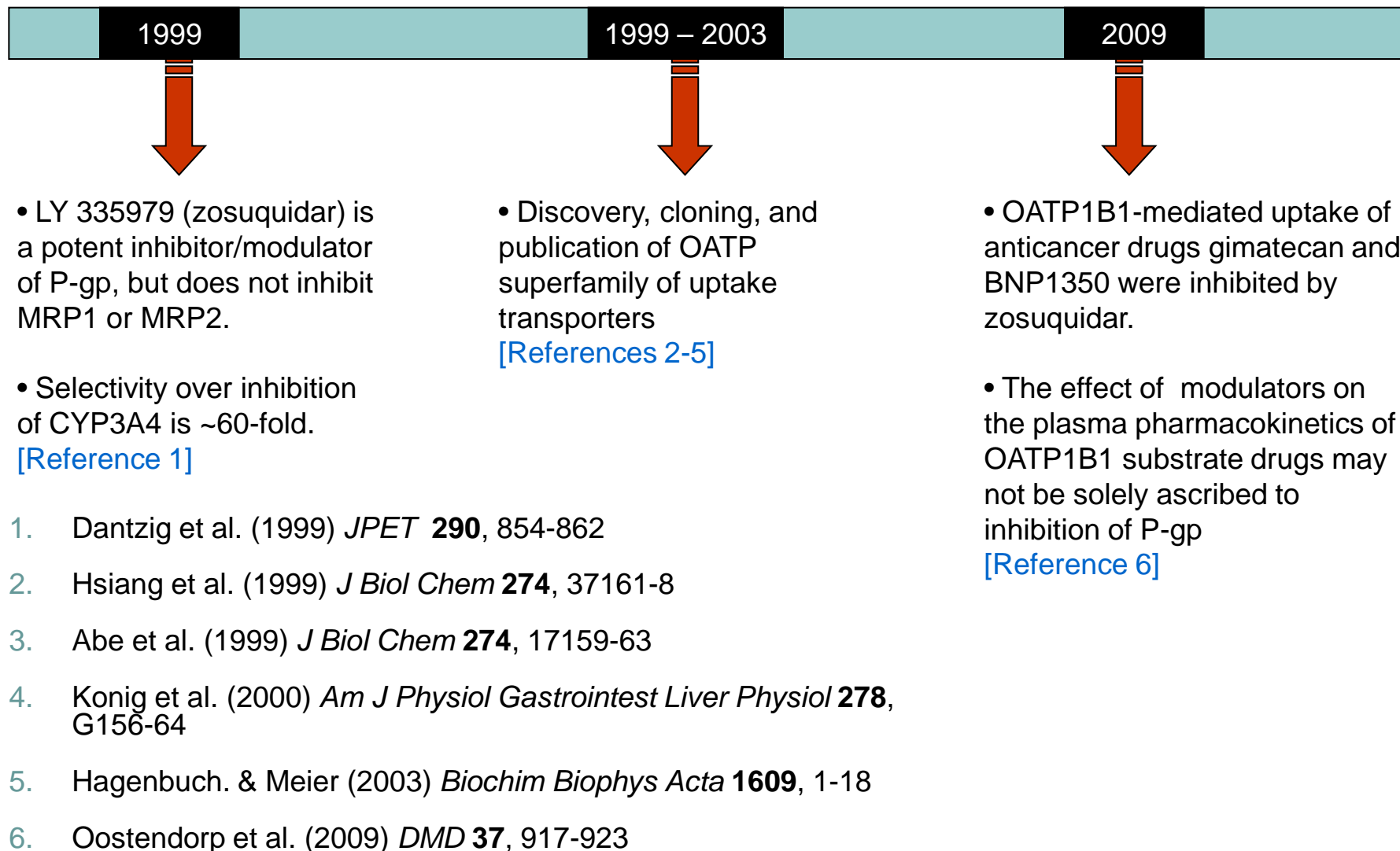
OATP1B1	OATP1B3	BCRP	MRP2
Anticancer drugs	Anticancer drugs	Anticancer drugs	Anticancer drugs
Methotrexate 	Docetaxel	Daunorubicin	Cisplatin
SN-38 	Methotrexate 	Doxorubicin	Daunorubicin
Antibiotics	Paclitaxel	Epirubicin	Doxorubicin
Benzylpenicillin	Antibiotics	Etoposide	Etoposide
Rifampicin	Rifampicin	Gefitinib	Imatinib
Antihypertensive drugs	Antihypertensive drugs	Imatinib	Irinotecan
Bosentan	Bosentan	Irinotecan	Methotrexate 
Olmesartan	Olmesartan	Methotrexate 	SN-38 
Valsartan	Telmisartan	Mitoxantrone	Topotecan
Statins	Valsartan	SN-38 	Vincristine
Pitavastatin	Antiallergic drugs	Topotecan	Vinblastine
Pravastatin 	Fexofenadine	Antibiotics	Antibiotics
Rosuvastatin	Cardioactive drugs	Ciprofloxacin	Ampicillin
Others	Digoxin	Ofloxacin	Statins
Bilirubin	Statins	Norfloxacin	Pravastatin 
Leukotriene C4	Pitavastatin	Antiviral drugs	Glucuronide (-G) conjugates
Leukotriene E4	Others	Zidovudine	Bilirubin-G
Prostaglandin E2	Bilirubin	Lamivudine	 Estradiol-17-β-D-glucuronide
T3 (triiodothyronine)	Leukotriene C4	Flavonoids	SN-38-G
T4 (thyroxine)	T3 (triiodothyronine)	Genestein	Acetaminophen-G
Thromboxane B2	T4 (thyroxine)	Quercetin	Diclofenac-G
Conjugates	Conjugates	Statins	Indomethacin-G
Estrone-3-sulfate	Estrone-3-sulfate	Pravastatin 	
 Estradiol-17-β-D-glucuronide	Estradiol-17-β-D-glucuronide 	Rosuvastatin	
Troglitazone sulfate		Others	
		Prazosin	
		Nitrofurantoin	
		Cimetidine	
		Conjugates	
		Estrone-3-sulfate	
		Dehydroepiandrosterone sulfate	
	 Estradiol-17-β-D-glucuronide		
		dinitrophenyl-S-glutathione	

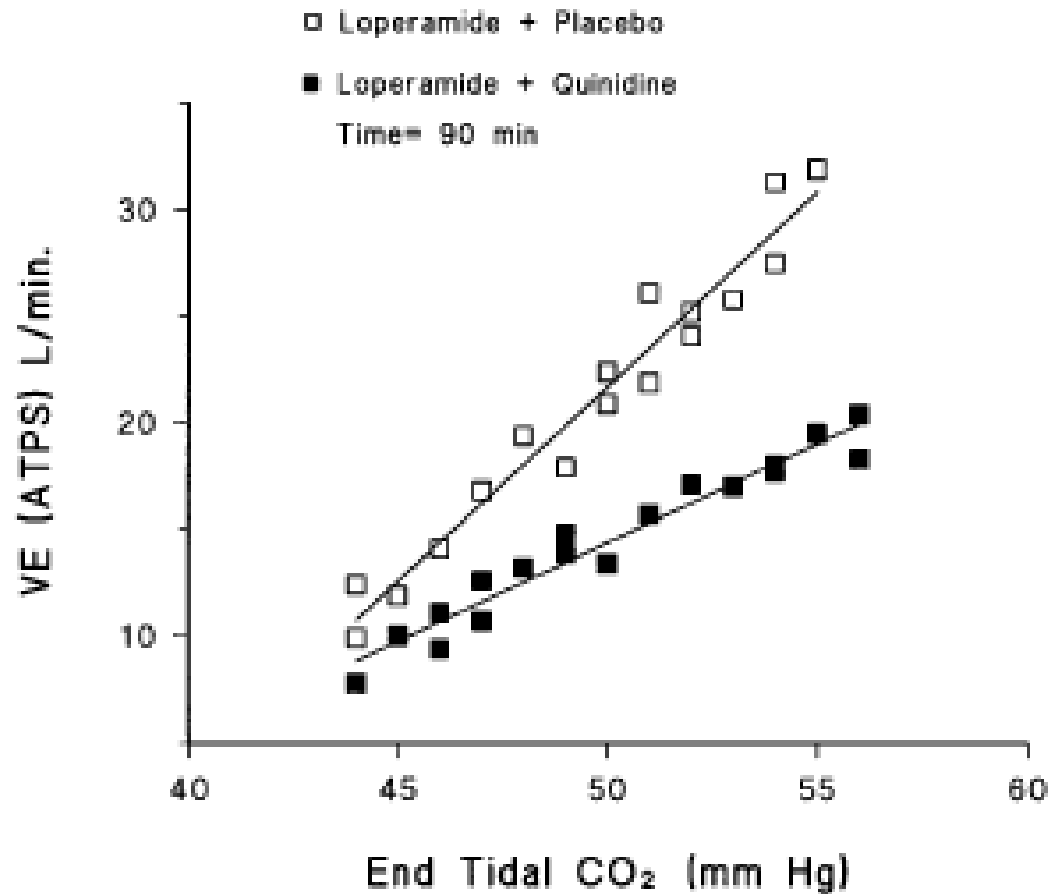
Transporter Interaction Redundancy:

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

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

leiri et al. (2009) Expert Opinion in Drug Metabolism and Toxicology, 5: 703-729.





P-gp at the Blood-Brain Barrier: Species Differences

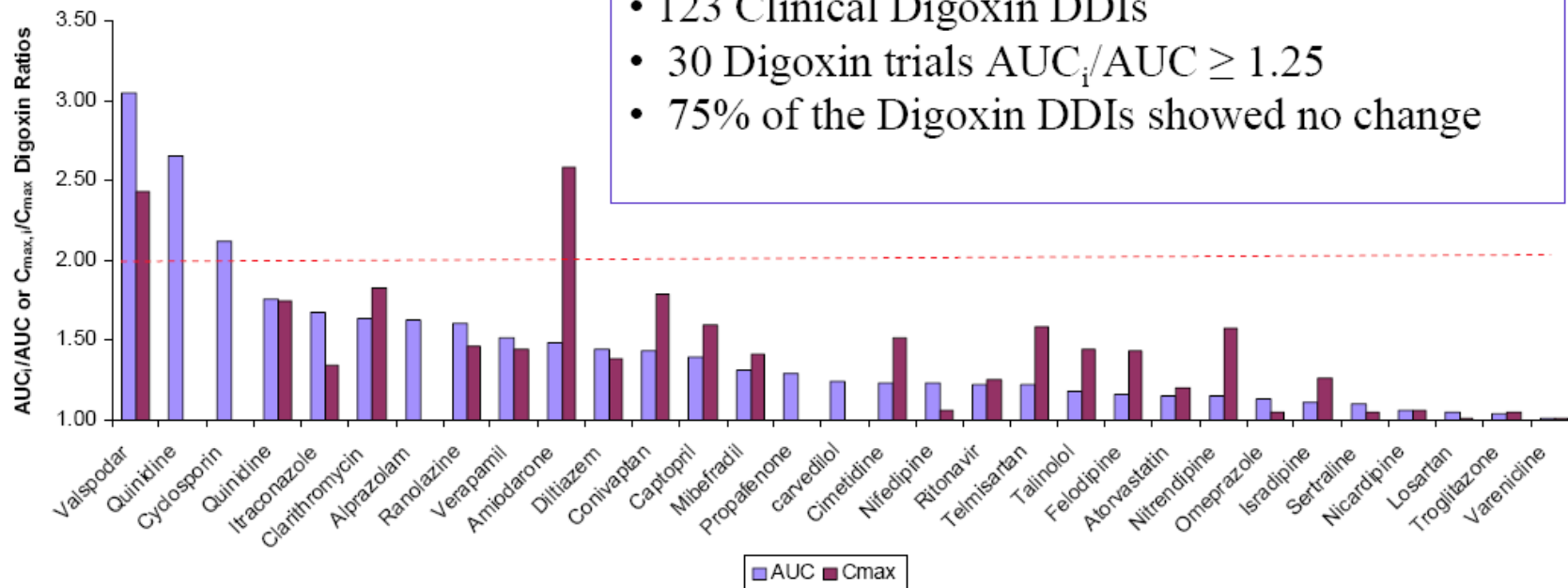
P-gp inhibitor	P-gp inhibitor dosage	Drug (P-gp substrate)	Clinical usage of the drug	CNS exposure index	Plasma AUC and C _{max}	CNS effect	Brain P-gp inhibition	Reference
Quinidine	600 mg	Fentanyl	Synthetic opioid	Pupil diameter	Oral AUC ↑ 171%, C _{max} ↑ 162%	Quinidine had no major influence on fentanyl pharmacodynamics in humans.	No	1
Quinidine	600 mg	Loperamide	A peripherally acting opioid receptor agonist for treatment of chronic diarrhea	Respiratory response to CO ₂ rebreathing	AUC ↑ 148%	Respiratory depression occurred when loperamide was given with quinidine.	Yes?	
Quinidine	800 mg	Loperamide	A peripherally acting opioid receptor agonist for treatment of chronic diarrhea	Pupil size	AUC ↑ 80%	Pupil size decreased with co-administration of quinidine.	Yes?	3
Quinidine	600 mg	Methadone	Opioid	Pupil diameter	i.v. AUC and C _{max} , no changes	No effect on methadone miosis after i.v. administration	No	4
Quinidine	600 mg	Morphine	Opioid	Pupil diameter	Oral AUC ↑ 60%, C _{max} ↑ 88%	No effect on i.v. morphine miosis, Difference in oral morphine miosis were commensurated with changes in plasma morphine concentration.	No	5
Quinidine	800 mg	Morphine	Opioid	Pupil diameter and respiratory response to CO ₂ rebreathing	Plasma concentration, no change	Not result in an enhancement of central nervous opioid effects.	No	6
Quinidine	800 mg	Morphine 6-glucuronide	An active metabolite of morphine	Pupil size	No effect on the pharmacokinetics of morphine 6-glucuronide	No effect.	No	7

(1) Kharasch et al. J Clin Pharmacol. 44:224-233 (2004) (2) Sadeque et al. Clin Pharmacol Ther. 68:231-237 (2000) (3) Skarke et al. Pharmacogenetics. 13:651-660 (2003) (4) Kharasch et al. Br J Clin Pharmacol. 57:600-610 (2004) (5) Kharasch et al. Clin Pharmacol Ther. 74:543-554 (2003) (6) Skarke et al. Clin Pharmacol Ther. 74:303-311 (2003) (7) Skarke et al. Anesthesiology. 101:1394-1399 (2004)

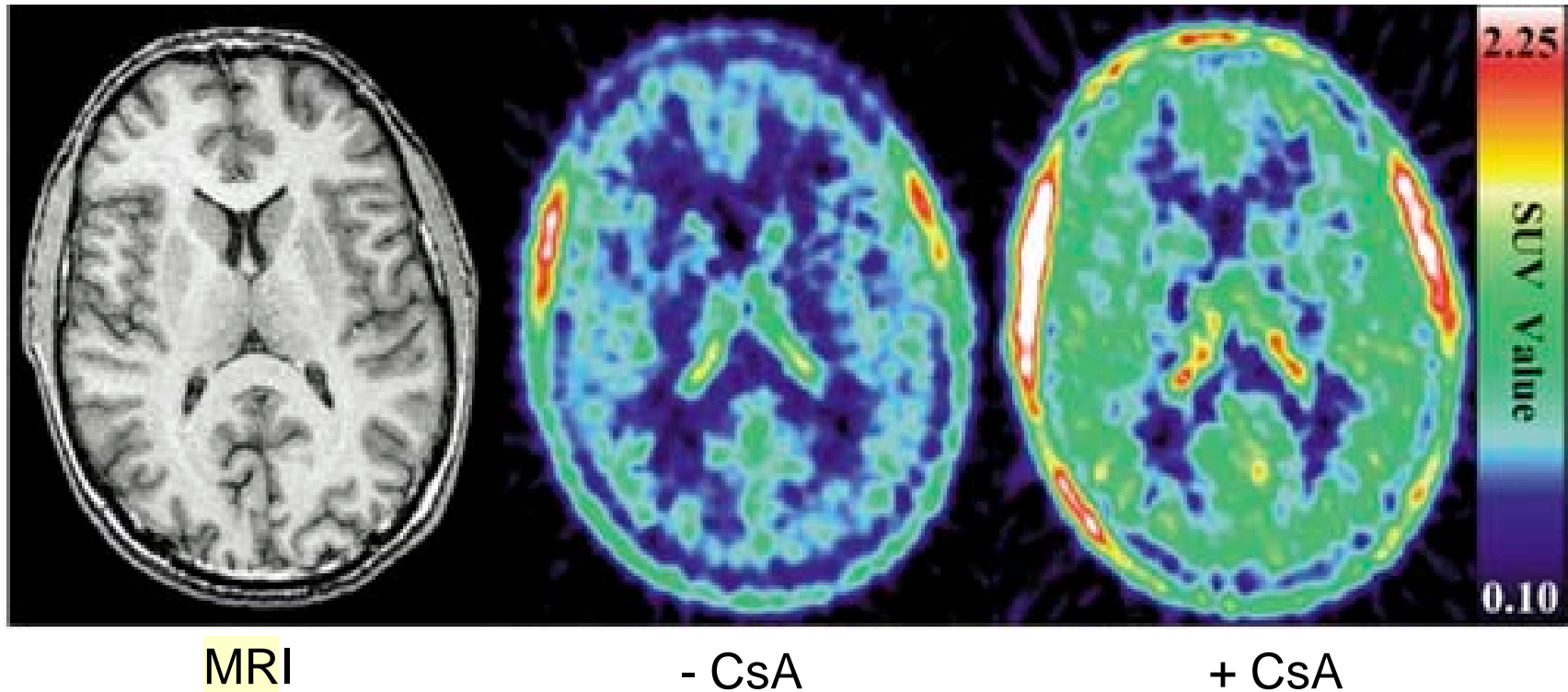
Can digoxin be used as a clinical P-gp probe substrate?

Fenner et al. (2009) *CPT* **85**, 173-

181



- Narrow therapeutic window of digoxin requires close monitoring
- Abundant digoxin clinical DDI study data – especially for relatively new drugs
- Digoxin currently viewed as the “gold standard” probe for studying clinical P-gp–related DDIs
- recent data may indicate that digoxin interacts with other transporters; OATPs



- ^{11}C -verapamil and CsA dosed IV
- $\text{AUC}_{\text{brain}}/\text{AUC}_{\text{blood}}$ of ^{11}C -radioactivity \uparrow 88% in the presence of CsA
- \uparrow 770% in similar study in mouse

Sasongko et al CPT (2005) 77:503-514; Hendrikse et al Br. J. Pharmacol. (1998)

Drug	Brain level ratio mdr1a (-/-):mdr1a(+/+)	Therapeutic category
Amprenavir	27	HIV protease inhibitor
Asimadoline*	11	analgesic
Azasetron	7	anti-emetic
Carebastin	8	antihistamine
Cyclosporin	17	immune suppressant
Dexamethasone	3	glucocorticoid
Digoxin	35	cardiotonic
Doxorubicin*	3	antineoplastic
Ebastine	7	antihistamine
Grepafloxacin	3	antibacterial
Indinavir	11	HIV protease inhibitor
Ivermectin	87	anthelminitic
Loperamide	14	antidiarrheal
Morphine	2	analgesic
Nelfinavir	36	HIV protease inhibitor
Ondansetron	4	anti-emetic
Paclitaxel*	12	antineoplastic
Quinidine	29	anti-arrythmic
Saquinavir	7	HIV protease inhibitor
Tacrolimus*	33	immunosuppressant
Verapamil	10	antihypertensive
Vinblastine*	22	antineoplastic

A. Ayrton and P. Morgan. Role of transport proteins in drug absorption, distribution and excretion, *Xenobiotica*. 31:469-497 (2001)

ITC Transporter Workshop (2008)

Mikko Niemi - University of Helsinki

Potential OATP1B1 probe substrates *in vivo*

- **Atorvastatin** (K_m 12.4 μ M, Kameyama et al 2005)
 - OATP2B1, P-glycoprotein and BCRP substrate
 - Metabolized (CYP3A4, CYP2C8)
- **Pitavastatin** (K_m 3.0-6.7 μ M, Hirano et al 2004, Deng et al 2008)
 - OATP1B3, P-glycoprotein and BCRP substrate
 - Metabolized to a minor extent only (CYP2C9)
- **Pravastatin** (K_m 13.7-86 μ M, Hsiang et al 1999, Nakai et al 2001, Sasaki et al 2002, Kameyama et al 2005, Deng et al 2008)
 - OATP2B1, P-glycoprotein, BCRP and MRP2 substrate
 - Metabolized to a minor extent only (non-CYP mediated)
- **Repaglinide** (K_m ?)
 - Metabolized (CYP2C8, CYP3A4)
- **Rosuvastatin** (K_m 4.0-8.5 μ M, Brown et al 2001, Schneck et al 2004, Simonson et al 2004, Ho et al 2006)
 - OATP1A2, OATP1B3, OATP2B1, NTCP and BCRP substrate
 - Metabolized to a minor extent only (CYP2C9)
- **Simvastatin (acid)** (K_m ?)
 - P-glycoprotein substrate
 - Metabolized (CYP3A4, CYP2C8)

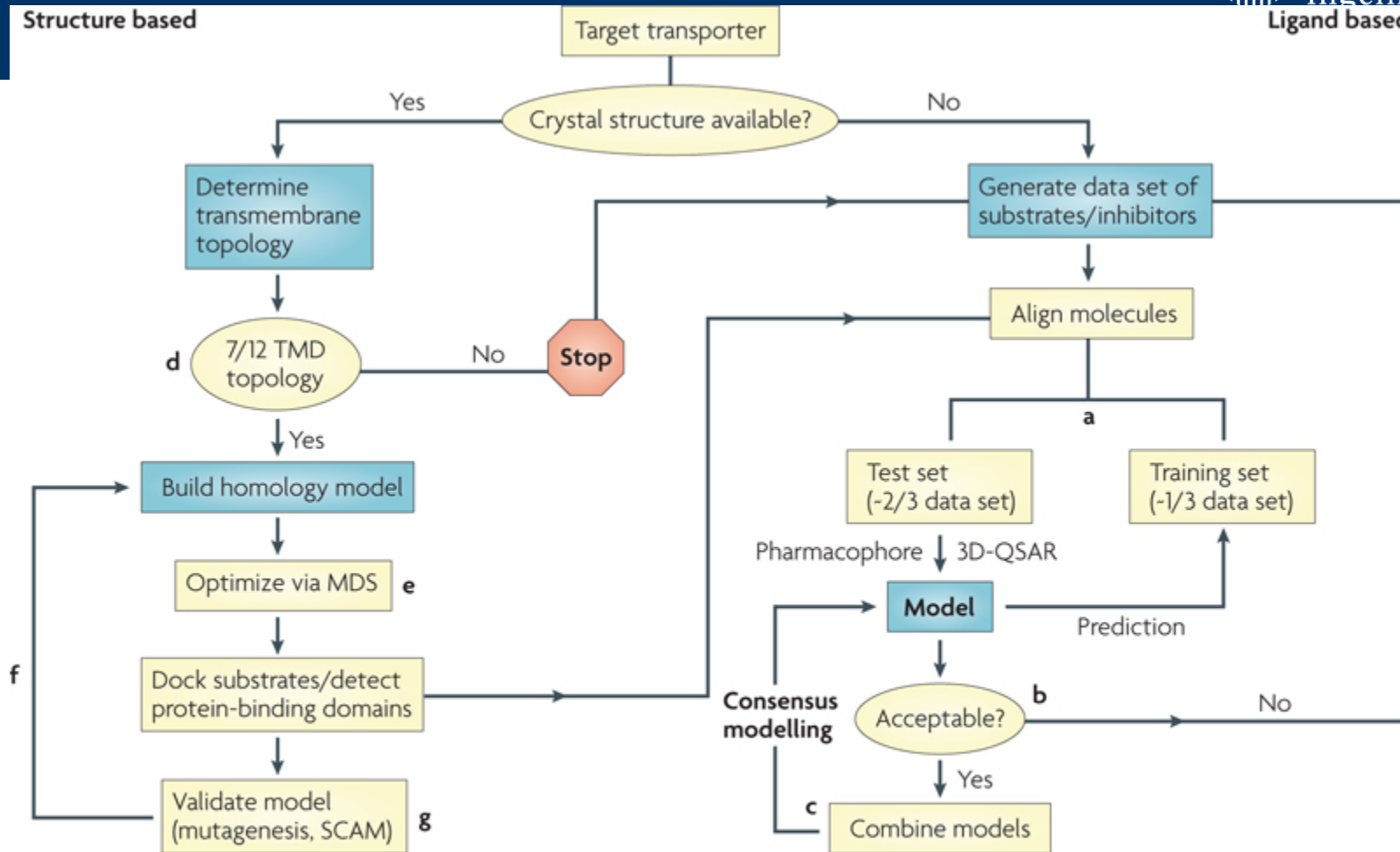
- Transporters are a very dynamic field – the white paper is intended to be a snapshot
- White paper will need to be updated (timeline?)
- White paper provides framework for FDA to add to current guidance(s) – DDI
- Emphasizes the need for flexibility
 - which provides some realistic challenges for regulatory agencies
- Has identified areas of highest immediate need
 - decision trees for other transporters
 - relevance of unbound drug concentrations
- Never intended to be a panacea
- Focus group for collating new data

- Committee of FDA and Pharma
 - Lei Zhang (leik.zhang@fda.hhs.gov) and Donald Tweedie (donald.tweedie@boehringer-ingelheim.com)
- Main committee with sub-committees for specific topics
 - Identify experts for different transporters
 - Identify experts for selected topics (P-gp and digoxin, kinetics)
- Outcome
 - Provide feedback on discussions, action items
 - Make recommendations
 - change current practices
 - monitor specific practices
 - Publish mini-white papers

- ITC members
 - Shiew Mei Huang, FDA
 - Kathy Giacomini, UCSF
- DMTG, PhRMA
 - Volker Fischer
- DIA (Drug Information Association)
- Mitch Taub, Boehringer Ingelheim
- Yongmei Li, Boehringer Ingelheim

Backup Slides

Structure based



Transporter/alias (Gene)	Selected substrates	Selected inhibitors	Organs/cells	Comments
OATP1B1/OATP-C, OATP2, LST-1 (SLC01B1)	Bromosulphophthalein, oestrone-3-sulphate, oestradiol-17 β -glucuronide, statins*, repaglinide*, valsartan, olmesartan*, bilirubin glucuronide, bilirubin, bile acids	Saquinavir, ritonavir*, lopinevir*, rifampicin*, cyclosporine*	Hepatocytes (sinusoidal)	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has clinically relevant polymorphisms • Has a role in clinical drug-drug interactions
OATP1B3/OATP-8 (SLC01B3)	Bromosulphophthalein, cholecystokinin 8, statins*, digoxin, fexofenadine, telmisartan glucuronide, telmisartan*, valsartan, olmesartan, oestradiol-17- β -glucuronide, bile acids	Rifampicin*, cyclosporine*, ritonavir, lopinevir*	Hepatocytes (sinusoidal)	<ul style="list-style-type: none"> • Has a role in disposition and excretion
OAT1 (SLC22A6)	Para-aminohippurate, adefovir, cidofovir, zidovudine*, lamivudine*, zalcitabine*, acyclovir*, tenofovir*, ciprofloxacin*, methotrexate*	Probenecid*, novobiocin	Kidney proximal tubule, placenta	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has a role in clinical drug-drug interactions
OAT3 (SLC22A8)	Oestrone-3-sulphate, non-steroidal anti-inflammatory drugs, cefaclor, ceftizoxime, furosemide*, bumetanide*	Probenecid*, novobiocin	Kidney proximal tubule, choroid plexus, blood-brain barrier	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has a role in clinical drug-drug interactions
OCT2 (SLC22A2)	<i>N</i> -Methylpyridinium, tetraethylammonium, metformin*, pindolol, procainamide, ranitidine, amantadine, amiloride, oxaliplatin, varenicline*	Cimetidine*, pilsicainide, cetirizine*, testosterone, quinidine	Kidney proximal tubule, neurons	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has clinically relevant genetic polymorphisms • Has a role in clinical drug-drug interactions
OATP1A2/OATP-A (SLC01A2)	Oestrone-3-sulphate, dehydroepiandrosterone sulphate, fexofenadine*, bile salts, methotrexate, bromosulphophthalein, ouabain, digoxin, levofloxacin, statins*	Naringin, ritonavir, lopinevir, saquinavir, rifampicin*	Brain capillaries endothelia, cholangiocytes, distal nephron	<ul style="list-style-type: none"> • Has role in disposition and excretion
OATP2B1/OATP-B (SLC02B1)	Oestrone-3-sulphate, bromosulphophthalein, taurocholate, *statins, fexofenadine, glyburide, taurocholate	Rifampicin, cyclosporine*	Hepatocytes (sinusoidal), endothelia	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has a role in clinical drug-drug interactions
OCT1 (SLC22A1)	Tetraethylammonium, <i>N</i> -methylpyridinium, metformin*, oxaliplatin	Quinine, quinidine, disopyramide	Hepatocytes (sinusoidal), intestinal enterocytes	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has clinically relevant genetic polymorphisms • Has a role in clinical drug-drug interactions
PEPT1 (SLC15A1)	Glycylsarcosine, cephalixin, cefadroxil, bestatin, valacyclovir, enalapril, aminolevulinic acid, captopril, dipeptides, tripeptides	Glycyl-proline	Intestinal enterocytes, kidney proximal tubule	<ul style="list-style-type: none"> • Has a role in absorption, disposition and excretion • Has a role in clinical drug-drug interactions
PEPT2 (SLC15A2)	Glycylsarcosine, cephalixin, cefadroxil, bestatin, valacyclovir, enalapril, aminolevulinic acid, captopril, dipeptides, tripeptides	Zofenopril, fosinopril	Kidney proximal tubule, choroid plexus, lung	<ul style="list-style-type: none"> • Has a role in excretion
MATE1 (SLC47A1)	Metformin, <i>N</i> -methylpyridinium, tetraethylammonium	Quinidine, cimetidine, procainamide	Kidney proximal tubule, liver (canalicular membrane), skeletal muscle	<ul style="list-style-type: none"> • Has a role in disposition and excretion • Has a role in clinical drug-drug interactions
MATE2-K (SLC47A2)	Metformin, <i>N</i> -methylpyridinium, tetraethylammonium	Cimetidine, quinidine, pramipexole	Kidney proximal tubule	<ul style="list-style-type: none"> • Has a role in disposition and excretion

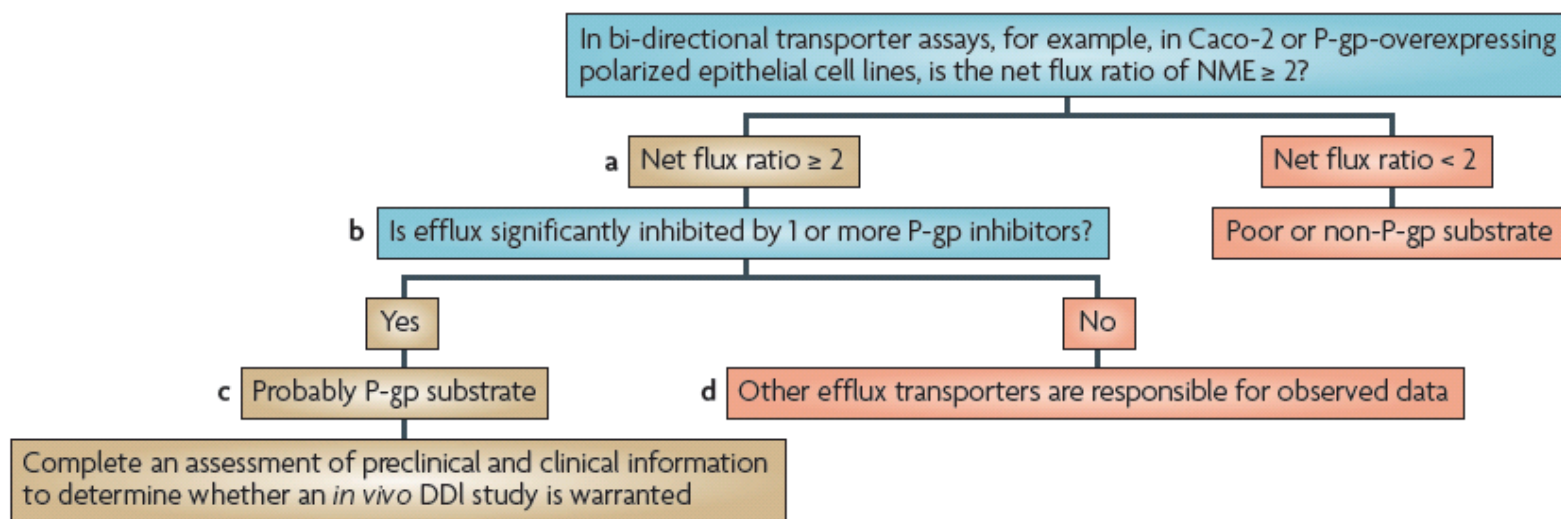
*Can potentially be used for in vivo (clinical) studies.

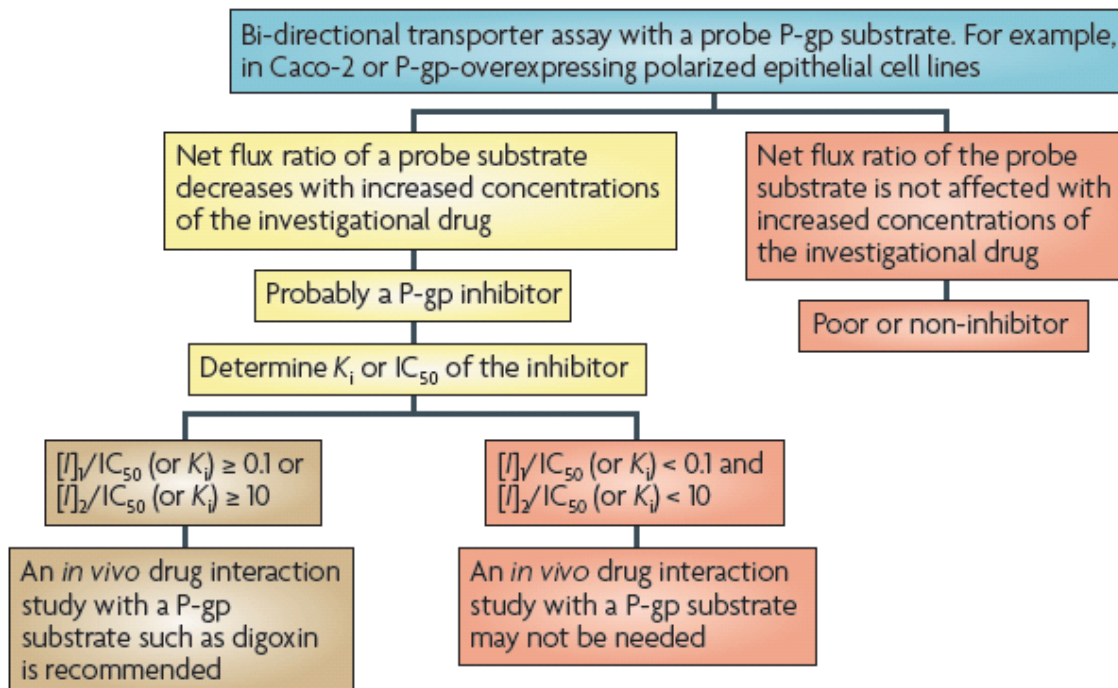
Transporter/ alias (Gene)	Selected substrates	Selected inhibitors	Organs/cells	Comments
MDR1/P-gp, ABCB1 (ABCB1)	Digoxin*, loperamide*, berberine, irinotecan, doxorubicin, vinblastine, paclitaxel, fexofenadine	Cyclosporine*, quinidine*, tariquidar, verapamil	Intestinal enterocytes, kidney proximal tubule, hepatocytes (canalicular), brain endothelia	<ul style="list-style-type: none"> • Has a role in absorption, disposition and excretion • Has a role in clinical drug–drug interactions
BCRP/MXR (ABCG2)	Mitoxantrone, methotrexate, topotecan, imatinib, irinotecan, statins*, sulphate conjugates, porphyrins	Oestrone, 17 β -oestradiol, fumitremogin C	Intestinal enterocytes, hepatocytes (canalicular), kidney proximal tubule, brain endothelia, placenta, stem cells, mammary glands (lactating)	<ul style="list-style-type: none"> • Has a role in absorption, disposition and excretion • Has clinically relevant genetic polymorphisms • Has a role in clinical drug–drug interactions
BSEP/SPGP, cBAT, ABCB11 (ABCB11)	Taurocholic acid, pravastatin, bile acids	Cyclosporin A, rifampicin, glibenclamide	Hepatocytes (canalicular)	<ul style="list-style-type: none"> • Has a role in excretion • Has clinically relevant genetic polymorphisms • Has a role in clinical drug–drug interactions
MRP2/ABCC2, cMOAT (ABCC2)	Glutathione and glucuronide conjugates, methotrexate, etoposide, mitoxantrone, valsartan, olmesartan, glucuronidated SN-38	Cyclosporine, delaviridine, efavirenz, emtricitabine	Hepatocytes (canalicular), kidney (proximal tubule, luminal), enterocytes (luminal)	<ul style="list-style-type: none"> • Has a role in absorption, disposition and excretion • Has clinically relevant genetic polymorphisms • Has a role in clinical drug–drug interactions
MRP3/ABCC3 (ABCC3)	Oestradiol-17 β - glucuronide, methotrexate, fexofenadine, glucuronate conjugates	Delaviridine, efavirenz, emtricitabine	Hepatocytes (sinusoidal), intestinal enterocytes (basolateral)	<ul style="list-style-type: none"> • Has a role in disposition
MRP4/ABCC4 (ABCC4)	Adefovir, tenofovir, cyclic AMP, dehydroepian- drosterone sulphate, methotrexate, topotecan, furosemide, cyclic GMP, bile acids plus glutathione	Celecoxib, diclofenac	Kidney proximal tubule (luminal), choroid plexus, hepatocytes (sinusoidal), platelets	<ul style="list-style-type: none"> • Has a role in disposition and excretion
MDR3/ABCB4 (ABCB4)	Phosphatidylcholine, paclitaxel, digoxin, vinblastine.	Verapamil, cyclosporine	Hepatocytes (canalicular)	<ul style="list-style-type: none"> • Has a role in disposition • Has a role in clinical drug–drug interactions

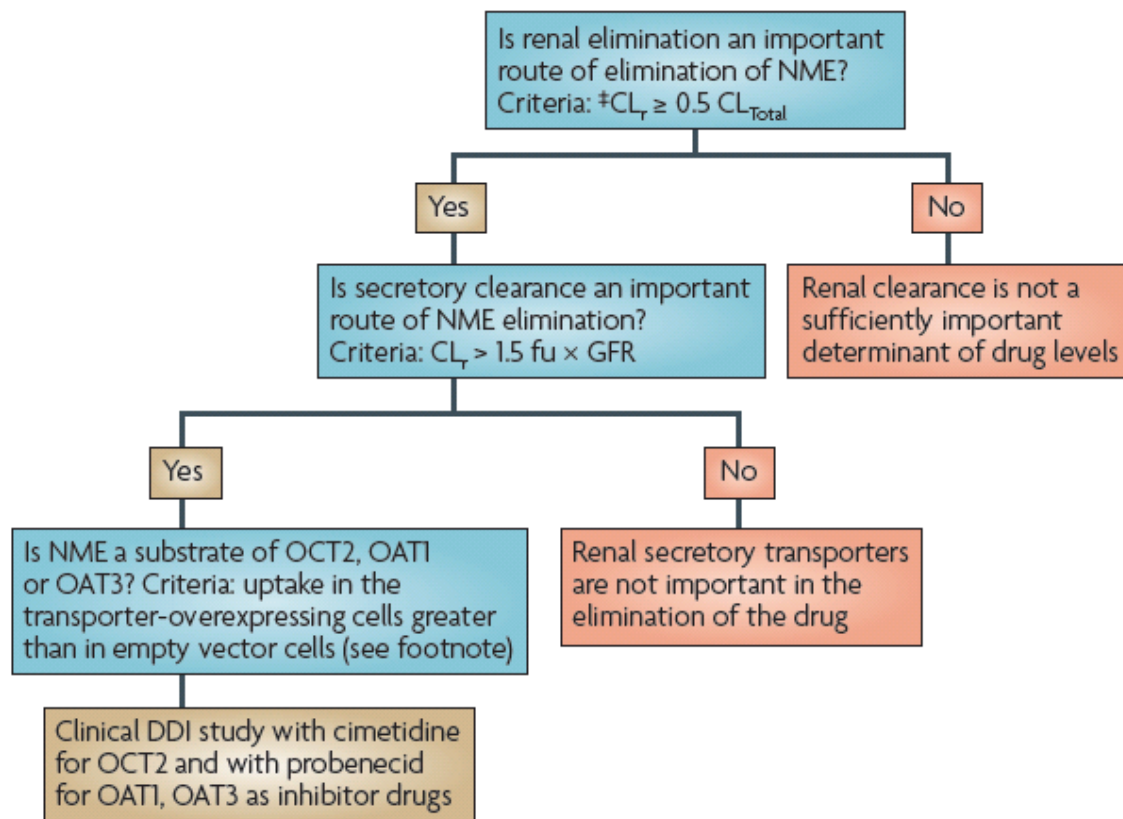
ABC, ATP-binding cassette. *Can potentially be used for *in vivo* (clinical) studies.

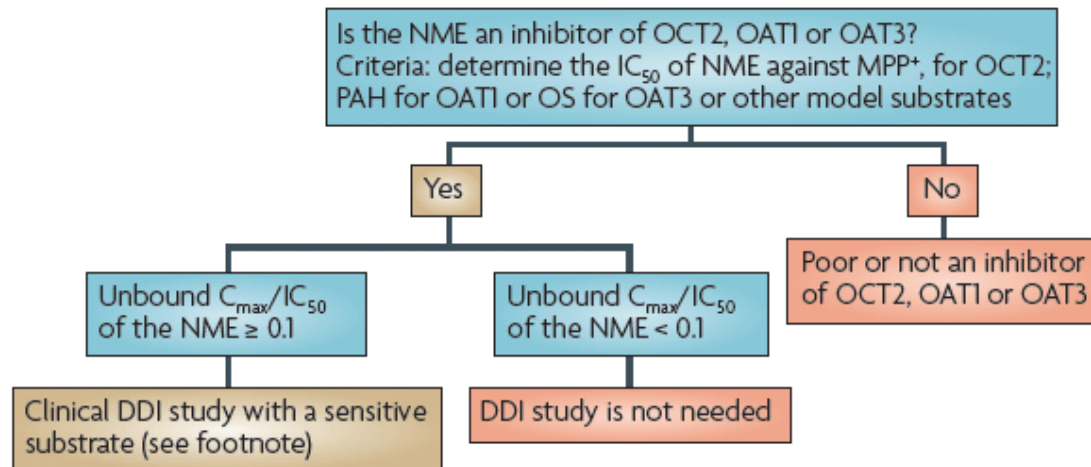
Implicated transporter*	Interacting drug	Affected drug	Clinical pharmacokinetic impact on affected drug [‡]
Organic anion transporting polypeptides	Cyclosporine	Pravastatin	AUC ↑890% and C _{max} ↑678% ^{102,204}
	Cyclosporine	Rosuvastatin	AUC ↑610% ²⁰⁵
	Cyclosporine	Pitavastatin	AUC ↑360% and C _{max} ↑560% ²⁰⁶
	Rifampicin (single dose)	Glyburide	AUC ↑125% ²⁰⁷
	Rifampicin (single dose)	Bosentan	C _{trough} ↑500% ²⁰⁸
	Lopinavir/ritonavir	Bosentan	Day 4: C _{trough} ↑4,700% ²⁰⁸ ; day 10: C _{trough} ↑400% ²⁰⁸
	Lopinavir/ritonavir	Rosuvastatin	AUC ↑107% and C _{max} ↑365% ²⁰⁹
Organic anion transporters	Probenecid	Cidofovir	CL _r ↓32% ^{210,211}
	Probenecid	Furosemide	CL _r ↓66% ²¹⁰
	Probenecid	Acyclovir	CL _r ↓32% and AUC ↑40% ^{210,212}
Organic cation transporters	Cimetidine	Metformin	AUC ↑50% and CL _r ↓27% ^{213,214}
	Cimetidine	Pindolol	CL _r ↓~34% ²¹⁵
	Cimetidine	Varenicline	AUC ↑29% ²¹⁶
	Cimetidine	Pilsicainide	AUC ↑33%, CL _r ↓28% ²¹⁷
	Cetirizine	Pilsicainide	CL _r ↓41% ²¹⁸
	Cimetidine	Dofetilide	CL _r ↓33% ²¹⁹
P-glycoprotein	Quinidine	Digoxin	CL _r ↓34–48% ^{220,221}
	Ritonavir	Digoxin	AUC ↑86% ²²²
	Dronedarone	Digoxin	AUC ↑157% and C _{max} ↑75% ²²³
	Ranolazine	Digoxin	AUC ↑60% and C _{max} ↑46% ²²⁴
Breast cancer resistance protein	GF120918	Topotecan	AUC ↑143% ²²⁵

*Implicated transporter refers to the likely transporter; however, because the studies are carried out *in vivo* it is not possible to assign specific transporters to the drug–drug interaction. [‡]Percent change refers to the difference between the area under the curve (AUC), or C_{max}, in the presence and the absence of the inhibitor (interacting drug) normalized to the AUC in the absence of the inhibitor. For clearance values (CL_r), the values are normalized for the absence of the inhibitor. C_{trough} is the minimum drug concentration observed after administration of a dose of the drug and the concentration prior to the administration of a subsequent dose.

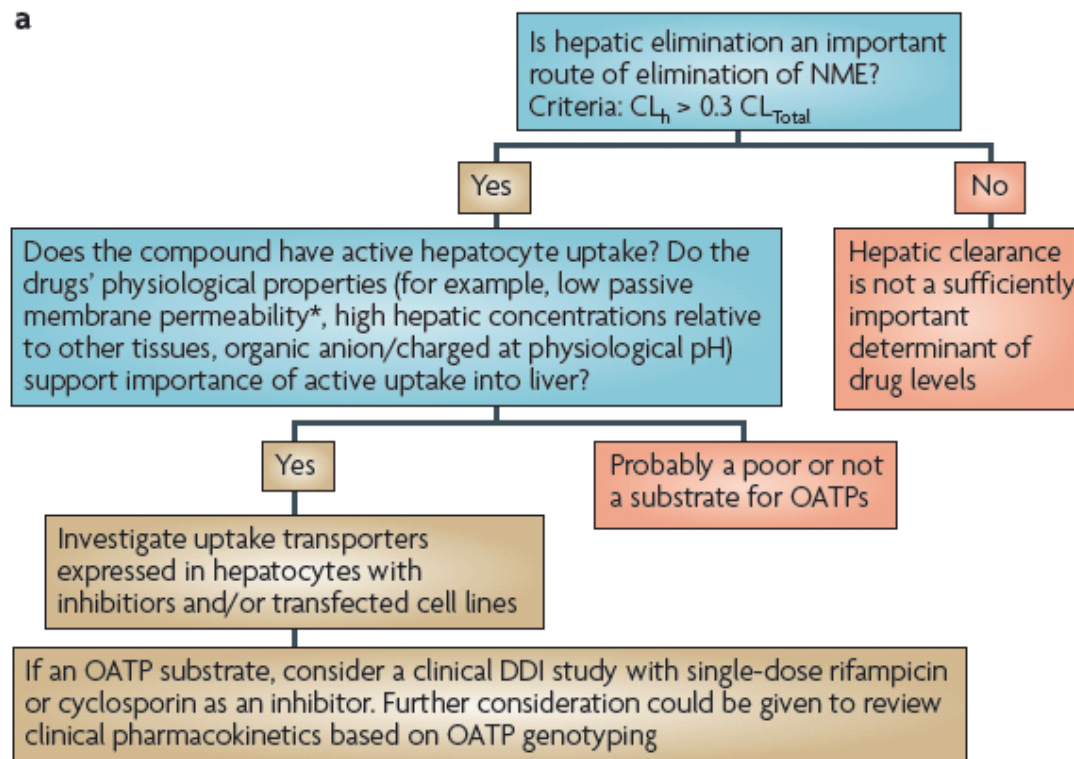




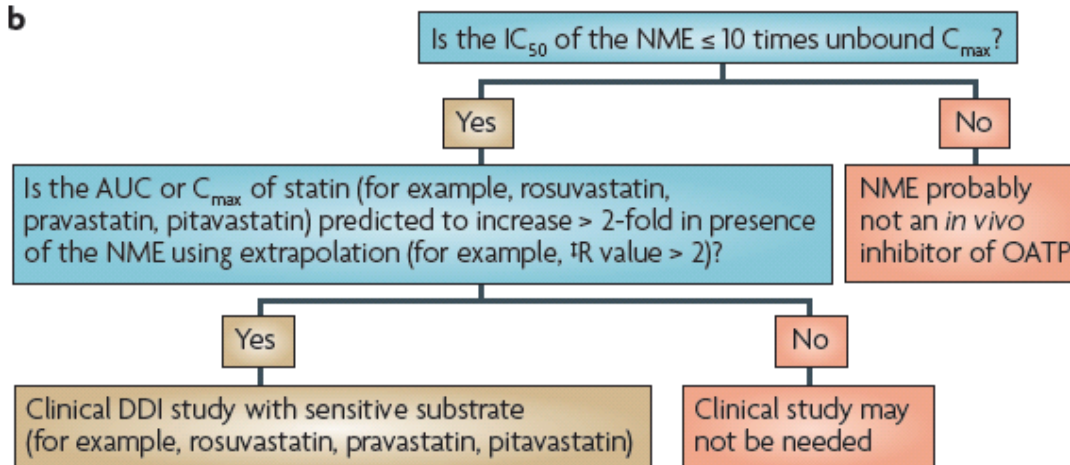




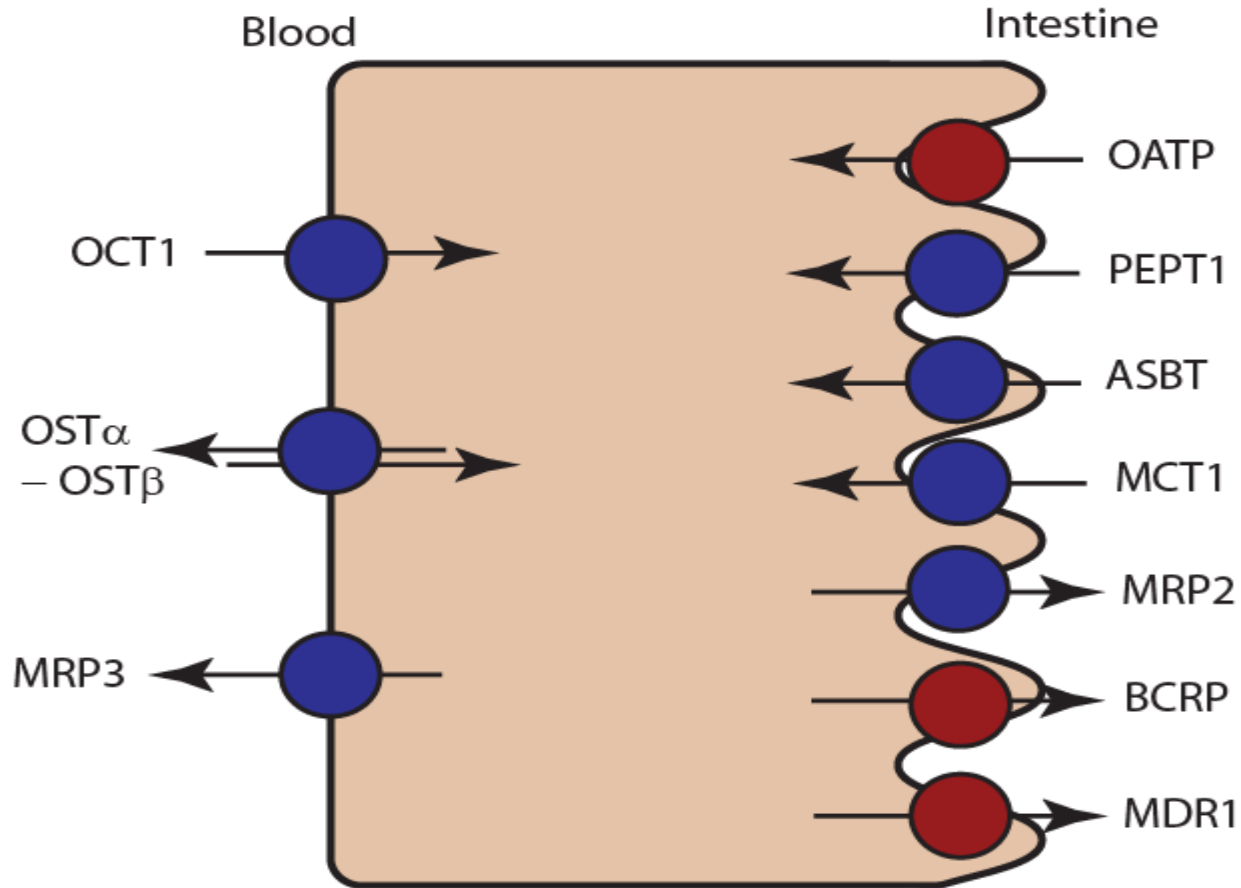
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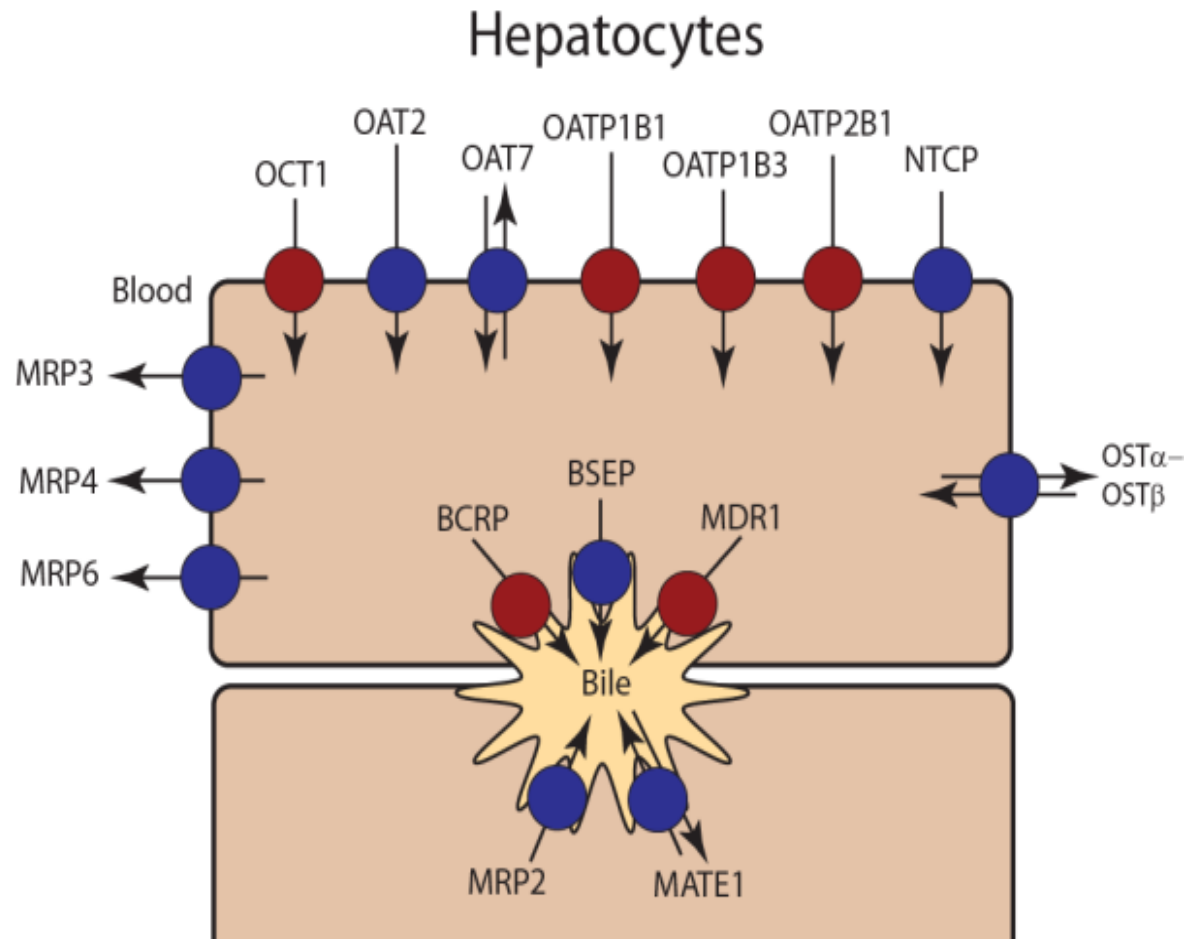


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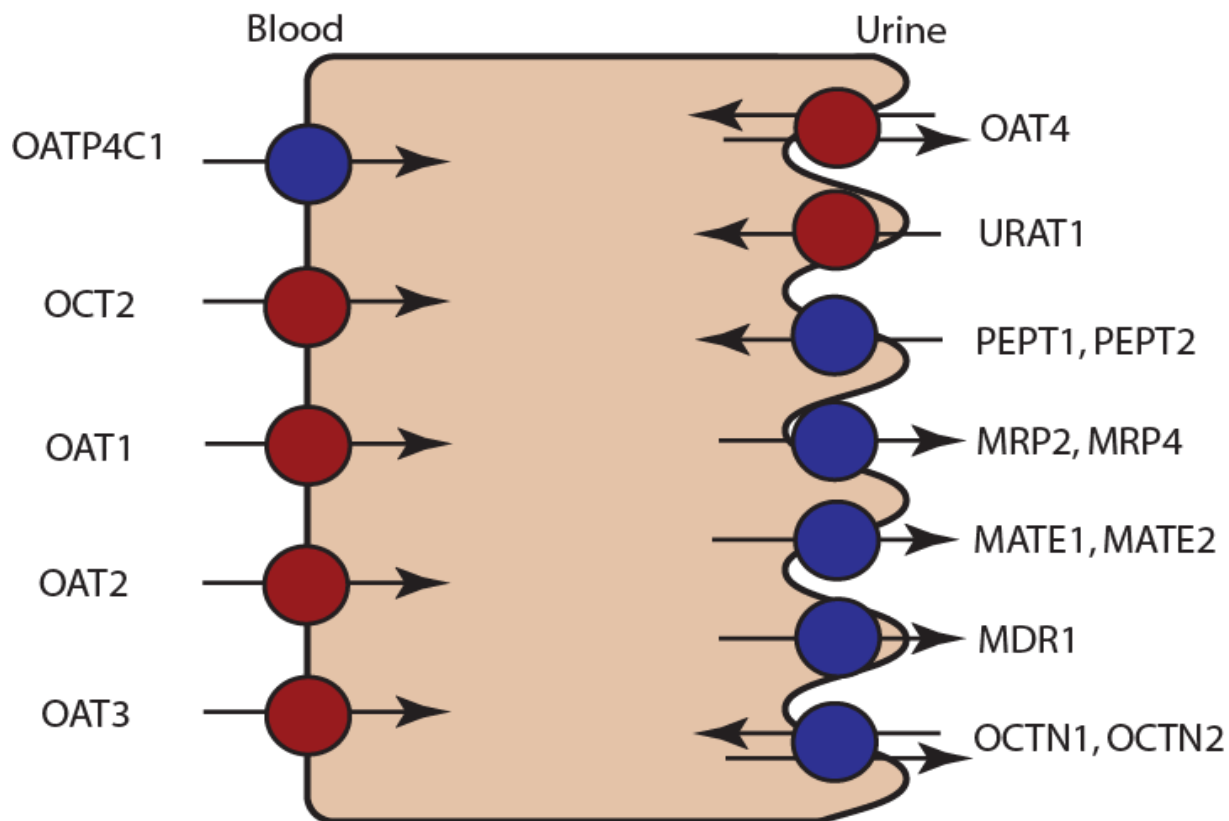


Intestinal Epithelia





Kidney Proximal Tubules



Blood Brain Barrier

