Databases 101 for Clinical Pharmacologists: What You Need to Know

Tools and Resources for Membrane Transporters

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2017
“We have a problem with one of our drug in Phase 3 clinical trial.”
Phase 3 Trial in Africa Anti-Tuberculosis

Kenya

Substrate of \textit{SLCO1B1} + Inhibitor

Uptake of Tuberzid®

Reported Side Effects

\begin{itemize}
  \item Seizures
  \item Bilirubin
\end{itemize}

\textit{What could cause this serious side effects?}

Clinical Pharmacologist Team

Hypothetical Example
Where can we find these information about SLCO1B1?

SLCO1B1 SNPs and Allele Frequency in Africans?

SLCO1B1 Expression Levels in Tissues?

Phenotypes Associated with SLCO1B1 variants?

Drugs that Inhibit SLCO1B1?
1. *SLCO1B1* **SNPs** and **Allele Frequencies** in Africans?

- ✔ Pharmacogenetics of Membrane Transporter Database [http://pharmacogenetics.ucsf.edu/](http://pharmacogenetics.ucsf.edu/)
  - ✔ PharmGKB
  - ✔ dbSNP
  - ✔ 1000 Genomes Browser
  - ✔ ExAC
  - ✔ Exome Variant Server
  - ✔ DiscovEHR
  - ✔ SPHINX
Obtain SNP Information for Transporter Gene and in Different Ethnic Populations

http://pharmacogenetics.ucsf.edu/
Example of SNP Information for SLCO1B1 in Different Ethnic Populations

http://pharmacogenetics.ucsf.edu/
SNP Information for SLCO1B1 in Different Ethnic Populations

Variant Data

Variant Data

1000 Genomes

1000 Genomes

SNPs

Colors:
- raw exp space
- intronic
- coding exon
- exon
- nonsynonymous snp
- synonymous snp
- indel snp
- promoter
- noncoding exon

Study Name: SLCO1B1 Resequencing
Experiments:
- SLC01B1-P
- SLC01B1_Exon_1
- SLC01B1_Exon_2
- SLC01B1_Exon_3
- SLC01B1_Exon_4
- SLC01B1_Exon_5
- SLC01B1_Exon_6
- SLC01B1_Exon_7
- SLC01B1_Exon_8
- SLC01B1_Exon_9
- SLC01B1_Exon_10
- SLC01B1_Exon_11
- SLC01B1_Exon_12
- SLC01B1_Exon_13
- SLC01B1_Exon_14
- SLC01B1_Exon_15a
- SLC01B1_Exon_15b
- SLC01B1_Exon_15c

PMT impact: P - Public D - Discovered E - Exclusive (dbSNP build 142)
Array availability: C - found on Illumina Human 1M-Duo BeadChip (2011-04-21) A - found on Affymetrix Genome-Wide SNP Array 6.0 (2011-06-21)
Download the SNP table data as a tab-delimited file.
### SNP Information for SLC01B1 in Different Ethnic Populations

<table>
<thead>
<tr>
<th>Gene region, rsID, Position, Transcript and Coding position, Nucleotide change</th>
</tr>
</thead>
</table>

#### 1000 Genomes

26 Populations across 5 Subpopulations (African, Ad Mixed American, East Asian, European, South Asian)

#### Who are these 26 Populations?

<table>
<thead>
<tr>
<th>Feature</th>
<th>PMT ID</th>
<th>rsSNP</th>
<th>Array Availability</th>
<th>Genomic Position</th>
<th>Transcript Position</th>
<th>Coding Position</th>
<th>Nucleotide Change</th>
<th>Strand</th>
<th>Amino Acid Position</th>
<th>Amino Acid Change</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 Populations across 5 Subpopulations (African, Ad Mixed American, East Asian, European, South Asian)</td>
<td>Who are these 26 Populations?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 1000 Genomes Populations: 5 Subpopulations

#### African
- **ACB**: African-Caribbean
- **ASW**: African American
- **ESN**: Nigeria
- **GWD**: Gambia
- **LWK**: Luhya in Webuye, Kenya
- **MSL**: Mende in Sierra Leone
- **YRI**: Yoruba

#### Asian
- **CHB**: Han Chinese
- **JPT**: Japanese
- **CHS**: Southern Han Chinese
- **CDX**: Chinese Dai
- **KHV**: Vietnamese

#### American
- **MXL**: Mexican
- **PUR**: Puerto Ricans
- **CLM**: Colombians
- **PEL**: Peruvians

#### South Asian
- **ITU**: Indian Telugu
- **GIH**: Gujarati Indian
- **PJL**: Punjabi
- **BEB**: Bengali
- **STU**: Sri Lankan

#### European
- **CEU**: Utah residents
- **TSI**: Toscani in Italia
- **FIN**: Finnish
- **GBR**: British
- **IBS**: Iberian in Spain
### SLCO1B1 SNPs Allele Frequency in Africans?

<table>
<thead>
<tr>
<th>Allele</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACB</td>
<td>2.1%</td>
</tr>
<tr>
<td>ASW</td>
<td>6.6%</td>
</tr>
<tr>
<td>ESN</td>
<td>0.0%</td>
</tr>
<tr>
<td>GWD</td>
<td>0.0%</td>
</tr>
<tr>
<td>LWK</td>
<td>2.0%</td>
</tr>
<tr>
<td>MSL</td>
<td>0.0%</td>
</tr>
<tr>
<td>YRI</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

#### rs4149056

<table>
<thead>
<tr>
<th>Pop.</th>
<th>rs4149056</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEU</td>
<td>14.6%</td>
</tr>
<tr>
<td>ASW</td>
<td>6.6%</td>
</tr>
<tr>
<td>CHB</td>
<td>13.6%</td>
</tr>
<tr>
<td>GIH</td>
<td>1.9%</td>
</tr>
<tr>
<td>MXL</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

**Allele Freq.**

rs4149056

OATP1B1 Val174Ala
SNPs and Allele Frequencies in Different Populations

• Transporters and pharmacogenes focused:
  – http://pharmacogenetics.ucsf.edu/
  – PharmGKB

• Other databases:
  ✓ dbSNP
  ✓ 1000 Genomes Browser
  ✓ ExAC
  ✓ Exome Variant Server
  ✓ DiscovEHR
  ✓ SPHINX
  • All genes
  • SNPs Allele Frequency
  • Other ethnic groups
    (European, Asian, African American)
  • Larger populations
  • Disease populations
2. Where Is SLCO1B1 Expressed?

- Pharmacogenetics of Membrane Transporter Database [http://pharmacogenetics.ucsf.edu/](http://pharmacogenetics.ucsf.edu/)
- GTEx Portal
- UCSF FDA Transportal
- Protein Atlas
- RNASEq Atlas
- Gene Expression across Normal and Tumor tissue (GENT)
- CCLE (>500 Cancer Cell-Lines)
Obtain Expression Levels of Transporter Genes in Different Tissues

http://pharmacogenetics.ucsf.edu/
Obtain Expression Levels of Transporter Genes in Different Tissues

http://pharmacogenetics.ucsf.edu/gtex/index.html

1. Select the Options: ABC, SLC, Both

2. Select the Options: Mean, Median
Comparison of the Transporter Genes Across Different Tissues

1. Select: SLC
2. Select: Median RPKM

Specific vs Ubiquitous

You can sort by tissue

Scroll your pointer to the square box for RPKM value
SLCO1B1 Gene Expression

Type gene name here

One Gene at a Time
Example SLCO2B1 Gene Expression
Expression Levels in Different Tissues and Cell Lines

- **Transporters** focused:
  - **Pharmacogenetics of Membrane Transporter Database**
    - UCSF FDA Transportal

- **All** other genes:
  - GTEx Portal
  - RNAsSeq Atlas
  - Protein Atlas
  - Gene Expression across Normal and Tumor tissue (GENT)
  - CCLE (>500 Cancer Cell-Lines)

• Normal and tumor tissues
3. **Phenotypes** Associated with **SLCO1B1** variants?

- Databases which you can find genetic association of the genes with phenotypes.
  - ✔ PharmGKB
  - ✔ ClinGen
  - ✔ ClinVar
  - ✔ GWAS Catalog
Searching Phenotypes/Traits Associated with a Gene (Transporter) or a Variant

https://www.ebi.ac.uk/gwas/
### Phenotypes/Traits Associated with Variants in SLCO1B1

<table>
<thead>
<tr>
<th>SNP</th>
<th>BAF</th>
<th>p-value</th>
<th>OR</th>
<th>Beta</th>
<th>CI</th>
<th>Region</th>
<th>Location</th>
<th>Function</th>
<th>Reported trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs4148080-C</td>
<td>0.18</td>
<td>6x10^{-21}</td>
<td>12</td>
<td></td>
<td></td>
<td>[NR]</td>
<td>chr12:21224625</td>
<td>intron_variant</td>
<td>Methotrexate clearance (acute lymphoblastic leukemia)</td>
</tr>
<tr>
<td>rs12829704-A</td>
<td>0.19</td>
<td>9x10^{-21}</td>
<td>0.042</td>
<td></td>
<td>[0.032-0.052]</td>
<td>12p12.1</td>
<td>chr12:21235687</td>
<td>Intronic_variant</td>
<td>Blood metabolite levels</td>
</tr>
<tr>
<td>rs4148056-T</td>
<td>0.84</td>
<td>1x10^{-18}</td>
<td>0.049</td>
<td></td>
<td>[0.037-0.061]</td>
<td>12p12.1</td>
<td>chr12:21178616</td>
<td>Missense_variant</td>
<td>Blood metabolite levels</td>
</tr>
<tr>
<td>rs4148056-T</td>
<td>0.84</td>
<td>3x10^{-18}</td>
<td>0.029</td>
<td></td>
<td>[0.023-0.035]</td>
<td>12p12.1</td>
<td>chr12:21178615</td>
<td>Missense_variant</td>
<td>Blood metabolite levels</td>
</tr>
<tr>
<td>rs11045879-C</td>
<td>NR</td>
<td>5x10^{-15}</td>
<td>0.062</td>
<td></td>
<td>[0.044-0.08]</td>
<td>12p12.1</td>
<td>chr12:21229865</td>
<td>Intronic_variant</td>
<td>Metabolite levels</td>
</tr>
<tr>
<td>rs113681054-T</td>
<td>0.184</td>
<td>4x10^{-13}</td>
<td>0.002</td>
<td></td>
<td>[0.03-0.07]</td>
<td>12p12.1</td>
<td>chr12:21250045</td>
<td>Intergenic</td>
<td>AF-C12491XX levels in individuals with acute coronary syndromes treated with ticagrelor</td>
</tr>
<tr>
<td>rs4148056-C</td>
<td>0.15</td>
<td>7x10^{-13}</td>
<td>0.05 umol/L increase in log(bili)</td>
<td>[0.03-0.07]</td>
<td>12p12.1</td>
<td>chr12:21178615</td>
<td>Missense_variant</td>
<td>Bilirubin levels</td>
<td></td>
</tr>
</tbody>
</table>
Phenotypes/Traits Associated with Variants in SLCO1B1

<table>
<thead>
<tr>
<th>SNP</th>
<th>BAF</th>
<th>p-value</th>
<th>OR</th>
<th>BETA</th>
<th>CI</th>
<th>Region</th>
<th>Location</th>
<th>Functional class</th>
<th>Reported gene(s)</th>
<th>Mapped gene(s)</th>
<th>Reported trait</th>
<th>Study</th>
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</thead>
<tbody>
<tr>
<td>rs43638557</td>
<td>NR</td>
<td>9 x 10^-48</td>
<td>X12063 levels</td>
<td>12p12.1</td>
<td>chr12:21215788</td>
<td>intron_variant</td>
<td>SLCO1B1</td>
<td>NR</td>
<td>SLCO1B1</td>
<td>Blood metabolite levels</td>
<td>Korostishevsky M (PMID: 25889820), 2015</td>
<td></td>
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<tr>
<td>rs12317268</td>
<td>0.84</td>
<td>2 x 10^-45</td>
<td>X-14626</td>
<td>0.054 unit decrease</td>
<td>[0.046-0.052]</td>
<td>12p12.1</td>
<td>chr12:21199667</td>
<td>intron_variant</td>
<td>SLCO1B1</td>
<td>Blood metabolite levels</td>
<td>Shin SY (PMID: 24816252), 2014</td>
<td></td>
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<tr>
<td>rs4149056</td>
<td>0.83</td>
<td>9 x 10^-44</td>
<td>X-12456</td>
<td>0.081 unit decrease</td>
<td>[0.069-0.093]</td>
<td>12p12.1</td>
<td>chr12:21178615</td>
<td>missense_variant</td>
<td>SLCO1B1</td>
<td>Blood metabolite levels</td>
<td>Shin SY (PMID: 24816252), 2014</td>
<td></td>
</tr>
<tr>
<td>rs4149056</td>
<td>0.83</td>
<td>3 x 10^-32</td>
<td>X-11491</td>
<td>0.086 unit decrease</td>
<td>[0.072-0.104]</td>
<td>12p12.1</td>
<td>chr12:21178615</td>
<td>missense_variant</td>
<td>SLCO1B1</td>
<td>Blood metabolite levels</td>
<td>Shin SY (PMID: 24816252), 2014</td>
<td></td>
</tr>
<tr>
<td>rs1871395-A</td>
<td>0.84</td>
<td>4 x 10^-31</td>
<td>1-arachidonoyl-sn-glycerophosphoethanolamide</td>
<td>0.04 unit decrease</td>
<td>[0.034-0.046]</td>
<td>12p12.1</td>
<td>chr12:21199381</td>
<td>intron_variant</td>
<td>SLCO1B1</td>
<td>Blood metabolite levels</td>
<td>Shin SY (PMID: 24816252), 2014</td>
<td></td>
</tr>
<tr>
<td>rs4149081-A</td>
<td>0.205</td>
<td>3 x 10^-22</td>
<td>SM-10 + 59 other traits</td>
<td>0.209 unit decrease</td>
<td>[NR]</td>
<td>12p12.1</td>
<td>chr12:21222907</td>
<td>intron_variant</td>
<td>SLCO1B1</td>
<td>Metabolic traits</td>
<td>Suhe K (PMID: 21888157), 2011</td>
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<tr>
<td>rs4149081</td>
<td>?</td>
<td>4 x 10^-22</td>
<td>Bilirubin levels</td>
<td>Bilirubin levels</td>
<td>12p12.1</td>
<td>chr12:21222907</td>
<td>intron_variant</td>
<td>SLCO1B1</td>
<td>Clinical lab measurements</td>
<td>Verma SS (PMID: 27897004), 2016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. **Drugs** that Inhibit *SLCO1B1*?

- Manually curated databases which provide information about drug interaction.
  - [UCSF-FDA TransPortal](#)
  - [P450 Drug Interaction Table](#) (Flockhart Table™)
  - [Drug Interaction Database](#)
Welcome to the FDA Transporter Database page. The purpose of this database is to be a useful repository of information on transporters important in the drug discovery process as a part of the US Food and Drug Administration-led Critical Path Initiative. Information includes transporter expression, localization, substrates, inhibitors, and drug-drug interactions.

A list of key transporters important in drug discovery
Are those patients with severe side-effects on another drug that inhibit OATP1B1?

### Clinical Drug-Drug Interactions

<table>
<thead>
<tr>
<th>DDI</th>
<th>Implicated Transporter</th>
<th>Interacting Drug</th>
<th>Affected Drug</th>
<th>AUC</th>
<th>Cmax</th>
<th>CLR</th>
<th>CL/F</th>
<th>t1/2</th>
<th>Effect on PD</th>
<th>Reference</th>
<th>More Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ABCG2/OATPs</td>
<td>Atazanavir / Ritonavir</td>
<td>Rosuvastatin</td>
<td>3.1</td>
<td>7.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Busti, 2008</td>
<td>DDI 1</td>
</tr>
<tr>
<td>2</td>
<td>ABCB1/OATPs</td>
<td>Cyclosporine</td>
<td>Docetaxel</td>
<td>7.3</td>
<td>5.7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Malingre, 2001</td>
<td>DDI 2</td>
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<tr>
<td>3</td>
<td>ABCB1/OATPs</td>
<td>Cyclosporine</td>
<td>Paclitaxel</td>
<td>8.5</td>
<td>2.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Meerum, 1999</td>
<td>DDI 3</td>
</tr>
<tr>
<td>4</td>
<td>ABCG2/OATPs</td>
<td>Cyclosporine</td>
<td>Pitavastatin</td>
<td>4.6</td>
<td>6.6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Livaco Drug Label</td>
<td>DDI 4</td>
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<tr>
<td>5</td>
<td>ABCG2/OATPs</td>
<td>Cyclosporine</td>
<td>Rosuvastatin</td>
<td>5.0</td>
<td>10.6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Simonson, 2004</td>
<td>DDI 5</td>
</tr>
<tr>
<td>6</td>
<td>ABCG2/OATPs</td>
<td>Cyclosporine</td>
<td>Rosuvastatin</td>
<td>6.4</td>
<td>18.2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Simonson, 2004</td>
<td>DDI 6</td>
</tr>
<tr>
<td>7</td>
<td>ABCB1/OATPs</td>
<td>Erythromycin</td>
<td>Simvastatin</td>
<td>6.2</td>
<td>3.5</td>
<td>ND</td>
<td>ND</td>
<td>NS</td>
<td>ND</td>
<td>Kantola, 1998</td>
<td>DDI 7</td>
</tr>
<tr>
<td>8</td>
<td>ABCB1/OATPs</td>
<td>Indinavir / Ritonavir</td>
<td>Fexofenadine</td>
<td>4.8</td>
<td>2.5</td>
<td>ND</td>
<td>0.2</td>
<td>0.7</td>
<td>ND</td>
<td>Kharasch, 2009</td>
<td>DDI 8</td>
</tr>
<tr>
<td>9</td>
<td>OATPs</td>
<td>Lopinavir / Ritonavir</td>
<td>Rosuvastatin</td>
<td>2.1</td>
<td>4.7</td>
<td>ND</td>
<td>0.5</td>
<td>NS</td>
<td>yes</td>
<td>Kiser, 2008</td>
<td>DDI 9</td>
</tr>
<tr>
<td>10</td>
<td>OATPs</td>
<td>Rifampicin</td>
<td>Glyburide</td>
<td>2.2</td>
<td>1.8</td>
<td>NS</td>
<td>0.5</td>
<td>ND</td>
<td>yes</td>
<td>Zheng, 2009</td>
<td>DDI 10</td>
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<tr>
<td>11</td>
<td>ABCB1/OATPs</td>
<td>Ritonavir</td>
<td>Digoxin</td>
<td>1.9</td>
<td>ND</td>
<td>0.6</td>
<td>0.6</td>
<td>2.6</td>
<td>ND</td>
<td>Ding, 2004</td>
<td>DDI 11</td>
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<tr>
<td>12</td>
<td>ABCB1/OATPs</td>
<td>Ritonavir</td>
<td>Saquinavir</td>
<td>29.9</td>
<td>22.5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>La, 2007</td>
<td>DDI 12</td>
</tr>
<tr>
<td>13</td>
<td>ABCB1/OATPs</td>
<td>Verapamil</td>
<td>Simvastatin</td>
<td>4.6</td>
<td>2.6</td>
<td>ND</td>
<td>ND</td>
<td>NS</td>
<td>ND</td>
<td>Kantola, 1998</td>
<td>DDI 13</td>
</tr>
</tbody>
</table>

The transporters are implicated by in vitro data and/or studies in humans with genetic polymorphisms of the transporter.

DDI = Drug Drug Interaction
PK = pharmacokinetic
PD = pharmacodynamic
ND = not determined
NS = not significant
N/A = information not available

Calculation of Fold Change: fold change in the presence of the interacting drug = (value with interacting drug)/(value without interacting drug)
fold change > 1: increase in pharmacokinetic value
fold change < 1: decrease in pharmacokinetic value

Click “Rifampicin” to find out what other transporter(s) it inhibits.
Summary

http://www.pgrn.org/tools.html
Acknowledgements

Pharmacogenetics of Membrane Transporters (PMT)

Creation of the PMT Website

Kathy Giacomini  Tom Ferrin  Doug Stryke  Pui-Yan Kwok

Funding of PMT

UCSF-FDA TransPortal

Kathy Giacomini  Kari Morrissey  Chris Wen

Lei Zhang  Susan Johns  Shiew-Mei Huang

Funding of TransPortal: FDA
Thank You

Questions About

D A T A B A S E

sookwah.yee@ucsf.edu
If you know what other drugs that were used by patients with the severe side-effects, you can search the drug name in the portal.

### TRIMETHOPRIM

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Synonyms</th>
<th>Inhibitor</th>
<th>IC50 (µM)</th>
<th>Ki (µM)</th>
<th>Substrate used</th>
<th>Cell System</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC22A2</td>
<td>OCT2</td>
<td>Trimethoprim</td>
<td>13.2</td>
<td></td>
<td>Lamivudine</td>
<td>HEK-OCT2</td>
<td>Muller, 2013</td>
</tr>
<tr>
<td>SLC47A2</td>
<td>MATE2K</td>
<td>Trimethoprim</td>
<td>0.66</td>
<td></td>
<td>Lamivudine</td>
<td>HEK-MATE2-K</td>
<td>Muller, 2013</td>
</tr>
<tr>
<td>SLC22A2</td>
<td>OCT2</td>
<td>Trimethoprim</td>
<td>1318</td>
<td></td>
<td>N-methylpyridinium</td>
<td>HEK293-OCT2</td>
<td>Zolk, 2009</td>
</tr>
</tbody>
</table>

### Clinical Drug-Drug Interactions

<table>
<thead>
<tr>
<th>DDI</th>
<th>Implicated Transporter*</th>
<th>Interacting Drug</th>
<th>Affected Drug</th>
<th>AUC</th>
<th>Cmax</th>
<th>CLR</th>
<th>CL/F</th>
<th>t1/2</th>
<th>Effect on PD</th>
<th>Reference</th>
<th>More Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SLC47A1</td>
<td>Trimethoprim</td>
<td>Metformin</td>
<td>1.295</td>
<td>ND</td>
<td>0.736</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Muller, 2015</td>
<td>DDI 1</td>
</tr>
<tr>
<td>2</td>
<td>OCTs</td>
<td>Trimethoprim</td>
<td>Zidovudine</td>
<td>NS</td>
<td>ND</td>
<td>0.5</td>
<td>NS</td>
<td>NS</td>
<td>ND</td>
<td>Chatton, 1992</td>
<td>DDI 2</td>
</tr>
</tbody>
</table>

PK = pharmacokinetic
The transporters are implicated by in vitro data and/or studies in humans with genetic polymorphisms of the transporter
DDI = Drug Drug Interaction
PD = pharmacodynamic
ND = not determined
NS = not significant
N/A = information not available
Calculation of Fold Change: fold change in the presence of the interacting drug = (value with interacting drug)/(value without interacting drug)
fold change > 1: increase in pharmacokinetic value
fold change < 1: decrease in pharmacokinetic value
Example SLCO1B1 Gene Expression