Drug – Drug Interaction and Drug Transporters: What’s new?

J.M. SCHERRMANN

Club Phase 1 Meeting, Paris, 22 March 2016
FROM WHERE DO WE COME?
"Drug transport in the intestine occurs mainly by diffusion"....

"Intestinal drug carriers contribution seems to be of minor importance."

"The liver is the organ where carrier-mediated drug transport predominates"

**ENZYMES and PHARMACOKINETICS in 1987**

« Genetic polymorphism of human cytochrome P450 (S)-mephenytoin 4-hydroxylase (P-450 meph)  
(U.T. MEIER and U.A. MEYER, 1987) »

« Metabolism of cyclosporin A. Interaction of erythromycin, using rabbit hepatocytes and microsome fractions  
(P-450 LM3c or P-450IIIA4)  
I. FABRE et al. (J.P. CANO), 1988"
**TRANSPORTERS and PHARMACOKINETICS in 1987**

Four hypothetical carrier systems for hepatocellular drug uptake

<table>
<thead>
<tr>
<th>OATPs</th>
<th>OATPs</th>
<th>OCT1, 3</th>
<th>OATPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTCP</td>
<td>NTCP</td>
<td>Morphine</td>
<td>Ouabain</td>
</tr>
<tr>
<td>Bile acids</td>
<td>Estronesulfate</td>
<td>Bromosulphophtalein</td>
<td>Nalorphine</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Estradiol</td>
<td>ANS</td>
<td>Indocyanine green</td>
</tr>
<tr>
<td>glucuronide</td>
<td>glucuronide</td>
<td>Indocyanine green</td>
<td></td>
</tr>
</tbody>
</table>
DIFFUSIONAL versus VECTORIAL PHARMACOKINETICS

Ante 2000 « Diffusional PK »

Passive Diffusion

X

X

CYPs

D

M

E

Passive Diffusion?

X-OH

X-OC

X-OC

Post 2000 « Vectorial PK »

Passive Diffusion

Active Influx

Active Efflux

X

X

X

CYPs

CEs

CEs

X-OH

X-OC

X-OC

Phase 0

Phase I

Phase II

Phase III
1st period: cancer research (1970 - )

MDR (Multi Drug Resistance) phenotype (Juliano and Ling, 1976)

MDR1, P-glycoprotein, ABCB1

Mdr1a et Mdr1b in rodents

2nd period: pharmacology (1990 - )

Expression in healthy tissues (Protection and Detoxification, the << GATEKEEPER >>)

1st PK-Pgp study published by Tsuji and Terasaki in 1992 (Life Sci. 51, 1427, 1992)

3rd period: Guidance for Industry (2006 - )

substrate/inhibitor identification

WHERE WE ARE TODAY?
SUPERFAMILIES and FAMILIES of DRUG TRANSPORTERS

• ABC (ATP Binding Cassette) SUPERFAMILY
  48 human genes; ≈ 9 drug transporters

• SLC (Solute Carrier) SUPERFAMILY
  > 362 mammalian genes; ≈ 30 drug transporters

« 15% of human genes code for 4500 transport proteins »

ABC and SLC TRANSPORTERS

**EFFLUX (Xenobiotics (MDR, Tissue Defense)**

- P-glycoprotein, ABCB1, MDR1
- Breast Cancer Resistance Protein (BCRP, ABCG2)

**PRIMARLY ACTIVE TRANSPORTERS**

- ABC Superfamily

**EFFLUX (Conjugated Metabolites)**

- MRPs, Multi-Drug resistance associated Proteins

**INFLUX and/or EFFLUX (Xenobiotics, Conjugated Metabolites)**

- OATs Organic Anion T.
- OATPs Organic Anion Polypeptide T.
- OCTs Organic Cation T.

**SECONDARY (TERTIARY) ACTIVE TRANSPORTERS**

- ABC and SLC TRANSPORTERS

- P-glycoprotein, ABCB1, MDR1
- Breast Cancer Resistance Protein (BCRP, ABCG2)

1. Na^+ (Influx)

2. H^+ (Influx)

K^+ (K out Flux)
### ABC Transporters

<table>
<thead>
<tr>
<th>Transporter/alias (Gene)</th>
<th>Selected substrates</th>
<th>Selected inhibitors</th>
<th>Organs/cells</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR1/P-gp, ABCB1 (ABCB1)</td>
<td>Digoxin*, loperamide*, berberine, irinotecan, doxorubicin, vinblastine, paclitaxel, fexofenadine</td>
<td>Cyclosporine*, quinidine*, tarquidar, verapamil</td>
<td>Intestinal enterocytes, kidney proximal tubule, hepatocytes (canalicular), brain endothelie</td>
<td>Has a role in absorption, disposition and excretion</td>
</tr>
<tr>
<td>P-gp</td>
<td></td>
<td></td>
<td></td>
<td>Has a role in clinical drug–drug interactions</td>
</tr>
<tr>
<td>BCRP/MXR (ABCG2)</td>
<td>Mitoxantrone, methotrexate, topotecan, imatinib, irinotecan, statins*, sulphate conjugates, porphyrins</td>
<td>Oestrone, 17β-oestradiol, fumitremorgin C</td>
<td>Intestinal enterocytes, hepatocytes (canalicular), kidney proximal tubule, brain endothelie, placenta, stem cells, mammary glands (lactating)</td>
<td>Has a role in absorption, disposition and excretion</td>
</tr>
<tr>
<td>BCP (ABCB11)</td>
<td>Taurocholic acid, pravastatin, bile acids</td>
<td>Cyclosporin A, rifampicin, glibenclamide</td>
<td>Hepatocytes (canalicular)</td>
<td>Has a role in excretion</td>
</tr>
<tr>
<td>MRP2/ABCC2, cMOAT (ABCC2)</td>
<td>Glutathione and glucuronide conjugates, methotrexate, etoposide, mitoxantrone, valsartan, olmesartan, glucuronidated SN-38</td>
<td>Cyclosporine, delavirdine, efavirenz, emtricitabine</td>
<td>Hepatocytes (canalicular), kidney (proximal tubule, luminal), enterocytes (luminal)</td>
<td>Has a role in absorption, disposition and excretion</td>
</tr>
<tr>
<td>MRP3/ABCC3 (ABCC3)</td>
<td>Oestradiol-17β-glucuronide, methotrexate, fexofenadine, gluturate conjugates</td>
<td>Delavirdine, efavirenz, emtricitabine</td>
<td>Hepatocytes (sinusoidal), intestinal enterocytes (basolateral)</td>
<td>Has a role in disposition</td>
</tr>
<tr>
<td>MRP4/ABCC4 (ABCC4)</td>
<td>Adefovir, tenofovir, cyclic AMP, dehydroepiandrosterone sulphate, methotrexate, topotecan, furosemide, cyclic GMP, bile acids plus glutathione</td>
<td>Celecoxib, diclofenac</td>
<td>Kidney proximal tubule (luminal), choroid plexus, hepatocytes (sinusoidal), platelets</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>MDR3/ABCB4 (ABCB4)</td>
<td>Phosphatidylcholine, paclitaxel, digoxin, vinblastine.</td>
<td>Verapamil, cyclosporine</td>
<td>Hepatocytes (canalicular)</td>
<td>Has a role in disposition</td>
</tr>
</tbody>
</table>

### White Paper 2010

Membrane Transporters in Drug Development:

Giacomini et al., Nature Rev Drug Disc 2010

International Transporter Consortium in 2007

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

<table>
<thead>
<tr>
<th>Transporter/alias (Gene)</th>
<th>Selected substrates</th>
<th>Selected inhibitors</th>
<th>Organs/cells</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATP1B1/OATP-C, OATP2, LST-1 (SLCO1B1)</td>
<td>Bromosulphonphthalaein, oestrone-3-sulphate, oestrone-17-beta-glucuronide, sterins*, ropaglinide*, valsartan, olmesartan*, bilirubin glucuronide, bilirubin, bile acids</td>
<td>Saquinavir, ritonavir*, lapinavir, rifampicin*, cyclosporine</td>
<td>Hepatocytes (sinusoids)</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>OATP1B3/OATP-B (SLCO1B3)</td>
<td>Bromosulphonphthalaein, cholesterylosin 8, sterins*, digoxin, fosfomycin, telmisartan glucuronide, telmisartan*, valsartan, olmesartan, oestrone-17-beta-glucuronide, bile acids</td>
<td>Rifampicin*, cyclosporine*, lapinavir, ritonavir*</td>
<td>Hepatocytes (sinusoids)</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>OAT1 (SLC22A6)</td>
<td>Para-aminoglutamic acid, adefovir, cidoflovir, zidovudine*, lamivudine*, zalcitabine*, acyclovir*, tenofovir*, ciprofloxacin*, methotrexate*</td>
<td>Probendicil*, novobiocin</td>
<td>Kidney proximal tubule, placenta</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>OAT3 (SLC22A8)</td>
<td>Oestrone-3-sulphate, non-steroidal anti-inflammatory drugs, celecoxib, cetuximab, furosemide*, bumetanide*</td>
<td>Probendicil*, novobiocin</td>
<td>Kidney proximal tubule, choroid plexus, blood–brain barrier</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>OCT2 (SLC22A2)</td>
<td>N-Methylpyridinium, tetraethylammonium, metformin*, pindolol, procainamide, ranitidine amantadine, amiloride, oxisleptin, veramidine*</td>
<td>Cimetiidine*, pilicaainide*, cetirizine*, testosterone, quinidine</td>
<td>Kidney proximal tubule, neurons</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>OATP1A2/OATP-A (SLCO2A2)</td>
<td>Oestrone-3-sulphate, dihydroxyprogesterone, oestrone sulphate, fosfomycin*, bile salts, methotrexate, bromosulphonphthalaein, ouabain, digoxin, levofloxacin, sterins*</td>
<td>Narinavir, ritonavir, lapinavir, saquinavir, rifampicin*</td>
<td>Kidney proximal tubule, cholangiocytes, distal nephron</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>OCT1 (SLC22A1)</td>
<td>Tetrathymanol, N-methylpyridinium, metformin*, oxalacetin</td>
<td>Quinine, quinidine, disopyramide</td>
<td>Hepatocytes (sinusoids), intestinal enterocytes</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>PEPT1 (SLC15A1)</td>
<td>Glycyglycine, cephalosin, cephalosporin, benzylpenicillin, enalapril, amiodarone, acid, captopril, dipeptides, tripeptides</td>
<td>Glycyl-proline</td>
<td>Intestinal enterocytes, kidney proximal tubule</td>
<td>Has a role in absorption, disposition and excretion</td>
</tr>
<tr>
<td>PEPT2 (SLC15A2)</td>
<td>Glycyglycine, cephalosin, cephalosporin, benzylpenicillin, enalapril, amiodarone, acid, captopril, dipeptides, tripeptides</td>
<td>Zofenopril, fosinopril</td>
<td>Kidney proximal tubule, choroid plexus, lung</td>
<td>Has a role in excretion</td>
</tr>
<tr>
<td>MATE1 (SLC47A1)</td>
<td>Metformin, N-methylpyridinium, tetraethylammonium</td>
<td>Quinine, cinemidine, procainamide</td>
<td>Kidney proximal tubule, liver (canalicular membrane), skeletal muscle</td>
<td>Has a role in disposition and excretion</td>
</tr>
<tr>
<td>MATE2 (SLC47A2)</td>
<td>Metformin, N-methylpyridinium, tetraethylammonium</td>
<td>Cinemidine, quinine, pramipexole</td>
<td>Kidney proximal tubule</td>
<td>Has a role in disposition and excretion</td>
</tr>
</tbody>
</table>

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

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Giacomini et al., *Nature Rev Drug Disc* 2010

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Membrane Transporters in Drug Development

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White Paper 2010
P-gp/BCRP Inhibition Tree

Bicirectional transport assay with a probe P-gp substrate (e.g., in Caco-2 or MDR1-overexpressing polarized epithelial cell lines)

- Net flux ratio of a probe substrate decreases with increasing concentrations of the investigational drug
  - Probably a P-gp inhibitor
    - Determine $K_i$ or $IC_{50}$ of the inhibitor
      - $[I]_1/IC_{50}$ (or $K_i$) $\geq 0.1$ or $[I]_2/IC_{50}$ (or $K_i$) $\geq 10$
        - An in vivo drug interaction study with a P-gp substrate such as digoxin is recommended
      - $[I]_1/IC_{50}$ (or $K_i$) $< 0.1$ and $[I]_2/IC_{50}$ (or $K_i$) $< 10$
        - An in vivo drug interaction study with a P-gp substrate is not needed

- Net flux ratio of a probe substrate is not affected by increasing concentrations of the investigational drug
  - Poor or noninhibitor
# The Biopharmaceutics Classification System and Transporters

<table>
<thead>
<tr>
<th>High Solubility</th>
<th>Low Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Permeability</strong></td>
<td><strong>Low Permeability</strong></td>
</tr>
<tr>
<td><strong>Class 1</strong> (High Solubility, High Permeability)</td>
<td><strong>Class 2</strong> (Low Solubility, High Permeability)</td>
</tr>
<tr>
<td>Metabolism</td>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td>“High hepatic extraction”</td>
<td>Efflux transporter effects predominate</td>
</tr>
<tr>
<td>Transporter effects minimal</td>
<td></td>
</tr>
<tr>
<td><strong>Class 3</strong> (High Solubility, Low Permeability)</td>
<td><strong>Class 4</strong> (Low Solubility, Low Permeability)</td>
</tr>
<tr>
<td>Renal and/or Biliary Elimination</td>
<td>Renal and/or Biliary Elimination</td>
</tr>
<tr>
<td>Absorptive transporter effects predominate</td>
<td>Absorptive and efflux transporter effects could be important</td>
</tr>
</tbody>
</table>

From G. Amidon, Pharm. Res, 12, 413, 1995 and C.Y. Wu, Pharm Res, 22, 11, 2005
PHARMACOKINETIC ROLE OF TRANSPORTERS

ORAL EXPOSURE

INTESTINE (enterocyte)

LIVER (hepatocyte)

KIDNEY (tubule proximal cell)

BRAIN (brain microcapillary endothelial cell)

BBB

Absorption

Secretion

Reabsorption

Excretion

Filtration

Efflux

Uptake

From JM SCHERRMANN-Comprehensive Med.Chem, 2007
Drugs as substrate, inhibitor or regulator?

And Candidates for DDI?

INHIBITION
MDR Reversal

TRANSPORTER PROTEIN

TRANSPORT
SUBSTRATE

EXPRESSION

(Induction or Repression of Regulation Pathways Genetic Polymorphisms)
IMPACT OF TRANSPORTERS ON DRUG ABSORPTION

**INTESTINAL LUMEN**

**SYSTEMIC BLOOD**

- MRP5
- MRP4
- MRP3
- OCT1
- MCT1
- MRP2
- BCRP
- MDR1
- OATP1A2
- OATP2B1
- OATP3A1
- OATP4A1
- PEPT1
- MCT1

Basolateral membrane

Apical (brush border) membrane
FRUIT JUICE, A GLASS FULL OF DRUG INTERACTIONS

Fexofenadine (57 %), Talinolol (44 %), Celiprolol (87 %)

From DG Bailey et al, CPT, 81, 2007
BIOAVAILABILITY OF FEXOFENADINE

Influence of delay between grapefruit juice and fexofenadine intake

<table>
<thead>
<tr>
<th>Herb</th>
<th>Active compounds</th>
<th>Transporter target</th>
<th>DDI risks</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhubarb</td>
<td>Anthraquinones</td>
<td>OAT1 OAT3 (kidney)</td>
<td>Yes Inhibition</td>
<td>Ma L J. Ethnopharmacol 2014</td>
</tr>
<tr>
<td>Turmeric (Curcuma longa)</td>
<td>Curcumin</td>
<td>ABCA1 ABCB1 ABCC1 ABCG2</td>
<td>Inhibition (MDR reversal)</td>
<td>Zhang X Front. Physiol 2014</td>
</tr>
<tr>
<td>Danshen</td>
<td>Rosmarinic acid Tanshinol Lithospermic acid</td>
<td>OAT1 OAT3 (kidney)</td>
<td>Yes Inhibition</td>
<td>Wang L Drug Metab Pharmacokinet. 2013</td>
</tr>
<tr>
<td>Huang-Qin-Tang</td>
<td>Multiple</td>
<td>MCT1 (intestine and BBB)</td>
<td>Yes Inhibition</td>
<td>Yu CP Phytomedicine 2013</td>
</tr>
<tr>
<td>Yanhusuo (YHS)</td>
<td>glaucine</td>
<td>ABCB1 ABCC1</td>
<td>Yes Inhibition (MDR reversal)</td>
<td>Lei Y Food Chem 2013</td>
</tr>
</tbody>
</table>
IMPACT OF TRANSPORTERS ON DRUG AT THE HEPATO-BILIARY LEVEL

From JM SCHERRMANN-Comprehensive Med.Chem, 2007
DRUG INTERACTIONS MEDIATED BY TRANSPORTERS

CERIVASTATIN (0.2 mg/d)-CYCLOSPORINE (400mg/d)
in kidney transplant recipients
⇒ Myopathy and Rhabdomyolysis

From W. Muck, Clin Pharmacol Ther, 65, 251, 1999

AUC X 5
SIROLIMUS AUC X 3
TACROLIMUS AUC X 1,3

Pgp
CsA
(Ki≈0,2µM)
Cerivastatin

CYP3A
bile

CsA
(IC$_{50}$ ≈30µM)

SNP
c521T>C
Atorvastatin

OATP1B1

⇒ Effect
⇒ Rhabdomyolysis (OR 16)

Link et al, NEJM 2010
**Pravastatine**

**Posologie usuelle:** 40 mg/j  
**Extrêmes:** 10-40 mg/j  
**Forme lactone:** Non

**LogP:** -0,2  
**Liaison aux protéines:** 48%  
**$T_{1/2}$:** 1-3 h  
**$V_d$:** 35 L (0,5 L/kg)  
**$C_{l_{tot}}$:** 945 mL/min
**Posologie usuelle**: 5-10 mg/j  
**Extrêmes**: 5-40 mg/j  
**Forme lactone**: Non

**LogP**: -0.3  
**T_{1/2}**: 20 h  
**Vd**: 134 L  
**Cl_{tot}**: 833 mL/min

**Liaison aux protéines**: 90%  
**Tmax**: 3 h
HEPATIC UPTAKE AND BILIARY EXCRETION OF VALSARTAN

Valsartan (angiotensin II AT1-receptor antagonist)

Absorption ($F \approx 30\text{-}50\%$)
Faecal excretion $\approx 85\%$ (bile)
$V_{ss} \approx 17\ L$
$Cl_t \approx 2.2\ L/h$
$t_{1/2} \approx 7\ h$

From W. Yamashiro et al, Drug Metab Dispo. 2006
IMPACT OF TRANSPORTERS ON DRUG DISTRIBUTION
BLOOD-BRAIN BARRIER

BLOOD

BCRP

MDR1

MRP4-5

MCT1

OATP1A2

URAT1

OCTN2

BRAIN

MRP1-2-3-5-6

MCT1

OAT3

tight junctions

abluminal membrane

luminal membrane
P-Glycoprotein and Breast Cancer Resistance Protein: Two Dominant Transport Working Together in Limiting the Brain Penetration of Topotecan

- Erlotinib, Gefitinib, Lapatinib, Imatinib
- Flavopiridol, Mitoxantrone, Prazosin

Topotecan IV 5 mg/kg

« Synergistic Effect of P-gp and BCRP on common substrates »
IMAGING P-GLYCOPROTEIN TRANSPORT ACTIVITY AT THE HUMAN BBB WITH PET

Magnetic resonance image

$^{11}$C-Verapamil

Control + CSA

L. Sasongko et al, CPT, 2005

J. Bart, NeuroImage, 2003
IMpact of transporters on drug elimination

Renal level

Wartime tactic doubles power of scarce bird-flu drug

Phosphate d’Oseltamivir (Tamiflu®)

PK
Estérases

Carboxylate d’Oseltamivir

PD
neuraminidases (virus grippal)

\[ V \approx 25 \text{ L} \]
\[ f_{u_p} = 0.97 \]
\[ t_{1/2} = 6-10 \text{ h} \]
\[ \text{Clr} (\# 100\text{Cl}\text{t}) \]
\[ \text{Clr} = 250 \text{ ml/min} \]

activité extracellulaire

Nature 438, 3 novembre 2005
Wartime tactic doubles power of scarce bird-flu drug

Transporter-mediated Drug Interactions: OAT1, SLC22A1

Renal tubules

BLOOD LEVELS OF TAMIFLU

Concentration of Tamiflu’s active ingredient in the blood (ng ml⁻¹)

Time (h)

Tamiflu and probenecid
Tamiflu alone

Nature 438, 3 novembre 2005
Transporter-mediated Drug Interactions at Kidney

- **Paraquat**, 1-methyl-4-phenyl pyridinium (MPP⁺)
  - Lee W.K, Curr Drug Metab 2009
- **Pralidoxime**, (Antidote of organophosphate)
  - Renal secretion mediated by OCT1/2
  - Kayouka M, Crit Care Med, 2011

*From Koepsell and Endou, Eur J Physiol, 447, 666, 2004*
QUESTIONS ?
Question: Quantitative Prediction of in vivo Drug Interaction?

(I) *In vitro - in vivo* correlation

R = fold systemic AUC change (≈ CYP-based drug interactions)

\[ R = \frac{\text{AUC (inhibitor)}}{\text{AUC}} = \frac{1}{f_{\text{Cl}}} \left( 1 + \frac{f_u [I]}{K_i} \right) + 1 - f_{\text{Cl}} \]  

\( K_i = \) in vitro inhibition constant

\([I] = \) inhibitor plasma concentration

\( f_u = \) unbound plasma fraction

\( f_{\text{Cl}} = \) fraction of the total clearance mediated by the affected transporter

If \( f_{\text{Cl}} = 1 \)

\[ R = 1 + f_u \frac{[I]}{K_i} \]  

(2)
(1) *In vitro - in vivo* correlation

\[ R = \frac{AUC_I}{AUC} \]

From CJ. Endres, Eur J Pharm Sci 27, 501, 2006
(II) Quantitative prediction of *in vivo* drug interaction

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitor</th>
<th>Site of interaction</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$f_u$</td>
</tr>
<tr>
<td>Verapamil</td>
<td>CsA</td>
<td>Brain distribution</td>
<td>0.02$^{b,d}$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Itraconazole</td>
<td>Oral Cl</td>
<td>0.002$^a$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Ritonavir</td>
<td>Oral Cl</td>
<td>0.01$^e$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Ritonavir</td>
<td>Oral Cl</td>
<td>0.01$^e$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Quinidine</td>
<td>Biliary Cl</td>
<td>0.13$^e$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Verapamil</td>
<td>Biliary Cl</td>
<td>0.13$^e$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Itraconazole</td>
<td>Biliary Cl</td>
<td>0.002$^e$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Quinidine</td>
<td>Renal Cl</td>
<td>0.13$^e$</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Ritonavir</td>
<td>Renal Cl</td>
<td>0.01$^e$</td>
</tr>
</tbody>
</table>

- For explanation of symbols, see Section 4.
- He and Liu (2002).
- Sasonko et al. (2005).
- Hardman et al. (2001).
- Woodland et al. (1998).
- Jalava et al. (1997).
- Wandel et al. (1999).
- Hedman et al. (1990).
- Wandel et al. (1999).
- Ekins et al. (2001).
- Penzak et al. (2004).
- Ding et al. (2004).
Question: **Interspecies differences in Transporter Expression**

ABC and SLC differences between species in brain microvessels

K. Ball *et al.*, AAPS J., 2013
**Question**: Are in vitro models reproducing the in vivo conditions

ABC differences between *in vivo / in vitro* BBB (hCMEC/D3)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Relative Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR1</td>
<td>~0.001</td>
</tr>
<tr>
<td>BCRP</td>
<td>~0.01</td>
</tr>
<tr>
<td>MRP1</td>
<td>~1</td>
</tr>
<tr>
<td>MRP4</td>
<td>~10</td>
</tr>
<tr>
<td>MRP5</td>
<td>~100</td>
</tr>
</tbody>
</table>

Relative to human brain microvessels

S. Dauchy *et al.*, Biochem. Pharmacol., 2009
Question: role of active metabolites?

P-gp Efflux Ratio for Opioids

N. Tournier, Curr Pharm Design, 2011
Questions: Many others……

- Impact of Quantitative Proteomic MS-MS on transportome atlas - *the Terasaki Dream* –
- From single transfected cell models to quadruple transfected systems – *J. König* –
- Computational prospecting for drug-transporter Interactions
- Development of non-invasive technologies including imaging
- Ontogeny in the expression and localization of transporters in different tissues
- Establish clinically important transporter polymorphisms
- Intracellular concentrations: measurement modeling implications for the liver
WHERE IN ADME ?
FROM ADME TO ADE?

THE ADE-TM triangles:

« Transport and Metabolism are Effectors of the time course of Drug Absorption, Distribution, and Elimination »