



Clinical Pharmacology Advisory Committee Meeting
Topic 4: Transporter-Mediated Drug-Drug Interactions
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Transporter-Mediated Drug-Drug Interactions (DDIs)

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Drug Transporters: Contribute to variability in drug concentration and response

- Pharmacokinetic determinant
 - Absorption
 - Distribution

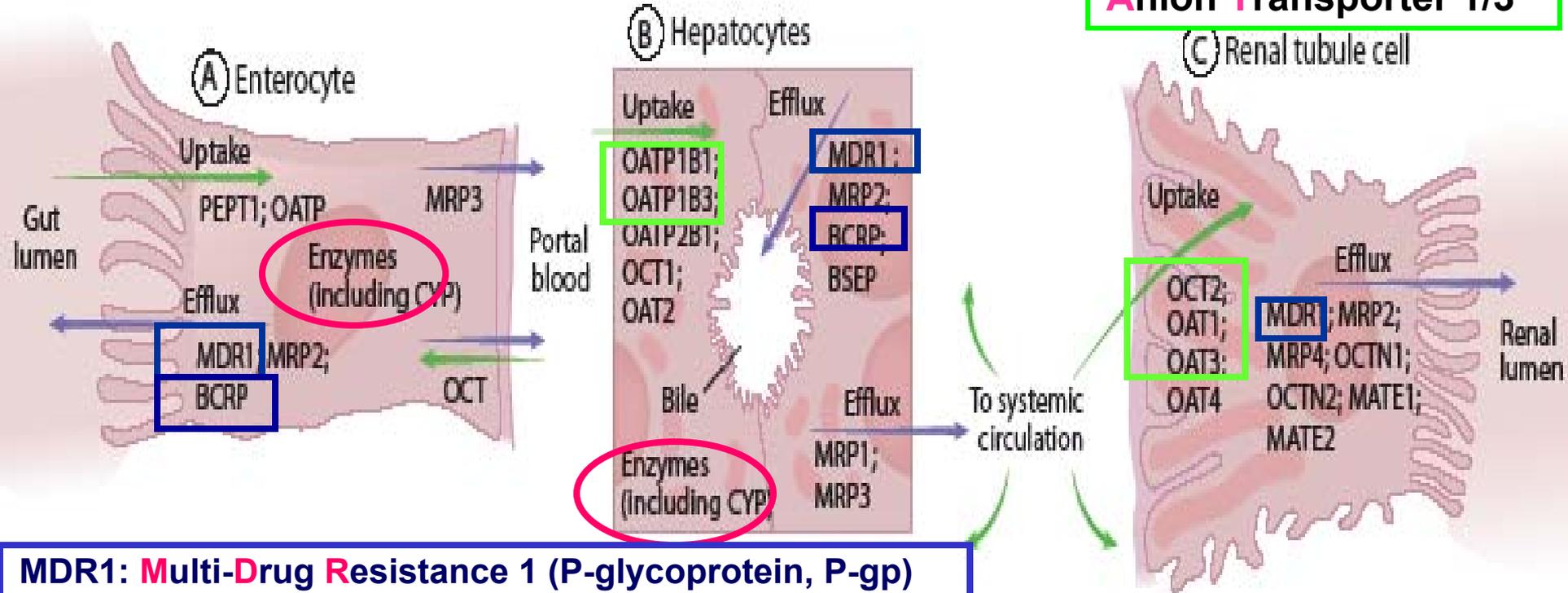
May cause unexpected toxicities or drug-drug interactions

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

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

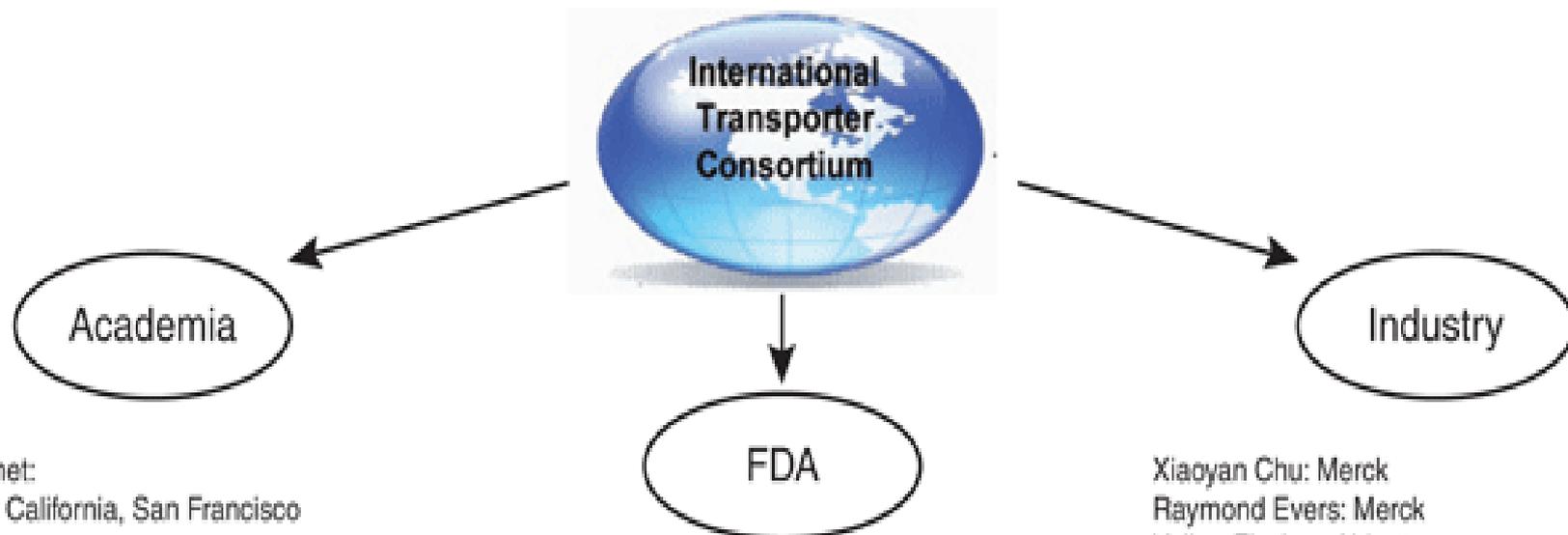
Examples of Transporter-Mediated Drug Interactions

Interacting Drug	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Quinidine	Digoxin	Digoxin Exposure 1.7-fold ↑	P-glycoprotein (P-gp, MDR1) Inhibition
Rifampin	Digoxin	Digoxin Exposure 30% ↓	P-gp Induction
Dronedarone	Digoxin	Digoxin Exposure 2.6-fold ↑	P-gp Inhibition
Probenecid	Cephhradine	Cephhradine Exposure 3.6-fold ↑	Organic Anion Transporter (OAT) Inhibition
Cimetidine	Metformin	Metformin Exposure 1.4-fold ↑	Organic Cation Transporter (OCT) Inhibition
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure 7-fold ↑	Organic Anion Transporting Polypeptide (OATP) Inhibition & Breast Cancer Resistance Protein (BCRP) Inhibition
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure 2-fold ↑	OATP Inhibition

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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***Co-chairs**

Transporter White Paper

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

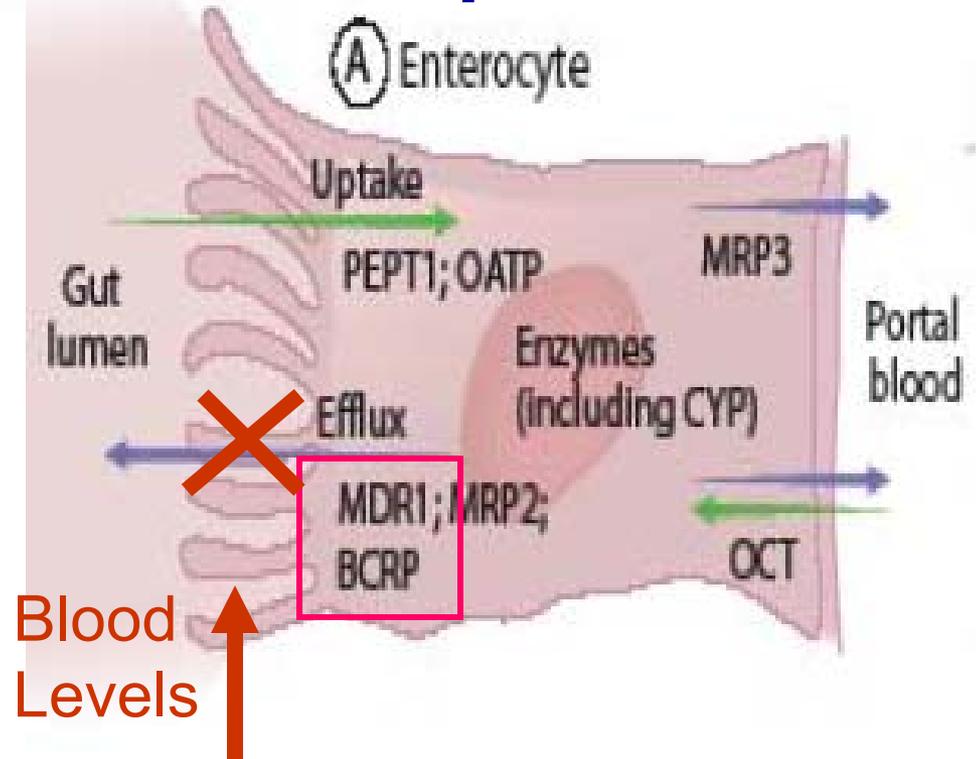
Transporters in Drug Absorption

Important Intestine Transporters

Efflux

(to intestinal lumen):

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



Inhibitor	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Quinidine	Digoxin	Digoxin Exposure ↑	1.7-fold ↑
GF120918	Topotecan	Topotecan Exposure ↑	2.4-fold ↑

Transporters in Drug Distribution, Uptake and Excretion—Important Liver Transporters

Uptake

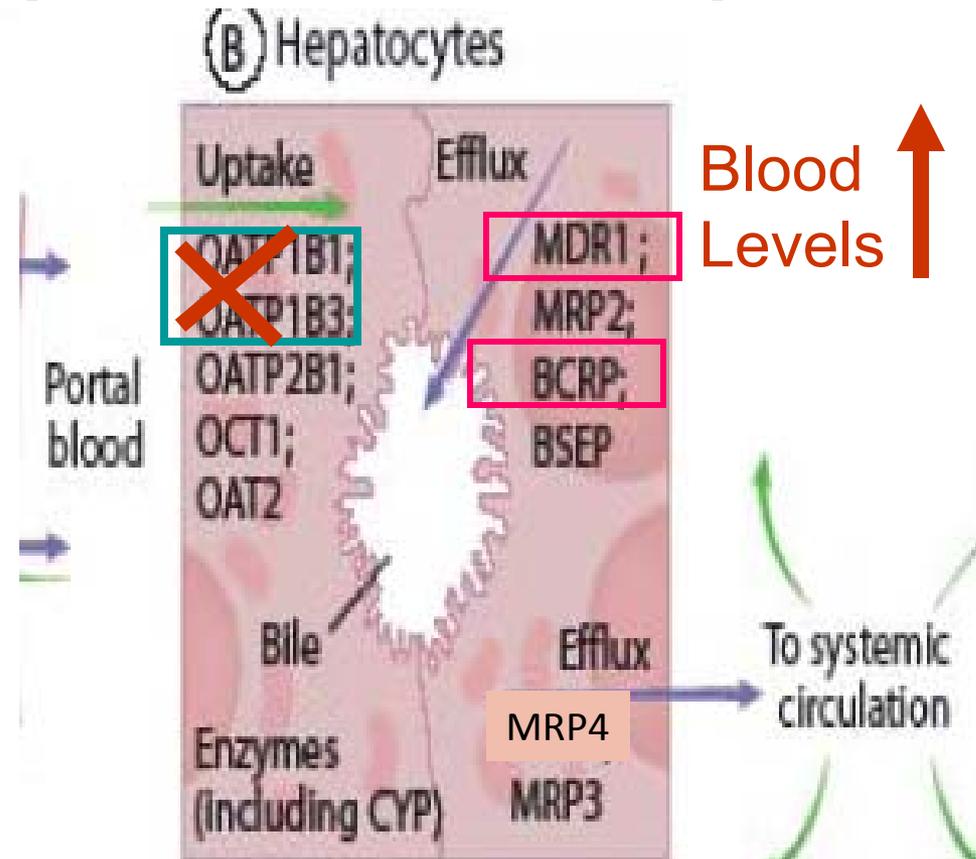
(from blood to hepatocytes):

- OATP1B1
- OATP1B3

Efflux

(excretion to bile):

- P-gp
- BCRP



Inhibitor	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure ↑	7-fold ↑
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure ↑	2-fold ↑

Transporters in Drug Distribution, Uptake and Excretion—Important Kidney Transporters

Uptake

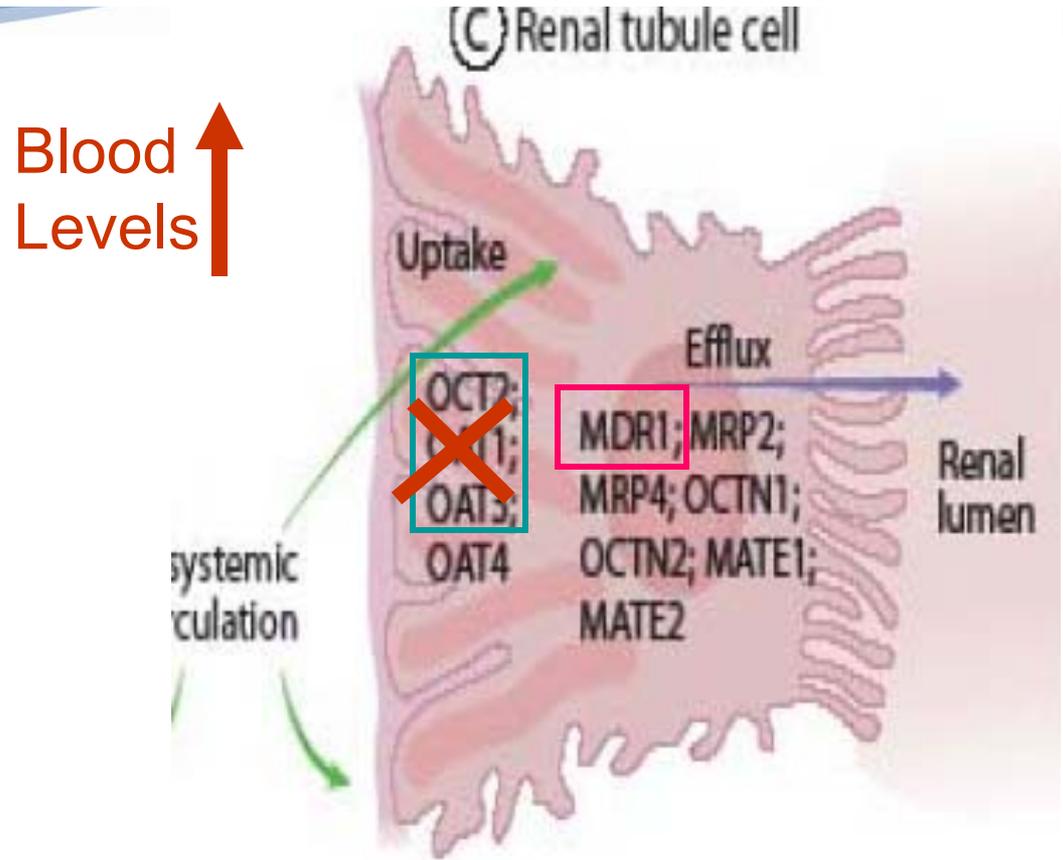
(from blood to kidney):

- OCT2
- OAT1
- OAT3

Efflux

(secretion to urine)

- **P-gp (MDR1)**



Inhibitor	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Probenecid	Cephadrine	Cephadrine Exposure ↑	3.6-fold ↑
Cimetidine	Metformin	Metformin Exposure ↑	1.4-fold ↑

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



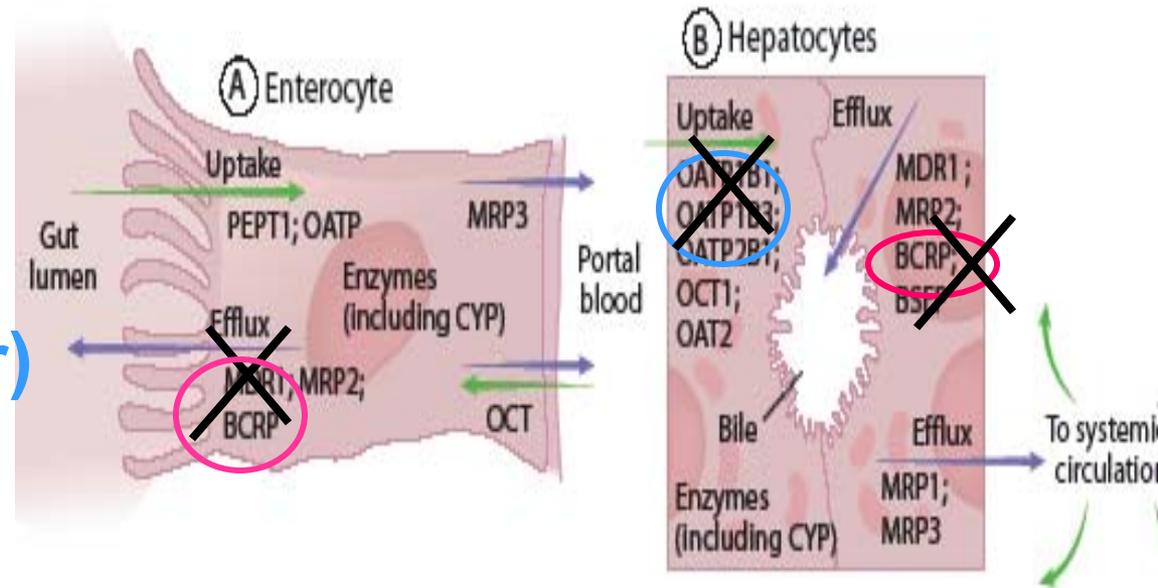
Rosuvastatin-Cyclosporine Interaction

Cyclosporine \uparrow 7-fold exposure of Rosuvastatin

Possible mechanism of inhibition by cyclosporine

\rightarrow OATP1B1/1B3 (uptake transporter)

\rightarrow BCRP (efflux transporter)



Crestor Labeling (AstraZeneca); <http://www.accessdata.fda.gov/scripts/cder/drugsatfda>

Simonson SG, et al. Clin Pharmacol Ther. 2004; 76(2):167; Kesjutaki JE, et al, Clini Pharmacol Ther 2009; 86:197; Tomlinson B, Clin Pharmacol Ther 2010

OATP-, BCRP-based Interactions

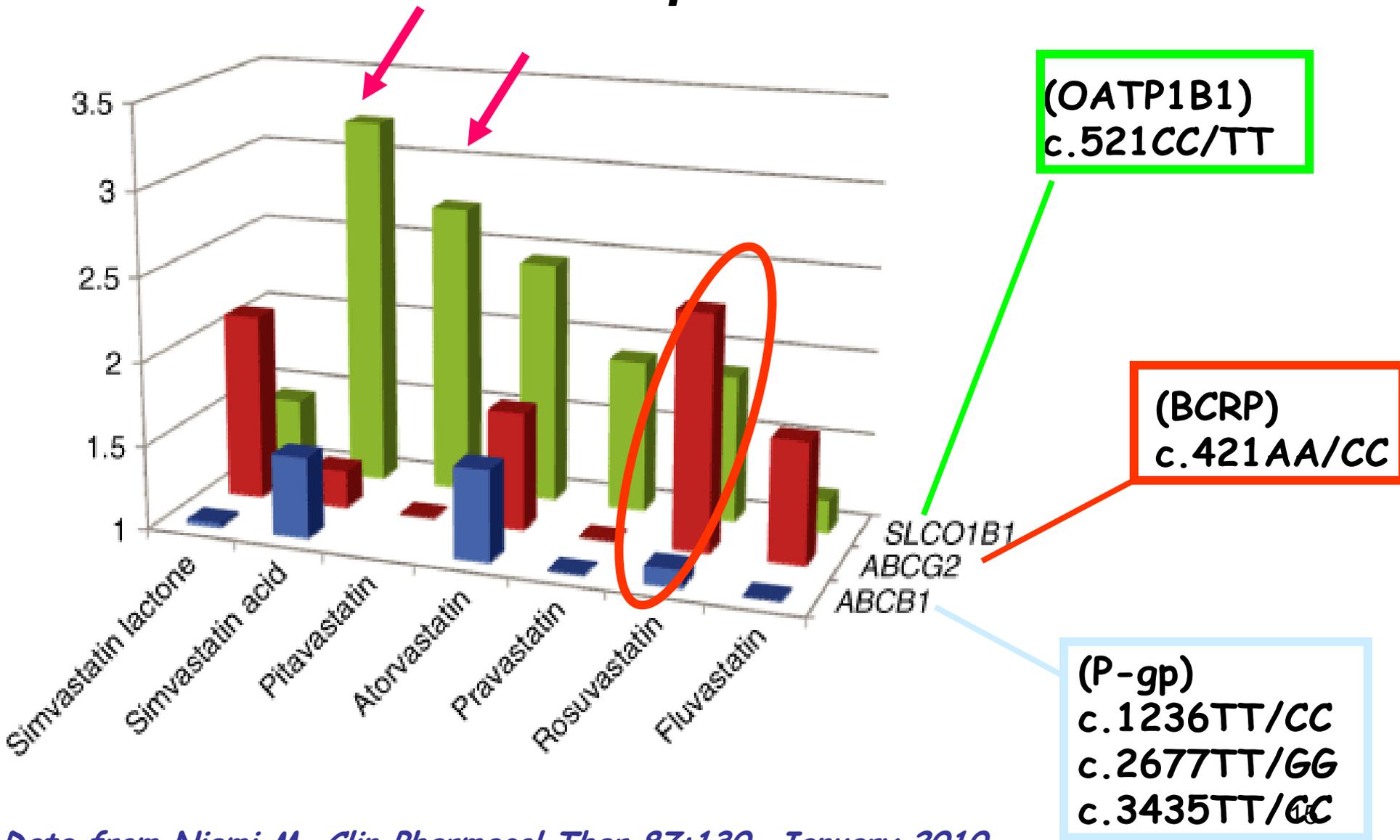
- **Cyclosporine inhibits other OATP or BCRP substrates**
 - e.g. Pitavastatin is a substrate of OATP1B1/1B3 and BCRP
 - Cyclosporine ↑ pitavastatin exposure 4.6-fold.
- **Rosuvastatin is inhibited by other OATP or BCRP inhibitors**
 - Lopinavir/ritonavir ↑ rosuvastatin exposure 2-fold
 - Lopinavir/ritonavir 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 -



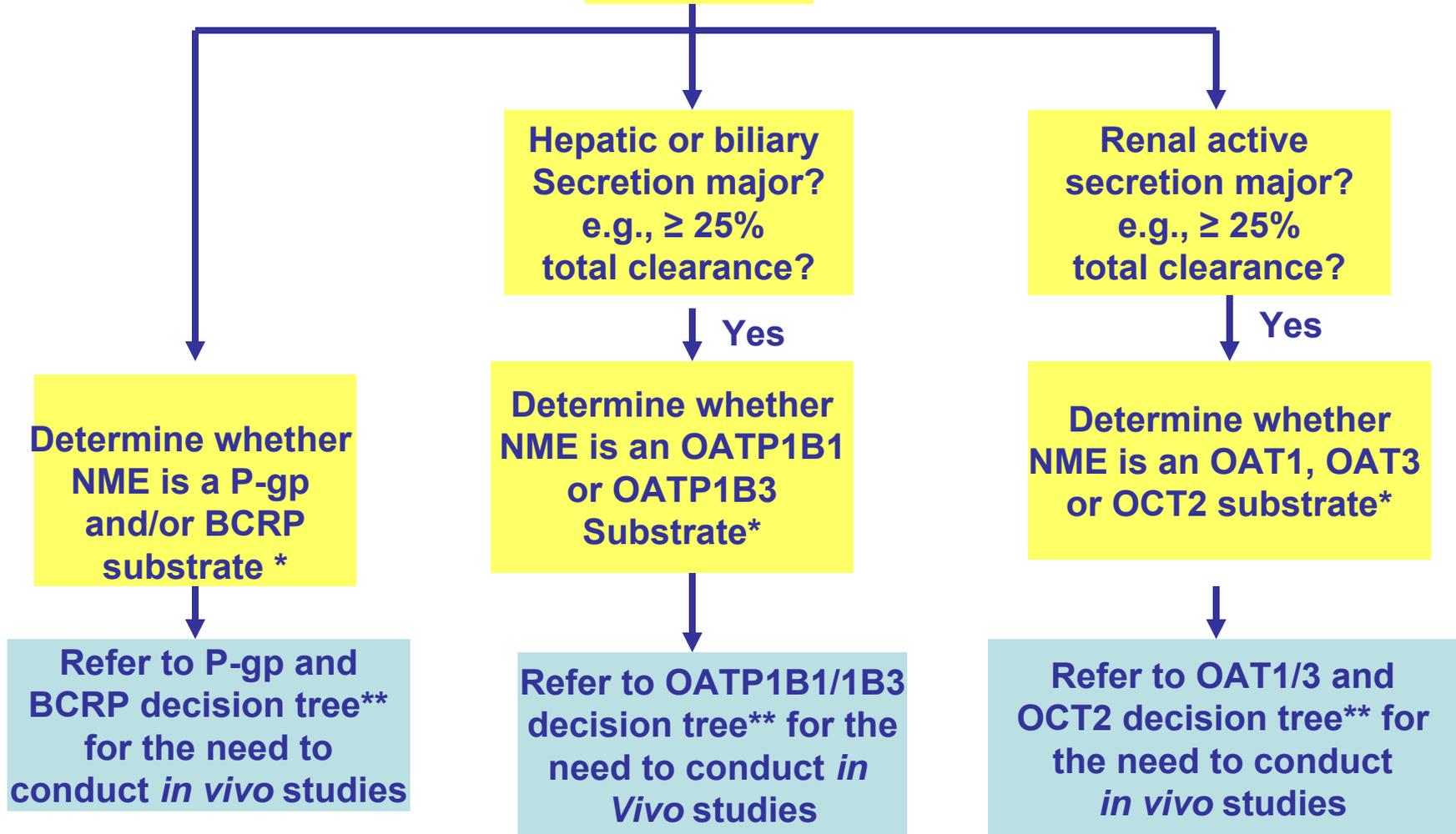
Relative contribution of each transporter/enzyme on the disposition of statin drugs is different

**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

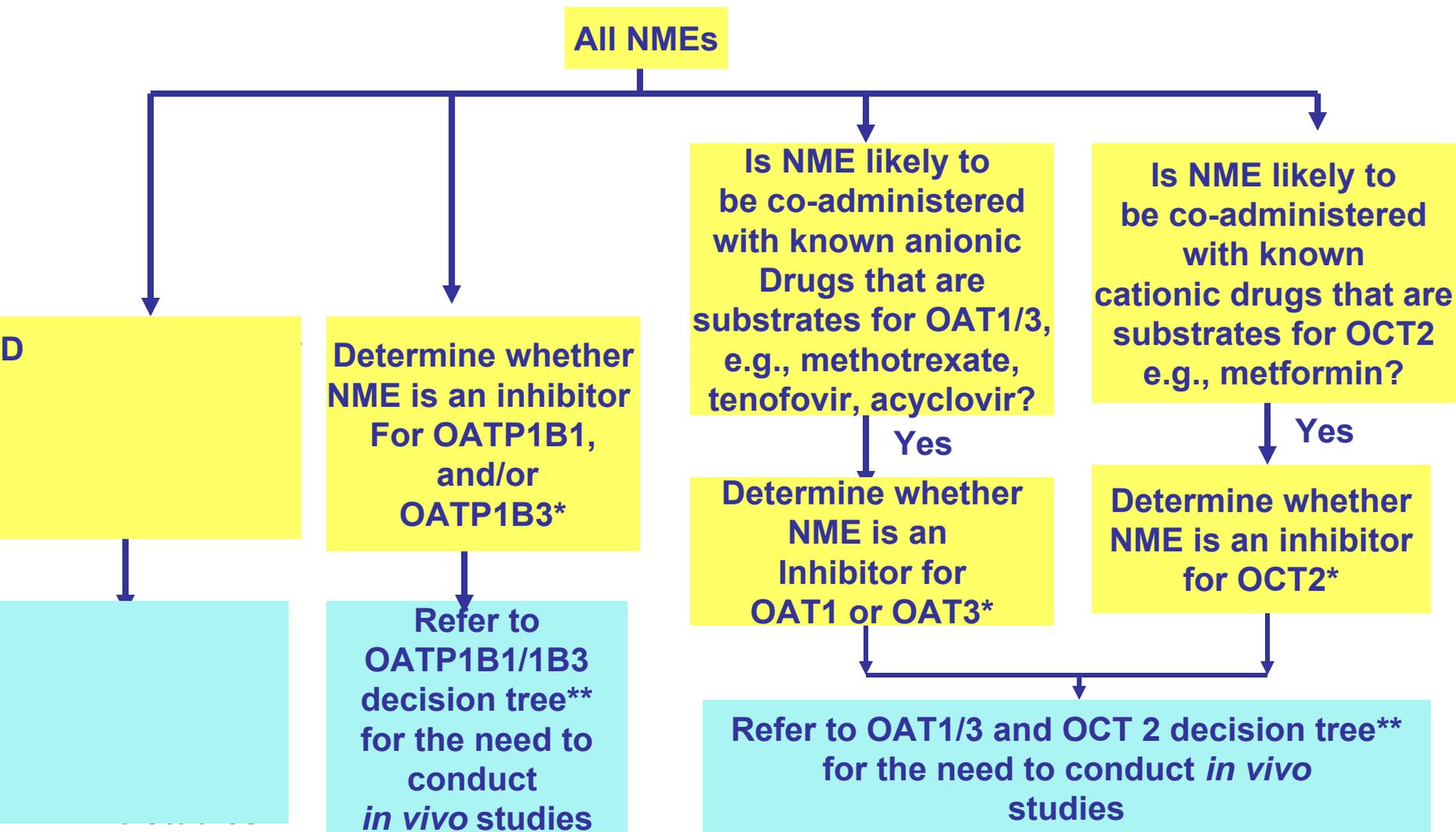
All NMEs



* 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



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

Examples of Transporter Inhibitors and Inducers

Transporter	Gene	Inhibitors	Inducers
P-gp	<i>ABCB1</i>	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, <u>cyclosporine</u> , diltiazem, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's Wort, tipranavir/ritonavir
BCRP	<i>ABCG2</i>	<u>Cyclosporine</u> , elacridar (GF120918), eltrombopag, gefitinib	Not known
OATP1B1	<i>SCLO1B1</i>	<u>Cyclosporine</u> , eltrombopag, lapatinib, lopinavir, rifampin, ritonavir,	Not known
OATP1B3	<i>SCLO1B3</i>	<u>Cyclosporine</u> , lopinavir, rifampin, ritonavir	Not known
OCT2	<i>SLC22A2</i>	Cimetidine, cetirizine, desipramine, quinidine	Not known
OAT1	<i>SLC22A6</i>	Probenecid, diclofenac	Not known
OAT3	<i>SLC22A8</i>	Probenecid, cimetidine	Not known



Transporter Information in Drug Labeling

Transporter	Drug Names*
P-gp	Aliskiren, ambrisentan, [aprepitant], <i>clarithromycin</i> , colchicine, <u><i>cyclosporine</i></u> , [dexvenafaxine], <i>dronedarone</i> , [eltrombopag], <i>everolimus</i> , fexofenadine, [fosaprepitant], [ixabepilone], <i>lapatinib</i> , <i>maraviroc</i> , <i>nilotinib</i> , <i>paliperidone</i> , posaconazole, [prasugrel], [[propafenone]], propranolol, <u><i>ranolazine</i></u> , saxagliptin, silodosin, sirolimus, sitagliptin, <i>tipranavir</i> **, <i>tolvaptan</i> , topotecan, [vorinostat]
OATP1B1	Atorvastatin, <u><i>cyclosporine</i></u> , <u><i>eltrombopag</i>***</u> , <i>lapatinib</i> , valsartan
OATP	Ambrisentan
OAT	Sitagliptin (OAT3)
OCT	Metformin, pramipexole, [saxagliptin], [sitagliptin], varenicline (OCT2)
BCRP	Lapatinib, topotecan
MRP	Mycophenolate (MRP2), [ixabepilone] (MRP1), valsartan (MRP2)

HIGHLIGHTS

*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

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)*].

Labeling Example

Eltrombopag

Drug Interactions Section

- 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 AUC_{0-∞} by 55% and C_{max} 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

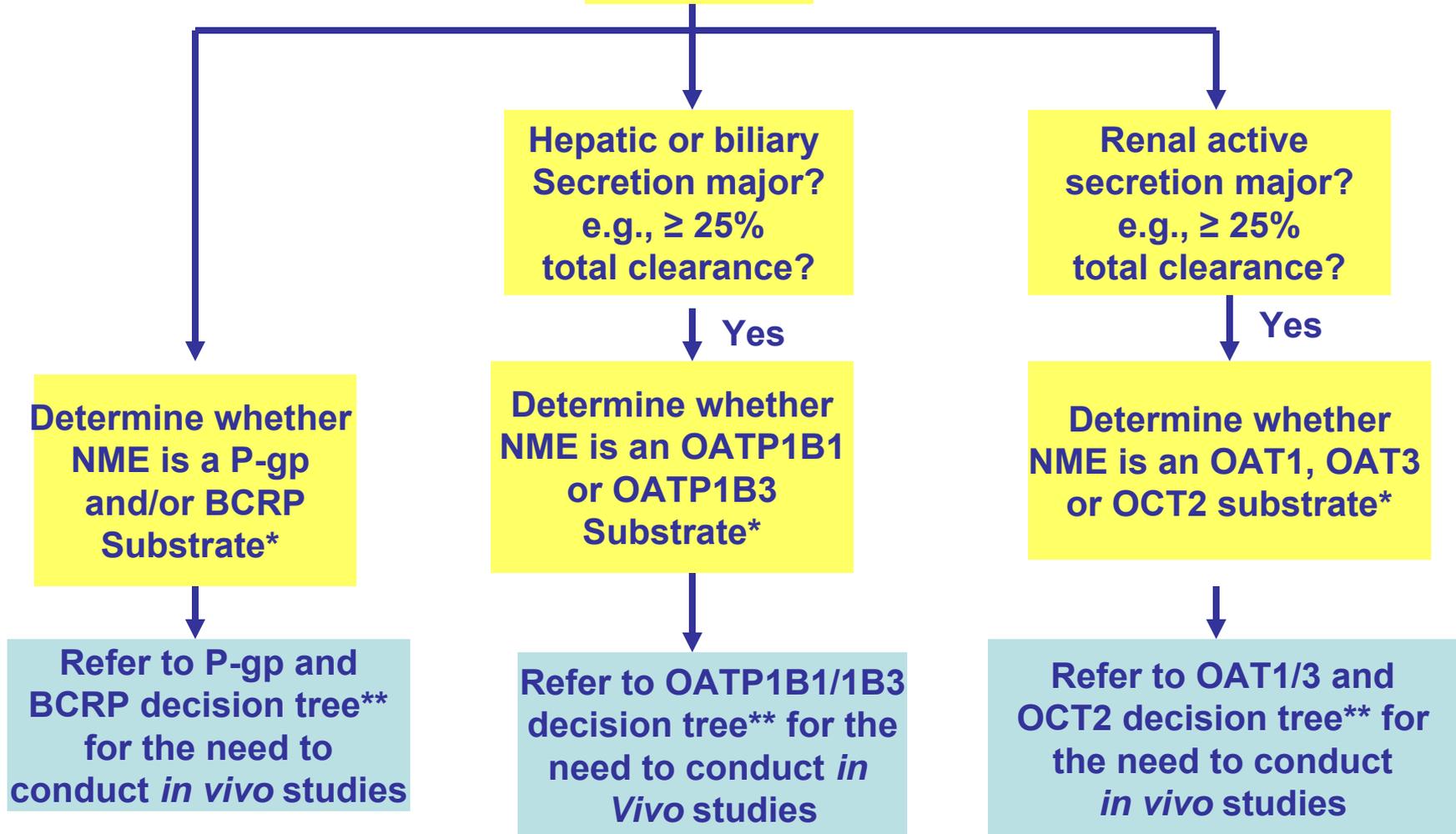
- What are the clinical questions?
- What transporters are mature enough to be studied?
- How to evaluate NME as transporter substrates?
- How to evaluate NME as transporter inhibitors?
- Interplay with metabolizing enzymes?
- What label information would be useful to prescribers?



Questions for the Advisory Committee

Evaluation of NME as a Substrate for Transporters—Other Drugs' Effect on NME

All NMEs



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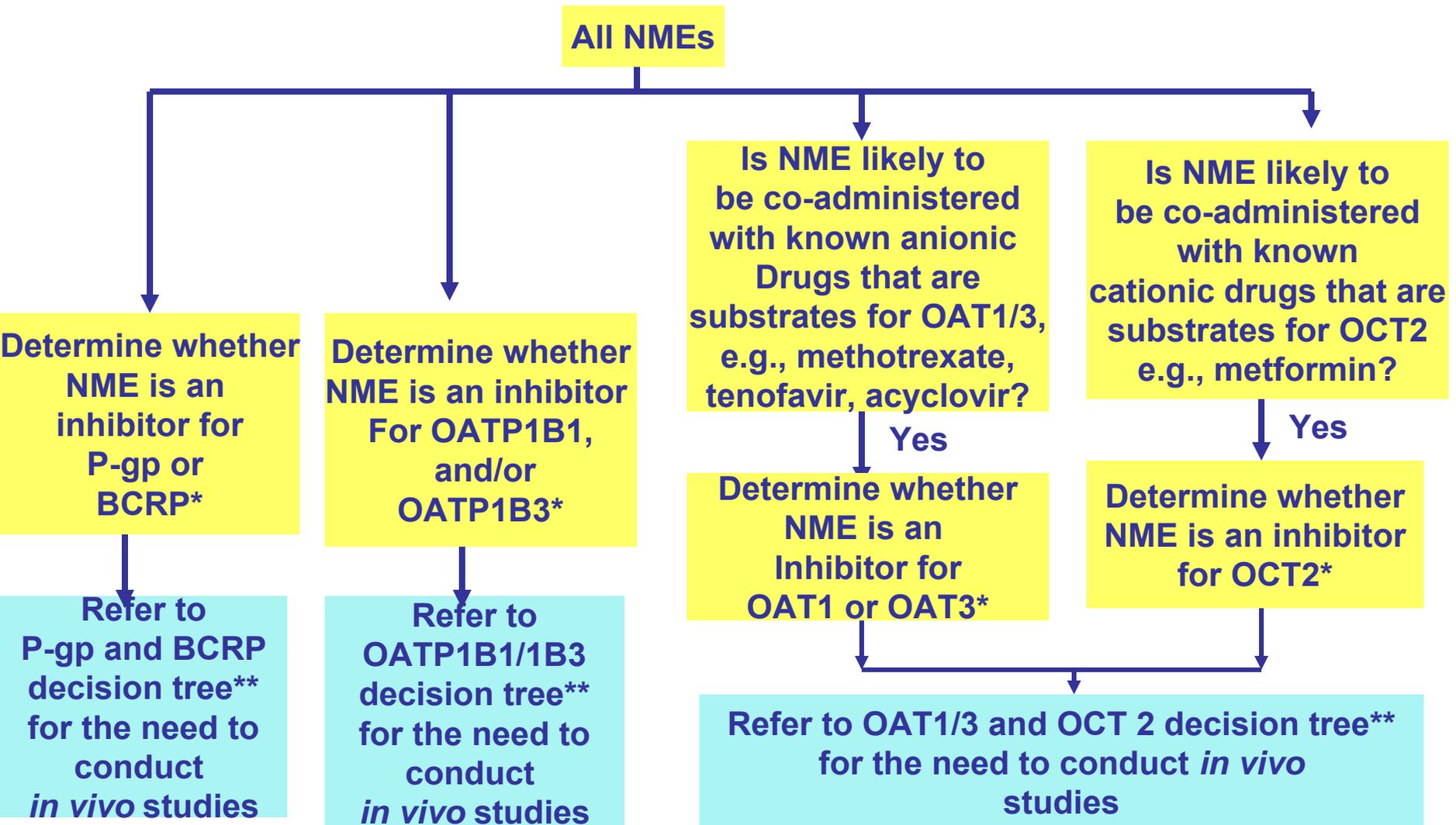
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter

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



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** 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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- Office of Clinical Pharmacology/OTS
- International Transporter Consortium
- Janet Woodcock/Critical Path Initiative

References

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- **Commentary**
 - Huang and Woodcock, Nature Reviews Drug Discovery 2010, 9, 175-176
- **International Transporter Consortium**
 - S-M Huang, L Zhang, K Giacomini. The International Transporter Consortium (ITC): A collaborative group of scientists from academia, industry and FDA. Clin Pharm Ther. 87(1):32-36, (2010)
- **Drug Development and Drug Interactions**
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>
- **Draft Drug Interaction Guidance**
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>