Pharmacogenetics of Drug Transport
(Part 5 in series)

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Disclosure

• I declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Outline

• Function and tissue distribution of drug transporters

• Genetic variation of drug transporters and its clinical significance
Transporters: ABC’s and SLC’s

• Transporters are classified by mechanism and genetic sequence
• Most drug transporters can be classified as a member of either the ABC or SLC Family
  – ATP-Binding Cassette Transporter Family
  – Solute Carrier Transporter Family
**ATP-Binding Cassette Transporters**

- Function to transport substances across biological membranes
  - Low MW compounds to polypeptides
- **ABC** transporters categorized into seven subfamilies based on phylogenetic analysis
  - ABCA to ABCG
  - 48 human ABC transporters
  - Common substrate characteristics between members of particular subfamilies
**ATP-Binding Cassette Transporters**

- Multidrug Resistance Protein
  - P-gp (MDR1 or **ABCB1**)
- Bile Salt Export Pump
  - BSEP (**ABCB11**)
- Multidrug Resistance-associated Proteins
  - MRP1 - MRP9 (**ABCC** subfamily)
- Breast Cancer Resistance Protein
  - BCRP (**ABCG2**
SoLute Carrier Transporters

- Most drug transporters belong to the SLC family
- ~350 transporters
- Do not contain ATP binding sites
- Transport diverse ionic and nonionic compounds – endogenous and xenobiotics

[Image from University of Florida]
SoLute Carrier Transporters

• Organic Anion Transporter Polypeptides
  – (OATPs)
• Organic Cation Transporters
  – (OCTs)
• Organic Anion Transporters
  – (OATs)
• Nucleoside Transporters
  – (CNTs, ENTs)
• And more...
Important role of drug transporters in ADME

- **Absorption** – Intestine
- **Distribution** – Brain, testis, fetus
- **Metabolism** – Liver
- **Elimination** – Biliary and renal
http://www.nature.com/nrd/journal/v9/n3/fig_tab/nrd3028_F1.html
Transporters and Pharmacokinetics

Intestinal transport

Giacomini Kathleen M, Sugiyama Yuichi. Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 11e
Transporters and Pharmacokinetics

Adapted from
Giacomini Kathleen M, Sugiyama Yuichi. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e
Transporters and Pharmacokinetics

Hepatic transport

Giacomini Kathleen M, Sugiyama Yuichi. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e
Genetic polymorphisms of drug transporters

- SCLO1B1 (OATP1B1)
- ABCG2 (BCRP)
- ABCB1 (MDR1, P-gp)
- SLC22A1 (OCT1)
**OATP1B1**

- SLC transporter, encoded by SLCO1B1 gene
- Expressed on the basolateral membrane of hepatocytes in human liver
- OATP1B1 mediates *uptake* of substrates from the blood into the liver
OATP1B1

Selected substrates

- Atorvastatin
- Enalapril
- Erythromycin
- Flavopiridol
- Lopinavir
- Maraviroc
- Methotrexate
- Nateglinide
- Pitavastatin
- Pravastatin
- Repaglinide
- Rosuvastatin
- Simvastatin

The c.521T>C variant, rs4149056, produces a p.V174A substitution and is contained within $SLCO1B1^*5$, $*15$, and $*17$ haplotypes.

*Clinical Pharmacology & Therapeutics* (2013); 94 1, 23–26. doi:10.1038/clpt.2013.12
CPIC Guideline: Assignment of likely SLC01B1 phenotype based on genotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype definition</th>
<th>Examples of diplotypes</th>
<th>Genotype at rs4149056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function; homozygous wild type or normal (55–88% of patients)</td>
<td>An individual carrying two normal-function alleles</td>
<td>*1a/*1a, *1a/*1b, *1b/*1b</td>
<td>TT</td>
</tr>
<tr>
<td>Intermediate function; heterozygous (11–36% of patients)</td>
<td>An individual carrying one normal-function allele plus one decreased-function allele</td>
<td>*1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17</td>
<td>TC</td>
</tr>
<tr>
<td>Low function; homozygous variant or mutant (0–6% of patients)</td>
<td>An individual carrying two decreased-function alleles</td>
<td>*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17</td>
<td>CC</td>
</tr>
</tbody>
</table>

*Clinical Pharmacology & Therapeutics (2014); 96 4, 423–428.*
SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid.

Pharmacogenetics and Genomics. 16(12):873-879.
DOI: 10.1097/01.fpc.0000230416.82349.90

Fig. 1b  Mean+/-SEM plasma concentrations of simvastatin acid (b) after a single 40-mg oral dose of simvastatin in 31 healthy Caucasians in relation to the SLCO1B1 c.521T>C SNP. Open squares indicate individuals with the c.521TT genotype (n=16); solid squares indicate individuals with the c.521TC genotype (n=11); solid triangles indicate individuals with the c.521CC genotype (n=4).
Effects of the SLCO1B1 c.521T>C (*5) variant on (A) simvastatin acid plasma concentrations (40-mg SD) and (B) cumulative incidence of myopathy during treatment with 80 mg/day simvastatin.
Statin exposure (AUC) and the \textit{SLCO1B1} c.521CC (\text{*5}) Genotype
P-glycoprotein (P-gp)

- ABC transporter, encoded by $ABCB1$ gene
- The most well characterized drug transporter
- Originally discovered in MDR cancer cells
- Extensively expressed in the intestine, liver, kidney, blood brain barrier, blood-placenta barrier
- Over 100 polymorphisms with a MAF > 5%
- C3435T is the most commonly studied variant
### P-gp substrates

#### Anticancer agents
- Actinomycin D
- Daunorubicin
- Docetaxel
- Doxorubicin
- Etoposide
- Imatinib
- Irinotecan
- Mitomycin C
- Mitoxantrone
- Paclitaxel
- Teniposide
- Topotecan
- Vincristine
- Vinblastine

#### Antimicrobial agents
- Doxycycline
- Erythromycin
- Itraconazole
- Ketoconazole
- Levofloxacin
- Rifampin
- Sparfloxacin
- Tetracycline

#### Antipsychotics
- Aripiprazole
- Olanzapine
- Paliperidone
- Risperidone

#### Anti-HIV agents
- Amprenavir
- Indinavir
- Neifinavir
- Ritonavir
- Saquinavir

#### Anticonvulsants
- Phenobarbital
- Phenytoin

#### Anti-emetics
- Domperidone
- Ondansetron

#### H2-antagonists
- Cimetidine
- Ranitidine

#### Immunosuppressants
- Cyclosporine
- Sirolimus
- Tacrolimus
- Valspodar

#### Neuroleptics
- Chlorpromazine
- Phenothiazine

#### Steroid hormones
- Aldosterone
- Cortisol
- Dexamethasone
- Methylprednisolone

#### Opioids
- Loperamide
- Morphine
- Pentazocine

#### Others
- Digoxin
- Ivermectin
- Terfenadine
- Vecuronium
Summary

• Drug transporters are important in ADME of substrate drugs.
• Genetic variation is one of the determinants of the expression and activity of drug transporters.
• PK and PD of substrate drugs can be affected by functional genetic polymorphisms, inhibitors, and inducers of drug transporters.
THE PHARMACIST’S ROLE IN CLINICAL PHARMACOGENETICS
Pharmacists and Clinical Pharmacogenomics

Personalized Medicine

**Pharmacists are ideally positioned**

- Experts in pharmacology, pharmacotherapy, and pharmacogenomics
- Traditional role in TDM/Individualized Drug Therapy
- Existing PK/TDM services can incorporate pharmacist-driven clinical pharmacogenomic testing.
Examples of Pharmacist-Led Pharmacogenomics Programs

- UF Personalized Medicine Program
- UI Health Warfarin Genetics Program
- St. Jude PG4KDS Program
Personalized Medicine

Clinical pharmacist’s role – multifaceted

• Choosing genotype platform/content
• Building clinical decision support
• Clinical interpretation of test results
• Facilitating communication among multi-disciplinary team members
• Providing education
  – Health care providers
  – Patients