Transporter-Mediated Drug-Drug Interactions (DDIs)

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Drug Transporters: Contribute to variability in drug concentration and response

- Pharmacokinetic determinant
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

- Pharmacodynamic determinant
  - Delivery to site of action
  - Control of tissue concentrations
  - Discovery Targets

May cause unexpected toxicities or drug-drug interactions
Selected efflux & uptake transporters in the gut wall (A), liver (B), and kidney (C)

OATP: Organic Anion Transporting Polypeptide

OCT2: Organic Cation Transporter 2
OAT1/3: Organic Anion Transporter 1/3

MDR1: Multi-Drug Resistance 1 (P-glycoprotein, P-gp)
BCRP: Breast Cancer Resistance Protein

In liver, intestine, kidney, brain

## Examples of Transporter-Mediated Drug Interactions

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Affected Drug</th>
<th>Consequence</th>
<th>Fold Changes in Substrate Plasma AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Digoxin</td>
<td>Digoxin Exposure 1.7-fold ↑</td>
<td>P-glycoprotein (P-gp, MDR1) Inhibition</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Digoxin</td>
<td>Digoxin Exposure 30% ↓</td>
<td>P-gp Induction</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Digoxin</td>
<td>Digoxin Exposure 2.6-fold ↑</td>
<td>P-gp Inhibition</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Cephradine</td>
<td>Cephradine Exposure 3.6-fold ↑</td>
<td>Organic Anion Transporter (OAT) Inhibition</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Metformin</td>
<td>Metformin Exposure 1.4-fold ↑</td>
<td>Organic Cation Transporter (OCT) Inhibition</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Rosuvastatin</td>
<td>Rosuvastatin Exposure 7-fold ↑</td>
<td>Organic Anion Transporting Polypeptide (OATP) Inhibition &amp; Breast Cancer Resistance Protein (BCRP) Inhibition</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Rosuvastatin</td>
<td>Rosuvastatin Exposure 2-fold ↑</td>
<td>OATP Inhibition</td>
</tr>
</tbody>
</table>
Which transporters are clinically important and should be considered for evaluation during drug development?

• For new molecular entity (NME) as a substrate
• For new molecular entity (NME) as an inhibitor
International Transporter Consortium

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Joseph A. Ware: Genentech
Maciej Zamek-Gliszczynski: Lilly Research Laboratories

<Huang, SM, Zhang L, Giacomini KM, Clin Pharmacol Ther January 2010>
1. Overview of Transporters
   Overview, P-gp, BCRP, OAT/OCT, OATP (7 transporters)

2. Methods for Studying Transporters
   Cell/membrane models, intact organ/in vivo models; modeling/imaging tools, enzyme/transporter interplay

3. Drug Development Issues
   Overview/example cases; decision trees

Transporters in Drug Absorption
Important Intestine Transporters

**Efflux**
(to intestinal lumen):
- P-glycoprotein (P-gp, MDR1, ABCB1)
- Breast Cancer Resistance Protein (BCRP, ABCG2)

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<tr>
<td>Quinidine</td>
<td>Digoxin</td>
<td>Digoxin Exposure ↑</td>
<td>1.7-fold ↑</td>
</tr>
<tr>
<td>GF120918</td>
<td>Topotecan</td>
<td>Topotecan Exposure ↑</td>
<td>2.4-fold ↑</td>
</tr>
</tbody>
</table>
Transporters in Drug Distribution, Uptake and Excretion—Important Liver Transporters

**Uptake**  
(from blood to hepatocytes):  
- OATP1B1  
- OATP1B3

**Efflux**  
(excretion to bile):  
- P-gp  
- BCRP

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<tbody>
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<td>Rosuvastatin</td>
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</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Rosuvastatin</td>
<td>Rosuvastatin Exposure ↑</td>
<td>2-fold ↑</td>
</tr>
</tbody>
</table>
**Transporters in Drug Distribution, Uptake and Excretion—Important Kidney Transporters**

**Uptake**
(from blood to kidney):
- OCT2
- OAT1
- OAT3

**Efflux**
(secretion to urine)
- P-gp (MDR1)

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<th>Affected Drug</th>
<th>Consequence</th>
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<td>Probenecid</td>
<td>Cephradine</td>
<td>Cephradine Exposure ↑</td>
<td>3.6-fold ↑</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Metformin</td>
<td>Metformin Exposure ↑</td>
<td>1.4-fold ↑</td>
</tr>
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Predicting Drug-Drug Interactions

• By understanding which enzymes or transporters may be involved in the ADME process and the potential for a drug to be a substrate, inhibitor, or inducer of that process, we can predict the potential for drug interactions.

*In Vitro* models/Tools → **Explain** → *In Vivo* DDI Studies → **Predict**
Rosuvastatin-Cyclosporine Interaction

Cyclosporine ↑ 7-fold exposure of Rosuvastatin

Possible mechanism of inhibition by cyclosporine

→ OATP1B1/1B3 (uptake transporter)

→ BCRP (efflux transporter)

OATP-, BCRP-based Interactions

• Cyclosporine inhibits other OATP or BCRP substrates
e.g. Pitavastatin is a substrate of OATP1B1/1B3 and BCRP
  – Cyclosporine ↑ pitavastatin exposure 4.6-fold.

• Rosuvastatin is inhibited by other OATP or BCRP inhibitors
  – Lopinavir/ritonavir ↑ rosuvastatin exposure 2-fold
  – Lopinavir/ritonavir are inhibitors of OATP1B1/1B3 based on *in vitro* studies
Role of transporters in the disposition of a drug

• Can be determined by
  – Genetic studies (polymorphism)
    • Comparative PK in people with gene of normal function vs. reduced/absent function
  – Specific inhibitors
Fold-Change in Plasma AUC
- Effect of Transporter Genetics -

Data from Niemi M, Clin Pharmacol Ther 87:130, January 2010
Relative contribution of each transporter/enzyme on the disposition of statin drugs is different

OATP1B1, BCRP, P-gp
CYP3A4, CYP2C8, CYP2C9

Depending on inhibitor specificity for these transporters/enzymes, interaction with different statins may be different
Evaluation of NME as a Substrate for Transporters—Other Drugs’ Effect on NME

All NMEs

Hepatic or biliary Secretion major? e.g., ≥ 25% total clearance?

Yes

Determine whether NME is a P-gp and/or BCRP substrate *

Refer to P-gp and BCRP decision tree** for the need to conduct in vivo studies

Determine whether NME is an OATP1B1 or OATP1B3 Substrate*

Refer to OATP1B1/1B3 decision tree** for the need to conduct in Vivo studies

Renal active secretion major? e.g., ≥ 25% total clearance?

Yes

Determine whether NME is an OAT1, OAT3 or OCT2 substrate*

Refer to OAT1/3 and OCT2 decision tree** for the need to conduct in vivo studies

* The sponsor has the option to use in vitro tools first for the evaluation.
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter
Evaluation of NME as an Inhibitor for Transporters—NMEs’ Effect on Other Drugs

All NMEs

D

Determine whether NME is an inhibitor for OATP1B1, and/or OATP1B3*

Refer to OATP1B1/1B3 decision tree** for the need to conduct in vivo studies

Is NME likely to be co-administered with known anionic Drugs that are substrates for OAT1/3, e.g., methotrexate, tenofovir, acyclovir?

Yes

Determine whether NME is an Inhibitor for OAT1 or OAT3*

Refer to OAT1/3 and OCT 2 decision tree** for the need to conduct in vivo studies

No

Is NME likely to be co-administered with known cationic drugs that are substrates for OCT2 e.g., metformin?

Yes

Determine whether NME is an inhibitor for OCT2*

No

* The sponsor has the option to use in vitro tools first for the evaluation.

** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter
# Examples of Transporter Substrates

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Gene</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>ABCB1</td>
<td>Aliskiren, ambrisentan, colchicine, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan</td>
</tr>
<tr>
<td>BCRP</td>
<td>ABCG2</td>
<td>Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosvastatin, sulfasalazine, topotecan</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>SCLO1B1</td>
<td>Atrasentan, bosentan, ezetimibe, irinotecan, statins (e.g., atorvastatin, rosvastatin, simvastatin, pitavastatin, pravastatin), repaglinide, rifampin, valsartan, olmesartan</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>SCLO1B3</td>
<td>Statins (e.g., atorvastatin, rosvastatin, pitavastatin), telmisartan, valsartan, olmesartan, rifampin</td>
</tr>
<tr>
<td>OCT2</td>
<td>SLC22A2</td>
<td>Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin</td>
</tr>
<tr>
<td>OAT1</td>
<td>SLC22A6</td>
<td>acyclovir, adefovir, ciprofloxacin, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine</td>
</tr>
<tr>
<td>OAT3</td>
<td>SLC22A8</td>
<td>Bumetanide, cimetidine, furosemide, methotrexate, zidovudine, sitagliptin, tenofovir</td>
</tr>
</tbody>
</table>

Please note this is not an exhaustive list and some are based on in vitro data. For an updated list, see the following: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
Examples of Transporter Inhibitors and Inducers

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Gene</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>ABCB1</td>
<td>Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil</td>
<td>Avasimibe, carbamazepine, phenytoin, rifampin, St John’s Wort, tipranavir/ritonavir</td>
</tr>
<tr>
<td>BCRP</td>
<td>ABCG2</td>
<td>Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib</td>
<td>Not known</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>SCL01B1</td>
<td>Cyclosporine, eltrombopag, lapatinib, lopinavir, rifampin, ritonavir, OATP1B3</td>
<td>Not known</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>SCL01B3</td>
<td>Cyclosporine, lopinavir, rifampin, ritonavir, OCT2</td>
<td>Not known</td>
</tr>
<tr>
<td>OCT2</td>
<td>SLC22A2</td>
<td>Cimetidine, cetirizine, desipramine, quinidine</td>
<td>Not known</td>
</tr>
<tr>
<td>OAT1</td>
<td>SLC22A6</td>
<td>Probenecid, diclofenac</td>
<td>Not known</td>
</tr>
<tr>
<td>OAT3</td>
<td>SLC22A8</td>
<td>Probenecid, cimetidine</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Please note this is not an exhaustive list and some are based on in vitro data. For an updated list, see the following: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
## Transporter Information in Drug Labeling

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Drug Names*</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>Aliskiren, ambrisentan, [aprepitant], <em>clarithromycin</em>, colchicine, <em>cyclosporine</em>, [dexvenafaxine], <em>dronedarone</em>, [eltrombopag], <em>everolimus</em>, fexofenadine, [fosaprepitant], [ixabepilone], <em>lapatinib</em>, <em>maraviroc</em>, <em>nilotinib</em>, <em>paliperidone</em>, posaconazole, [prasugrel], [[propafenone]], propranolol, <em>ranolazine</em>, saxagliptin, silodosin, sirolimus, sitagliptin, <em>tipranavir</em>**, tolvaptan, topotecan, [vorinostat]</td>
</tr>
</tbody>
</table>

| OATP1B1     | **Atorvastatin**, *cyclosporine*, **eltrombopag***, *lapatinib*, valsartan |
| OATP        | Ambrisentan |
| OAT         | Sitagliptin (OAT3) |
| OCT         | Metformin, pramipexole, [saxagliptin], [sitagliptin], varenicline (OCT2) |
| BCRP        | Lapatinib, topotecan |
| MRP         | Mycophenolate (MRP2), [ixabepilone] (MRP1), valsartan (MRP2) |

*Not an extensive list: data based on a preliminary survey of electronic PDR and Drugs@FDA on September 18, 2009. They are substrates, inhibitors, *both substrates and inhibitors*, [not a substrate or an inhibitor], or [[not studies as a substrate or an inhibitor]]; **: Tipranavir is also a P-gp inducer *** an inhibitor; its labeling contains a list of OATP1B1 substrates <Huang, SM, Zhang L, Giacomini KM, Clin Pharmacol Ther, January 2010>
Labeling Example
Atorvastatin
Drug Interactions Section

• 7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see Clinical Pharmacology (12.3)]. In cases where co-administration of LIPITOR with cyclosporine is necessary, the dose of LIPITOR should not exceed 10 mg [see Warnings and Precautions, Skeletal Muscle (5.1)].
7.2 Transporters

In vitro studies demonstrate that eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and can increase the systemic exposure of other drugs that are substrates of this transporter (e.g., benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin). In a clinical study of healthy adult subjects, administration of a single dose of rosuvastatin following repeated daily PROMACTA dosing increased plasma rosuvastatin AUC0-∞ by 55% and Cmax by 103% [see Clinical Pharmacology (12.3)].

Use caution when concomitantly administering PROMACTA and drugs that are substrates of OATP1B1. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and consider reduction of the dose of these drugs. In clinical trials with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for coadministration with eltrombopag.
Conclusion

• Understanding transporters and their interactions provides a mechanistic approach to
  – Explain variability in pharmacokinetics, pharmacodynamics, and safety in clinical trials
  – Identify patients at risk of developing adverse events associated with the drug in question or at risk drug combinations
  – Lead to actionable steps to manage the interactions
Tipping point for specific studies during development

• What are the clinical questions?
• What transporters are mature enough to be studied?
• How to evaluate NME as transporter substrates?
• How to evaluate NME as transporter inhibitors?
• Interplay with metabolizing enzymes?
• What label information would be useful to prescribers?
Questions for the Advisory Committee
Evaluation of NME as a Substrate for Transporters—Other Drugs’ Effect on NME

All NMEs

Hepatic or biliary Secretion major? e.g., ≥ 25% total clearance?

Yes

Determine whether NME is a P-gp and/or BCRP Substrate*

Refer to P-gp and BCRP decision tree** for the need to conduct in vivo studies

Determine whether NME is an OATP1B1 or OATP1B3 Substrate*

Refer to OATP1B1/1B3 decision tree** for the need to conduct in Vivo studies

Renal active secretion major? e.g., ≥ 25% total clearance?

Yes

Determine whether NME is an OAT1, OAT3 or OCT2 substrate*

Refer to OAT1/3 and OCT2 decision tree** for the need to conduct in vivo studies

* The sponsor has the option to use in vitro tools first for the evaluation.
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter
Question 1

For evaluation of NMEs as potential substrates of transporters:

**a.** Do you agree that P-gp, BCRP, OATP1B1/1B3, OAT1/3 and OCT2 are the major transporters that should be routinely evaluated based on the proposed flow chart during drug development? [VOTING]

**b.** What transporter(s) should be included in the flow chart for routine study and why?

**c.** What alternative criteria would you suggest to identify transporters that would have clinical significance and should be studied?
**Evaluation of NME as an Inhibitor for Transporters—NMEs’ Effect on Other Drugs**

- **All NMEs**
  - Determine whether NME is an inhibitor for P-gp or BCRP*:
    - Refer to P-gp and BCRP decision tree** for the need to conduct in vivo studies
  - Determine whether NME is an inhibitor for OATP1B1, and/or OATP1B3*:
    - Refer to OATP1B1/1B3 decision tree** for the need to conduct in vivo studies
  - Is NME likely to be co-administered with known anionic Drugs that are substrates for OAT1/3, e.g., methotrexate, tenofovir, acyclovir?
    - Yes
      - Determine whether NME is an Inhibitor for OAT1 or OAT3*
      - Refer to OAT1/3 and OCT 2 decision tree** for the need to conduct in vivo studies
  - Is NME likely to be co-administered with known cationic drugs that are substrates for OCT2 e.g., metformin?
    - Yes
      - Determine whether NME is an inhibitor for OCT2*

* The sponsor has the option to use in vitro tools first for the evaluation.
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter
Question 2

For evaluation of NMEs as potential inhibitors of transporters:

a. Do you agree that P-gp, BCRP, OATP1B1/1B3, OAT1/3 and OCT2 are the major transporters that should be routinely evaluated based on the proposed flow chart during drug development? [VOTING]

b. What transporter(s) should be included in the flow chart for routine study and why?

c. What alternative criteria would you suggest to identify transporters that would have clinical significance and should be studied?
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- Shiew-Mei Huang
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- Bob Temple
- K. Sandy Pang
- Office of Clinical Pharmacology/OTS
- International Transporter Consortium
- Janet Woodcock/Critical Path Initiative
References

• Transporter Whitepaper

• Commentary
  – Huang and Woodcock, Nature Reviews Drug Discovery 2010, 9, 175-176

• International Transporter Consortium

• Drug Development and Drug Interactions

• Draft Drug Interaction Guidance