ASCPT American Society for Clinical Pharmacology & Therapeutics

International Transporter Consortium (ITC)
4th Workshop (virtual)
April 19-21, 2021

https://www.itc-transporter.org/itcw4.html
provides links to agenda and registration at **ASCPT**

Pre-Workshop Webinar, March 31st, 2021, 5-6:30 PM EDT (**free registration**)
Prof Yuichi Sugiyama

Use of Extended Clearance Concept and PBPK Modeling in New Drug Discovery and Development: Predicting Target Tissue Exposure from In Vitro to In Vivo

Contents

1) Introduction;
Rate-determining process (focusing on the liver)
(Uptake, efflux, elimination, metabolism) DDI

2) PGx of OATP1B1: PBPK model based analysis

3-1) PBPK model based analysis of OATPs mediated drug-drug interaction
(Top down + Bottom-up)

(i) victim drugs-perpetrator drugs
(ii) endogenous biomarker (CP-I) – rifampicin

3-2) Simple bottom-up predictions dot not always work well.
(i) prediction of hepatic clearance of highly protein bound drugs
(albumin-mediated hepatic uptake mechanisms should be considered)
(ii) Time-dependent inhibition (inhibitors for OATP1B and OCTs)

4) Target-mediated drug disposition (TMDD); To obtain dose-dependent change in molecular target occupancies only from the plasma concentration time-profile

Drug-interaction between Cerivastatin and Gemfibrozil/CsA

日本では、重篤な副作用のためメーカー自主回収へ

薬事日報平成13年8月27日号

薬事日報平成13年8月15日号

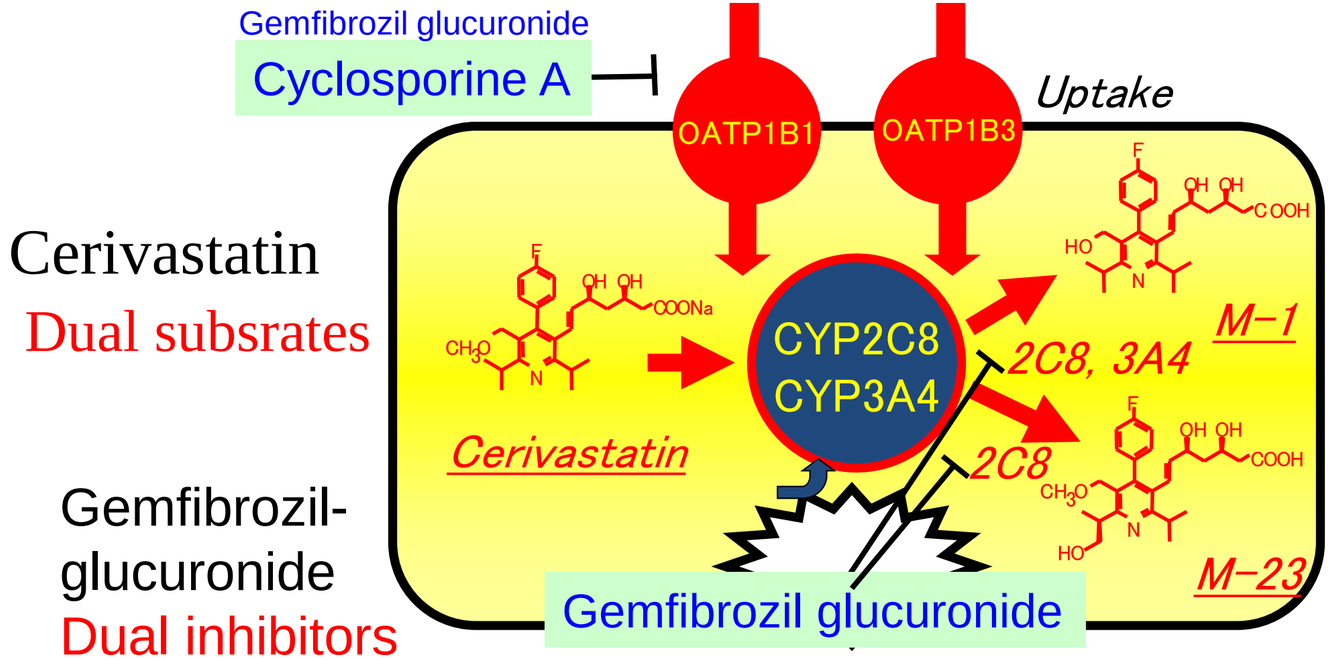
WORLD HEALTH ORGANIZATION — ORGANISATION MONDIALE DE LA SANTE

QSM/MC/IEA.102 — 09 August 2001

Voluntary withdrawal of Cerivastatin – Reports of Rhabdomyolysis

Baycol (cerivastatin) was initially approved in the U.S. in 1997. It belongs to a group of cholesterol lowering drugs referred to as "statins". While all statins could potentially cause this dangerous muscle reaction, rhabdomyolysis appears more frequent with cerivastatin, especially when used in high doses, in the elderly or, when taken along with gemfibrozil, another cholesterol lowering drug. In this connection it may be noted that Bayer has withdrawn all

- ***52 patients died (US 31).***
- ***Among 31 patients, 12 were given also gemfibrozil.***



Shitara, Y. et al.
J Pharmacol Exp Ther,
304(2): 610-6 (2003)

Shitara, Y. et al.
J Pharmacol Exp Ther,
311(1): 228-36 (2004)

Shitara, Y. and Sugiyama Y.
Pharmacol Ther,
112(1): 71-105 (2006)

Examples of substrates for uptake / efflux transporters and enzymes (1)

Substrates	Uptake transporter	Metabolic enzymes	Efflux transporter
Anti-Hyperlipidemic drugs (statins)			
atorvastatin	OATPs	CYP3A4	-
cerivastatin	OATPs	CYP2C8, 3A4	-
fluvastatin	OATPs	CYP2C9	-
pravastatin	OATPs	-	MRP2
rosuvastatin, pitavastatin	OATPs	-	BCRP
Anti-hypertension or -cardiovascular disease			
bosentan	OATPs	CYP3A4, 2C9	-
torasemide	OATPs	CYP2C9	-
telmisartan	OATP1B3	UGTs	-
valsartan	OATPs	-	MRP2
Anti-cancer drug			
docetaxel	OATP1B3	CYP3A4	-

Examples of substrates for uptake / efflux transporters and enzymes (2)

Substrates	Uptake transporter	Metabolic enzymes	Efflux transporter
Anti-diabetes			
repaglinide	OATPs	CYP2C8, 3A4	-
nateglinide, glibenclamide	OATPs	CYP2C9, 3A4	
Anti-HCV			
simeprevir, grazoprevir	OATP1B1	CYP3A4	-
asunaprevir, danoprevir, paritaprevir	OATPs	CYP3A4	Pgp
Etc.			
Montelukast	OATP2B1	CYP2C8, 2C9, 3A4	-
maraviroc	OATP1B1	CYP3A4	Pgp
fexofenadine	OATPs	-	Pgp

Understanding Extended Clearance Concept is very important (I have been training this concept to all the students , post-doc in my lab (UOT, RIKEN)

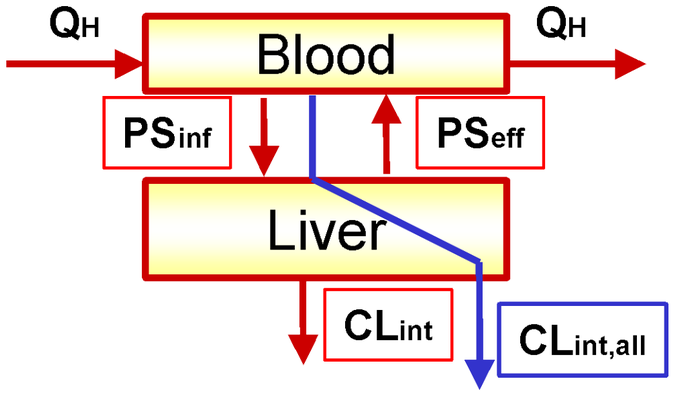
"Extended Clearance Concept"

- enough to predict the change in AUC and/or Css both in plasma and tissue
  (PGx, DDI (at least for static analyses,
  and not for dynamic analysis)

"PBPK modeling"

- Appropriate model for describing the drug conc-time course both in plasma and tissue as well as AUC, Css

Overall Hepatic Intrinsic Clearance (Clint,all)



Extended clearance concept

$$CL_{int,all} = PS_{inf} \times \frac{CL_{int}}{PS_{eff} + CL_{int}}$$

Degree of Sequestration (β)

1) When $PS_{eff} << CL_{int}$, (Case-1)

$$CL_{int,all} = PS_{inf}$$

Uptake – limited (anionic drugs,; statins, sartans)

$\beta = 1$

2) When $PS_{eff} >> CL_{int}$, (Case-2)

$$CL_{int,all} = \frac{PS_{inf}}{PS_{eff}} \times CL_{int}$$

Degree of Active Uptake (α)

When $PS_{inf} = PS_{eff}$ (passive diffusion),

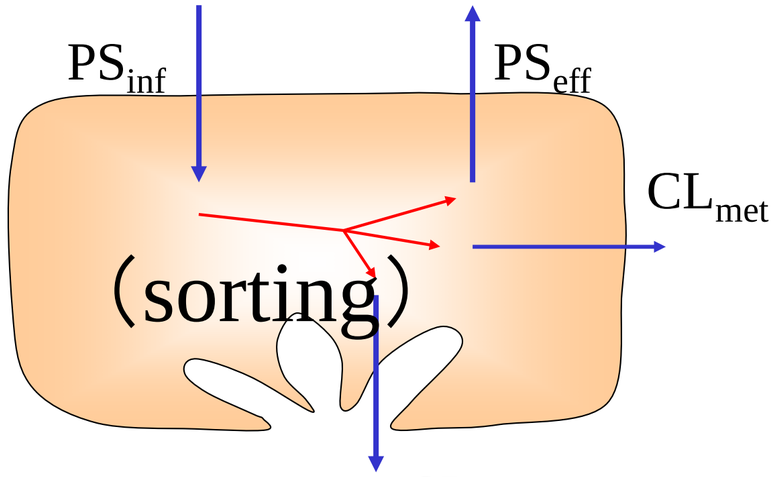
$$CL_{int,all} = CL_{int}$$

Intrinsic Clearance-limited $\alpha = 1$

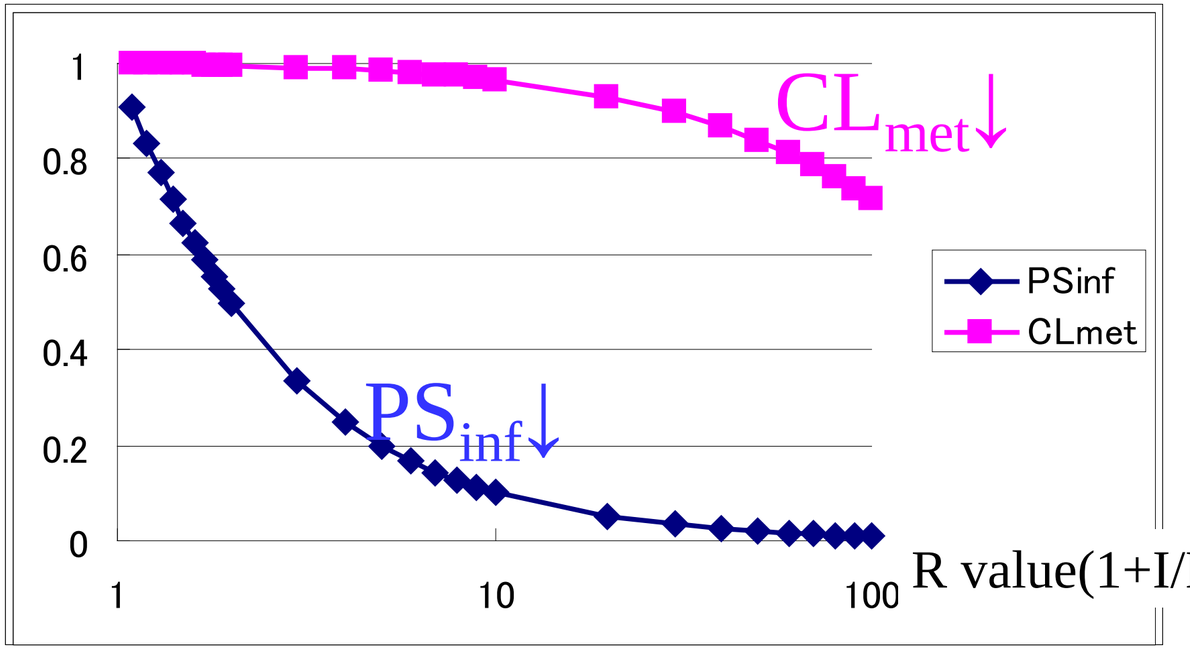
(lipophilic basic/neutral drugs; quinidine, diazepam)

$$CL_{int,all} = PS_{inf} \times \frac{CL_{bile} + CL_{met}}{PS_{eff} + CL_{bile} + CL_{met}}$$

(sorting)

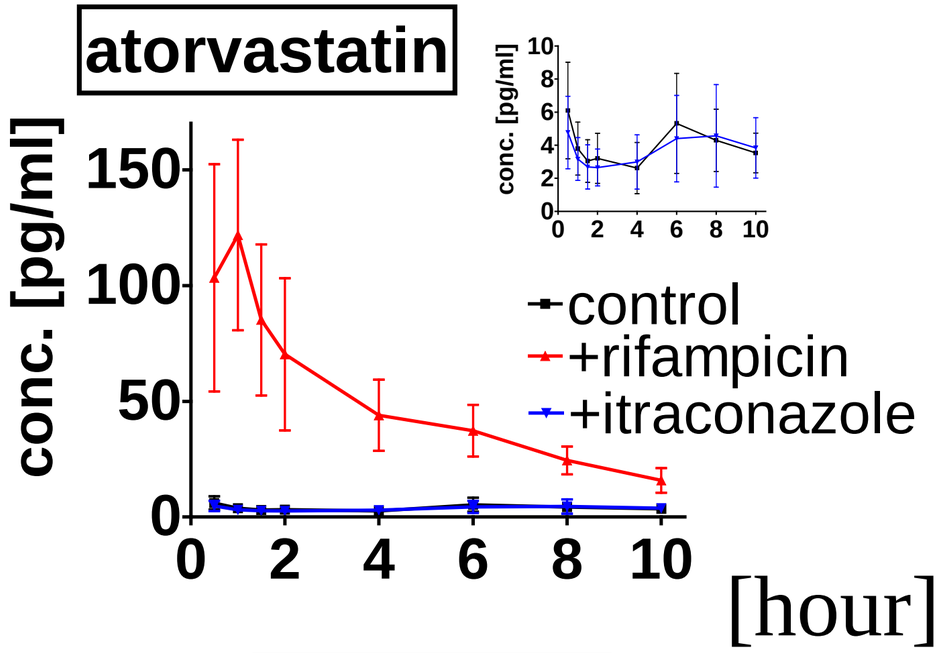


PS_{inf} =100, PS_{eff}=2, CL_{bile}+CL_{met}=500 (Case-1) 2)



Impact of the function of each pathway on the overall intrinsic clearance

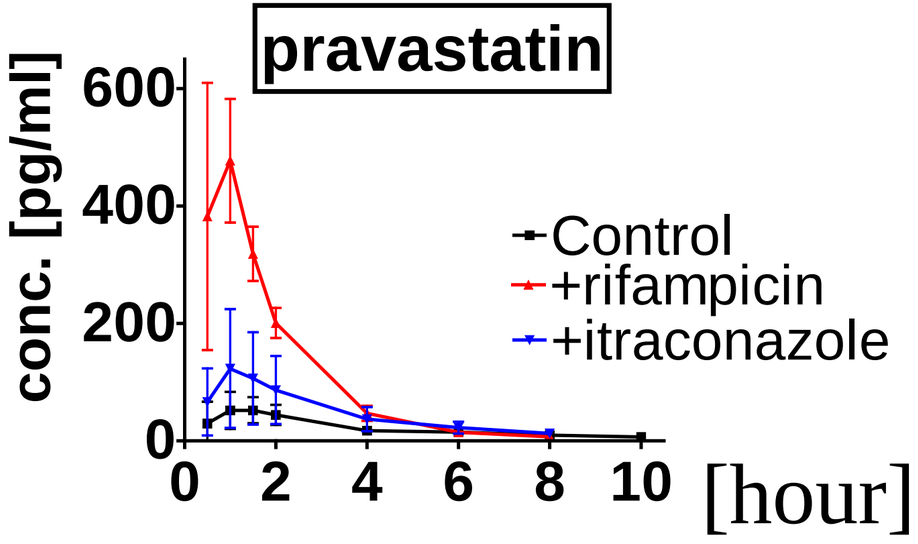
Plasma concentrations of atorvastatin and pravastatin were greatly increased by rifampicin, but not by itraconazole

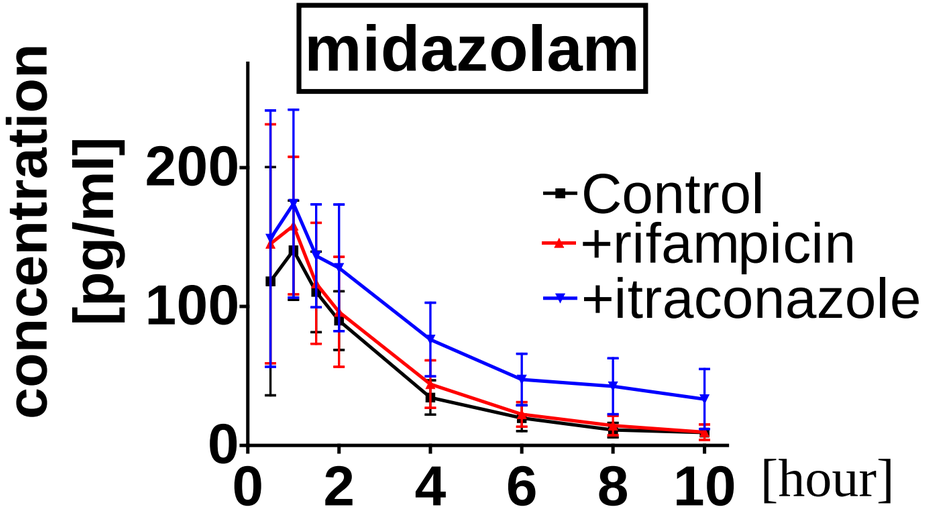


AUC_{0-10} [pg*hr/ml]	ATV	PRV (AUC_{0-8})	MDZ
Cont.	38.5 ±17.5	195 ±78.7	434 ±122
+RIF	439*** ±134	949*** ±179	471 ±168
+ITZ	36.0 ±19.2	386 ±254	755* ±276

***: P<0.0005

*: P<0.05

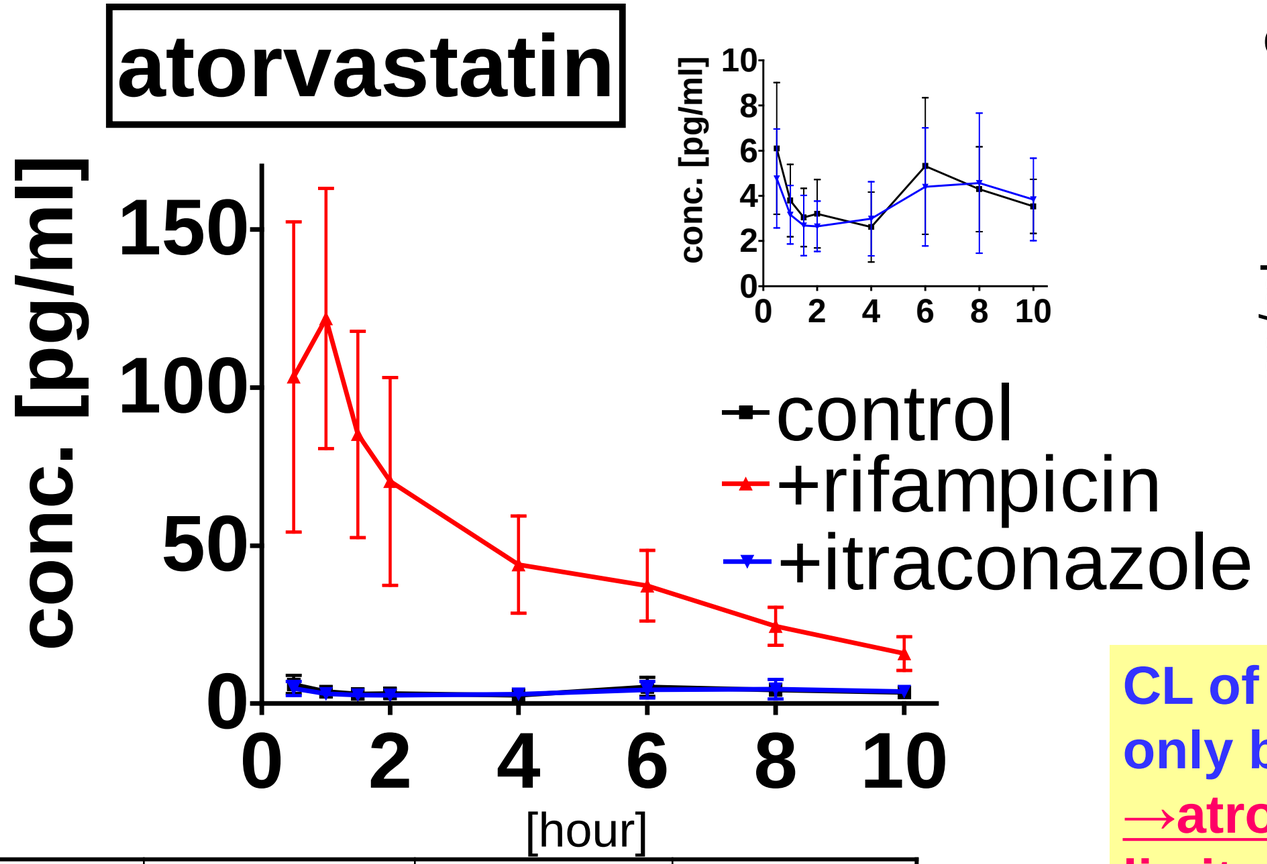




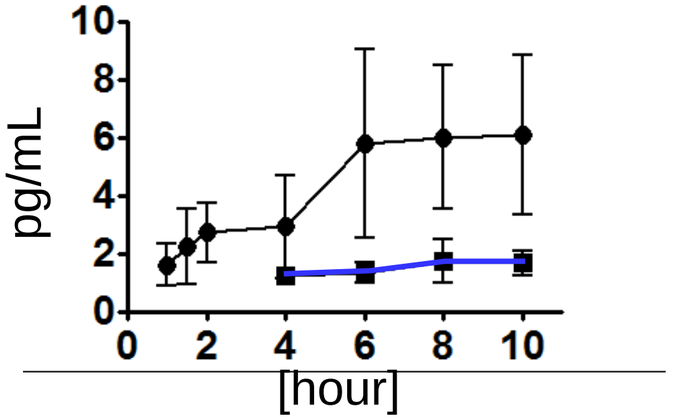
*Doses of each substrates are 33μg

Maeda K et al., CPT (2011)

Effects of rifampicin and itraconazole on the PK of atorvastatin



cf. 2-hydroxyatorvastatin



	Control	+RIF	+ITZ
AUC_{0-10} [pg*hr/mL]	38.5 ±17.5	439*** ±134	36.0 ±19.2

CL of atorvastatin was inhibited only by rifampicin.
→atrovastatin hepatic clearance is limited only by hepatic uptake

Maeda K, Ikeda Y, Fujita T, Yoshida K, Azuma Y, Haruyama Y, Yamane N, Kumagai Y and Sugiyama Y. Identification of the rate-determining process in the hepatic clearance of atorvastatin in a clinical cassette microdosing study. Clin Pharmacol Ther 90:575-581 (2011).

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The impact of OATP1B1 on the PK of drugs

～Plasma conc. of drugs is increased in subjects with OATP1B1*15～

HMG-CoA reductase inhibitors

pravastatin
simvastatin acid
pitavastatin
atorvastatin
rosuvastatin

Anti-diabetes

repaglinide
nateglinide
glybenclamide

Anti-allergic drug

fexofenadine

Anti-pulmonary hypertension drug

Atrasentan
bosentan

Anti-cancer drug

irinotecan（SN-38）
docetaxel, paclitaxel

Chol-absorption inhibitor

ezetimibe

Loop diuretics

Torasemide

Angiotensin receptor antagonists

Olmesartan

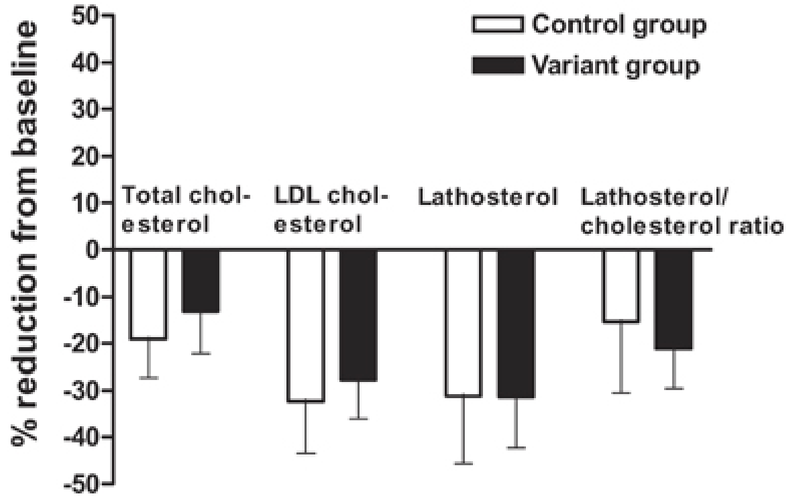
Relationship between OATP1B1 genetic polymorphism and Pharmacological effect and adverse effect of statins

★Pharmacological effect

Target; HMG CoA-reductase in the liver

No effect or small effect if any

(Igel M et al.,Clin Pharmacol Ther, 79, 419-26 (2006))



★Adverse Effect

Target; Muscle (via plasma)

Simvastatin-induced myopathy

strong correlation with OATP1B1 polymorphism

(SEARCH Collaborative Group et al., New Engl J Med, 359, 789-99 (2008))

Odds ratio of this SNPs for simvastatin-induced myopathy

521C/T vs T/T → 4.5 fold

521C/C vs T/T →16.9 fold

Summary

 # All of these pharmacogenetic and DDI studies on OATP1B1 suggested that the hepatic uptake plays an important role in the plasma clearance of therapeutically important drugs (mostly anionic drugs; statins, ARA, ACE inhibitors, anti-HCV drugs, anticancer drugs, etc).

Why did this polymorphism and/or DDI affect **only side-effect (myopathy; muscle is a target tissue),** and **not pharmacological effect (lipid lowering effect; liver is a target organ) ?**

To answer this question, it is important to estimate the exposure in the plasma (muscle ; side effect tartet) and in the liver (Pharmacological target) (statins, HCV drugs)

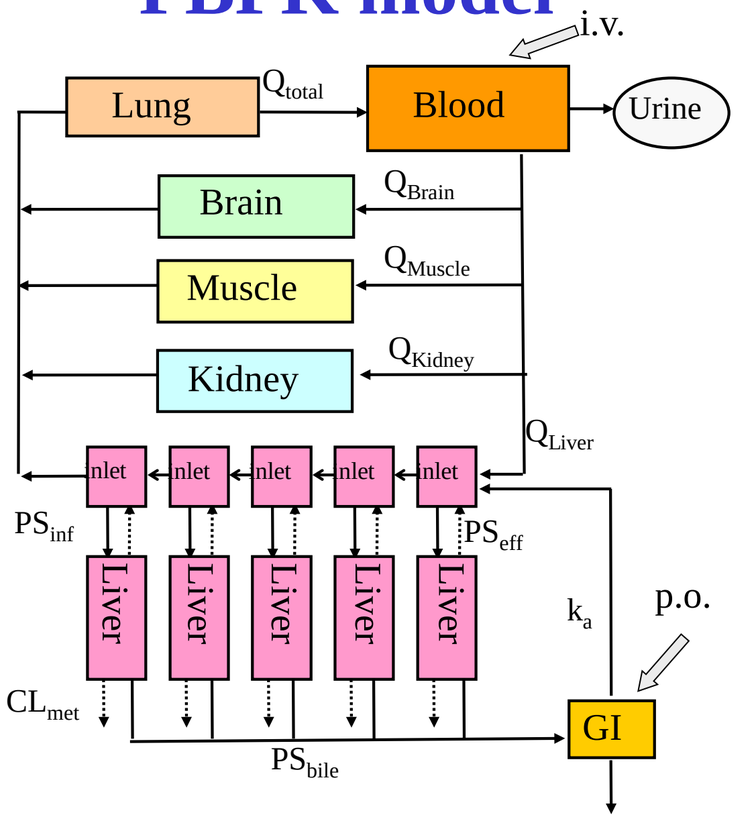
↓

Watanabe T, Kusuhara H, Maeda K, Shitara Y and Sugiyama Y. Physiologically based pharmacokinetic modeling to predict transporter-mediated clearance and distribution of pravastatin in humans. **J Pharmacol Exp Ther** 328:652-662 (2009)

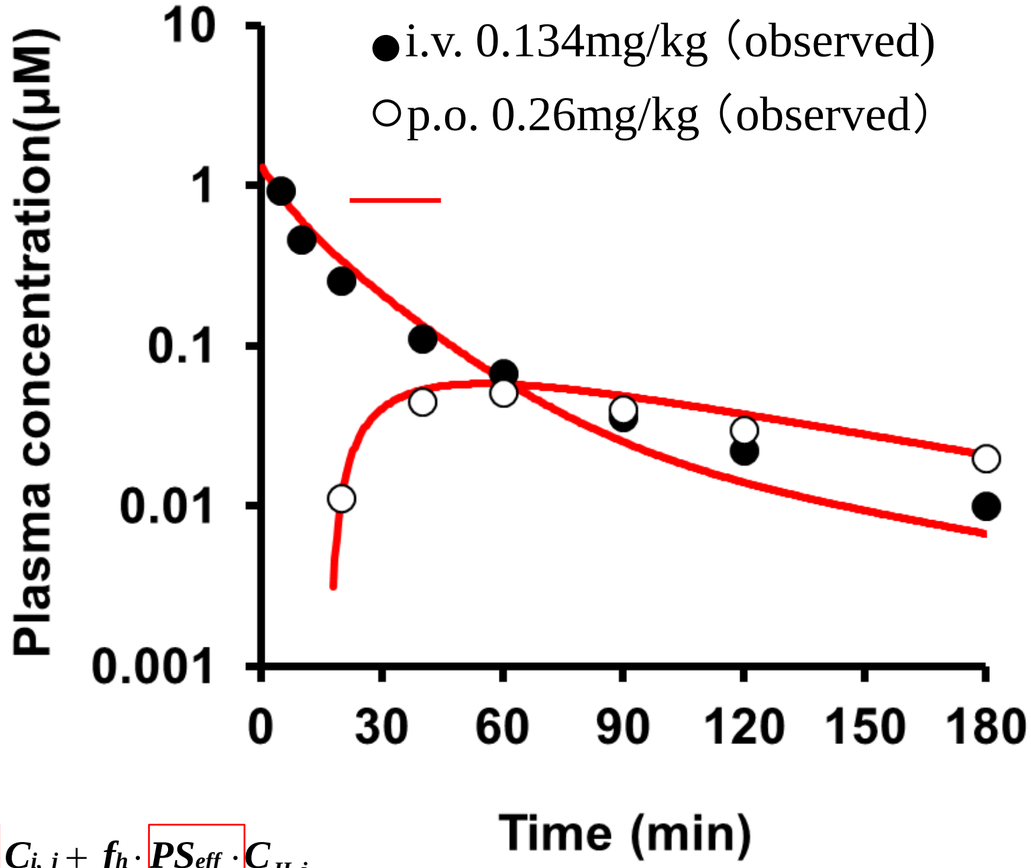
Yoshikado T, Yoshida K, Kotani N, Nakada T, Asaumi R, Toshimoto K, Maeda K, Kusuhara H, Sugiyama Y. Quantitative analyses of hepatic OATP-mediated interactions between statins and inhibitors using PBPK modeling with a parameter-optimization method.
Clin Pharmacol Ther. 100:513-523(2016)

(11)

PBPK model



Plasma conc-time profile of pravastatin in human



Blood $$V_b \cdot \frac{dC_b}{dt} = Q_h(C_i - C_b) - CL_r \cdot C_b$$

Capillary in the liver $$V_{i,j} \cdot \frac{dC_{i,j}}{dt} = Q_h(C_{b,j} - C_{i,j}) - f_b \cdot PS_{inf} \cdot C_{i,j} + f_h \cdot PS_{eff} \cdot C_{H,j}$$

Hepatocytes $$V_{H,j} \cdot \frac{dC_{H,j}}{dt} = f_b \cdot PS_{inf} \cdot C_{i,j} - f_h \cdot (PS_{eff} + CL_{met} + PS_{bile}) \cdot C_{H,j}$$

Extrapolated parameters based on in vitro(animal, human) and in vivo (animal)

PBPK modeling of pravastatin disappearance

Uptake-limited hepatic elimination of statins

We need PET studies to know the drug exposure change in the liver

$$CL_{int,all} = PS_{inf} \times \frac{CL_{int}}{PS_{eff} + CL_{int}}$$

Microsome

IVIVE

Liver

Blood

IVIVE

$CL_{int,all}$

CL_{int} Metabolism

Biliary excretion (MRP2, BCRP)

Statins

Pravastatin

Pitavastatin

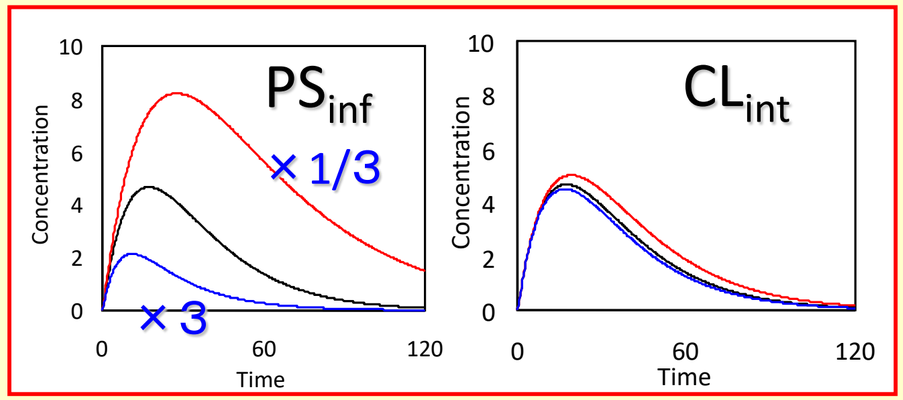
Atorvastatin

Fluvastatin

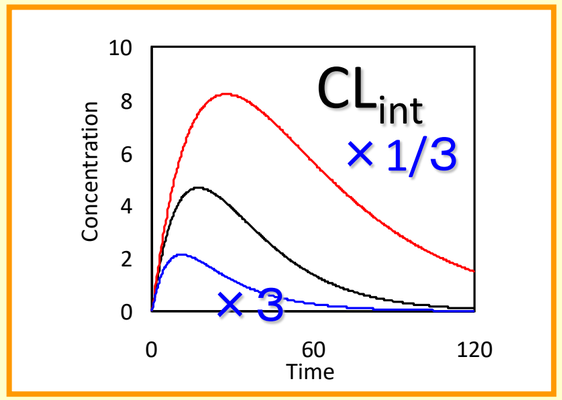
PS_{inf}

PS_{eff}

Systemic exposure



Liver concentration



Summary :

1) **Sensitivity analysis indicated that the change in hepatic uptake ability alters the plasma concentration profile sensitively (toxicity) and may not affect the profile in the liver, target tissue (pharamcological effect). GWAS for simvastatin in fact demonstrated it was the case.**

2) **Alteration in the biliary excretion ability (MRP2, BCRP) may affect the pharmacological effect（hepatic exposure) much more sensitively than that of the uptake, though there is little change in the plasma exposures.**

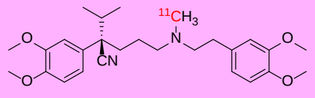
⇒ **We have to confirm it by PET analyses**

This prediction has been supported by several studies published by other groups (simvastatin GWAS study, rosuvastatin Jupiter trial)

Drug development with the Use of Microdosing Clinical Trial: Based on the Quantitative Prediction Technology of ADME

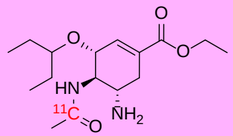
(NEDO Research Project (2008-2011) collaboration with Y.Watanabe

R(+)-[^{11}C]Verapamil



P-gp (BBB)

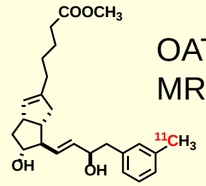
[^{11}C]Oseltamivir



Ontogeny in BBB penetration

Takashima T *et al.*, ***J Nucl Med.*** 2011: 52: 950-7

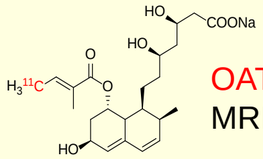
15*R*-[^{11}C]TIC-Me



OATP1B1,1B3, MRP2

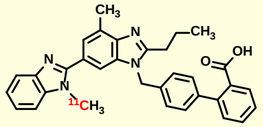
Takashima T *et al.*, ***JPET*** 2010; 335: 314-323
Takashima T *et al.*, ***J Nucl Med.*** 2012; 53: 1-8

[^{11}C]Dehydropravastatin



OATP1B1
MRP2

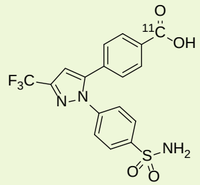
[^{11}C]Telmisartan



OATP1B3

Takashima T et al., ***Mol Pharm.*** 2011; 8: 1789-98

[^{11}C]SC-62807

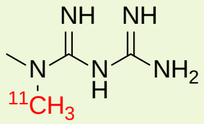


OATP1B1,1B3, BCRP

Takashima-Hirano M et al., ***Bioorg Med Chem.*** 2011; 19:2997-3004.

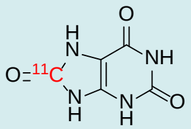
[^{11}C]Metformin

(*will be studied very soon*)



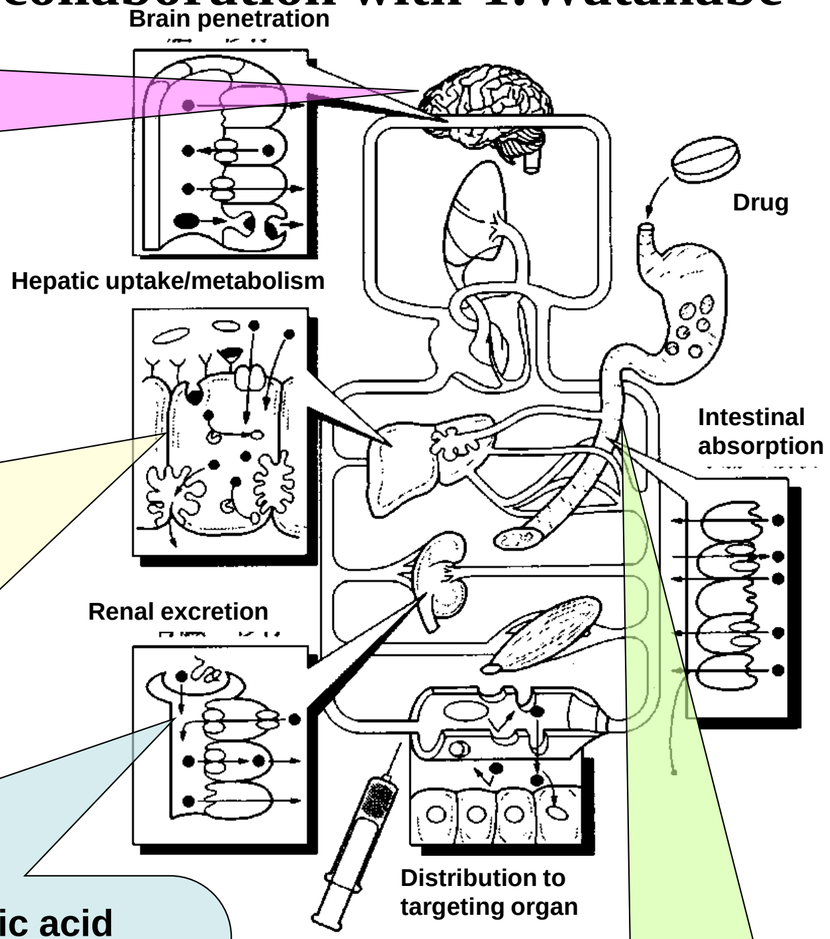
OCT2
MATE 1

[^{11}C]Uric acid

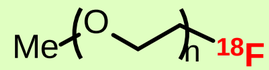


URAT1
BCRP

Yashio K *et al.*, ***Bioorg Med Chem Lett.*** *2012 ;22:115-9.*



[^{18}F]FPEG(2kDa)

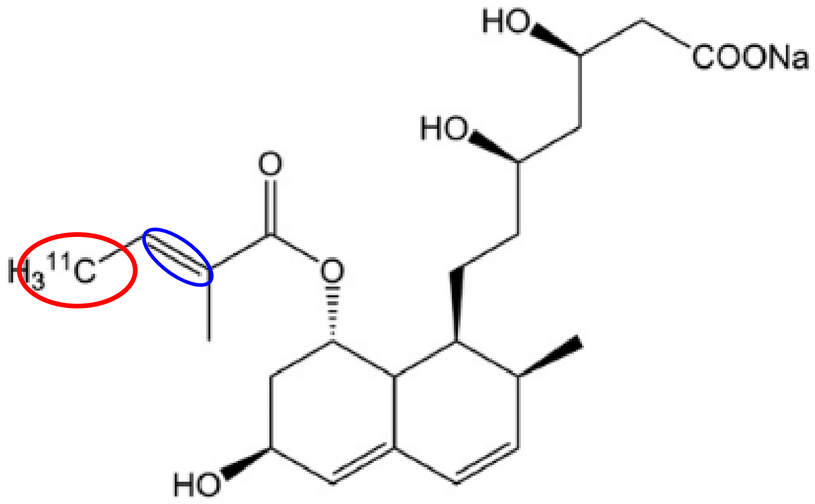


- Unabsorbed marker
- Application to PEGylation

PET imaging human studies

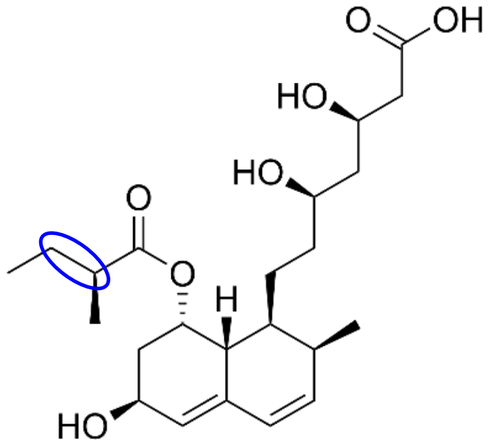
[^{11}C]DHP PET studies

[^{11}C]DPV chemical structure



Metabolsim is minimized

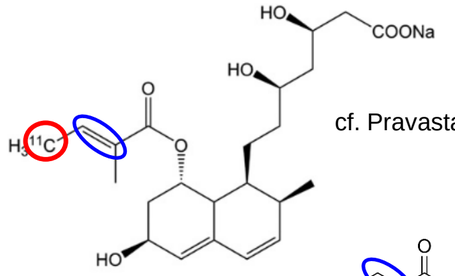
cf. Pravastatin chemical structure



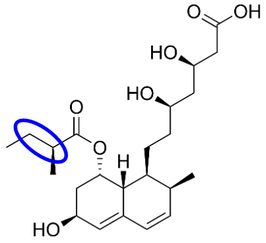
Kaneko K et al., A clinical quantitative evaluation of hepatobiliary transport of [11C]Dehydropravastatin in humans using positron emission tomography. Drug Metab Dispos. 46(5):719-728 (2018).

[^{11}C]DHP dynamic model fitting

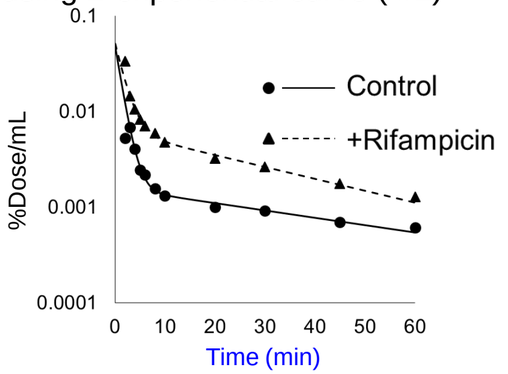
[^{11}C]DPV chemical structure



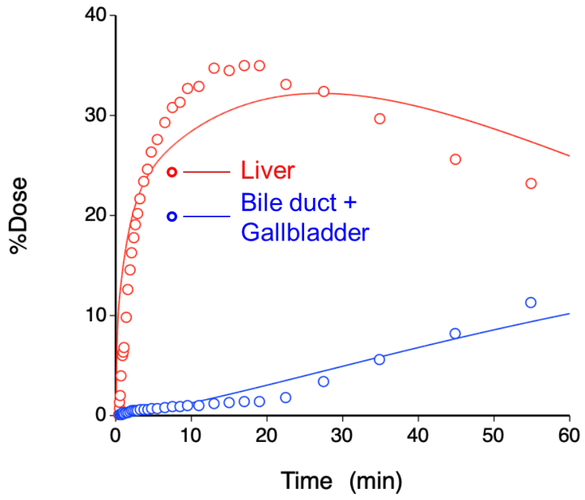
cf. Pravastatin chemical structure



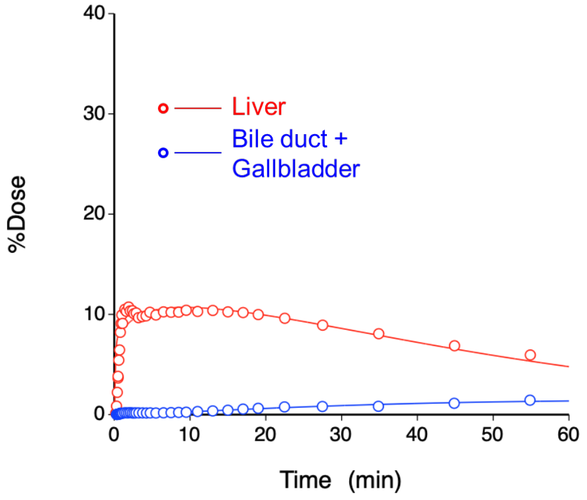
Fitted blood radioactivity-time profile of DPV using 2-exponential curve (#2)



Fitted radioactivity-time profile of DPV on control phase using dynamic model (#2)



Fitted radioactivity-time profile of DPV on +rifampicin phase using dynamic model (#2)



(17)

Contents

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Rate-determining process (focusing on the liver)
(Uptake, efflux, elimination, metabolism) DDI

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3-1) PBPK model based analysis of OATPs mediated drug-drug interaction
(Top down + Bottom-up)

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(ii)endogenous biomarker (CP-I) – rifampicin

3-2) Simple bottom-up predictions do not always work well.
(i) prediction of hepatic clearance of highly protein bound drugs
(albumin-mediated hepatic uptake mechanisms should be considered)
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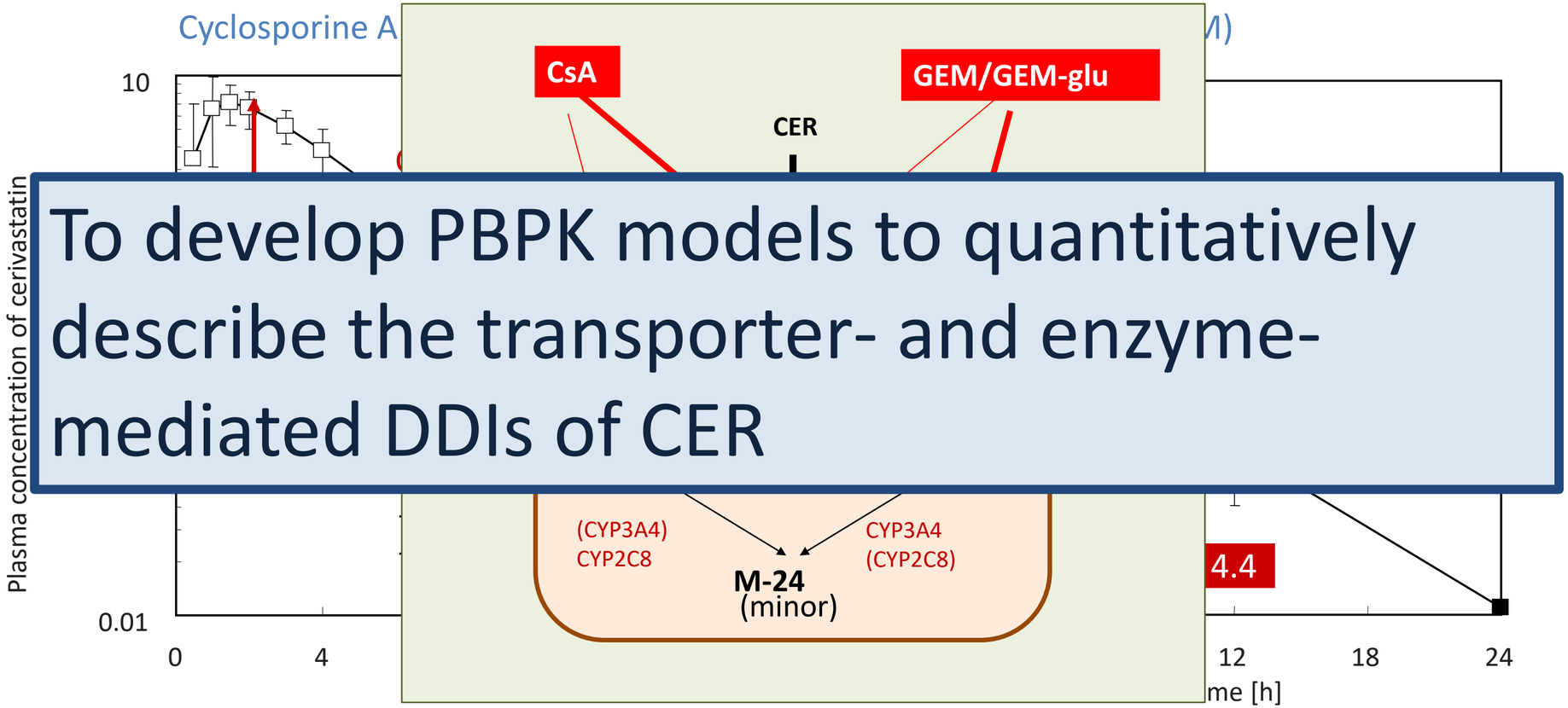
Drug-Drug Interaction between CER and Cyclosporine A/Gemfibrozil



To develop PBPK models to quantitatively describe the transporter- and enzyme-mediated DDIs of CER

Mück W et al., *Clin Pharmacol Ther.,* (1999)

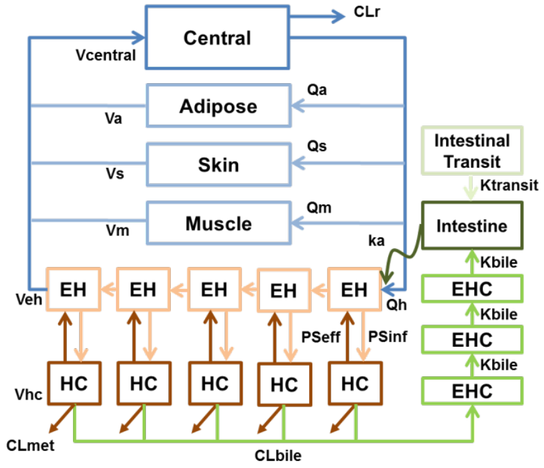
Backman JT et al. ,*Clin Pharmacol Ther.,* (2002)

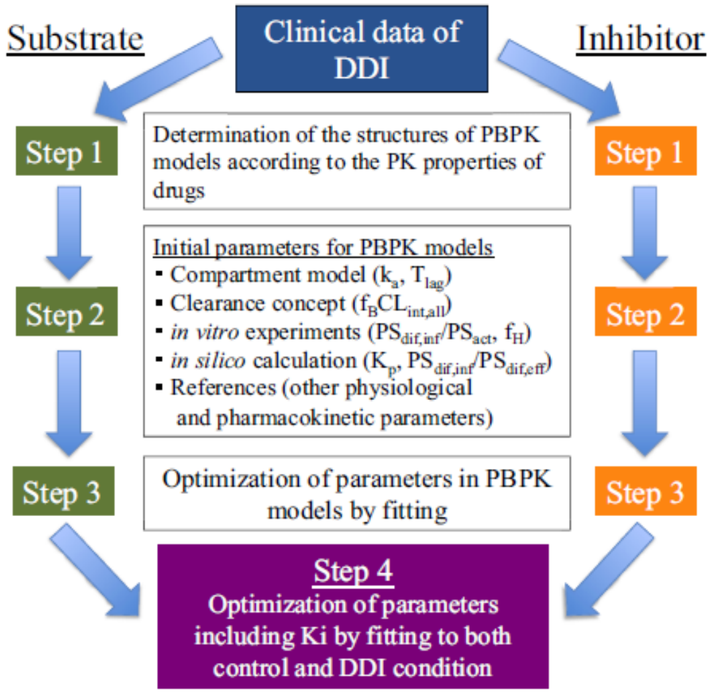
CLh ↓ Vd ↓ T ½ →

CLh ↓ Vd ↘ T ½ ↘

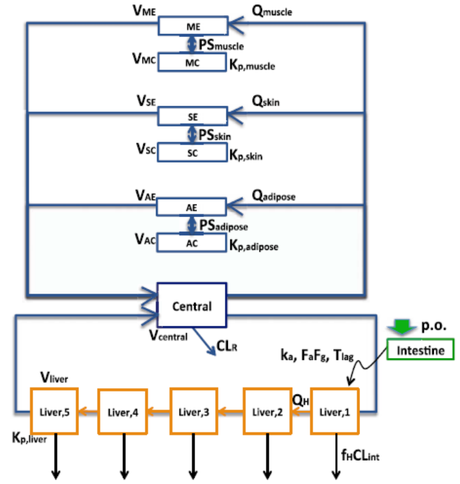
PBPK analyses of transporter/enzyme mediated complex DDI

Cerivastatin (CER)

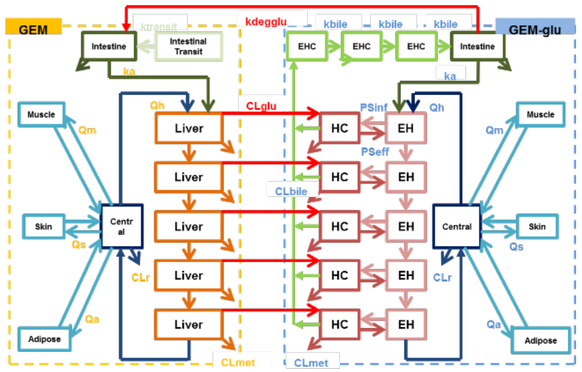




Cyclosporine A (CsA)



Gemfibrozil (GEM)

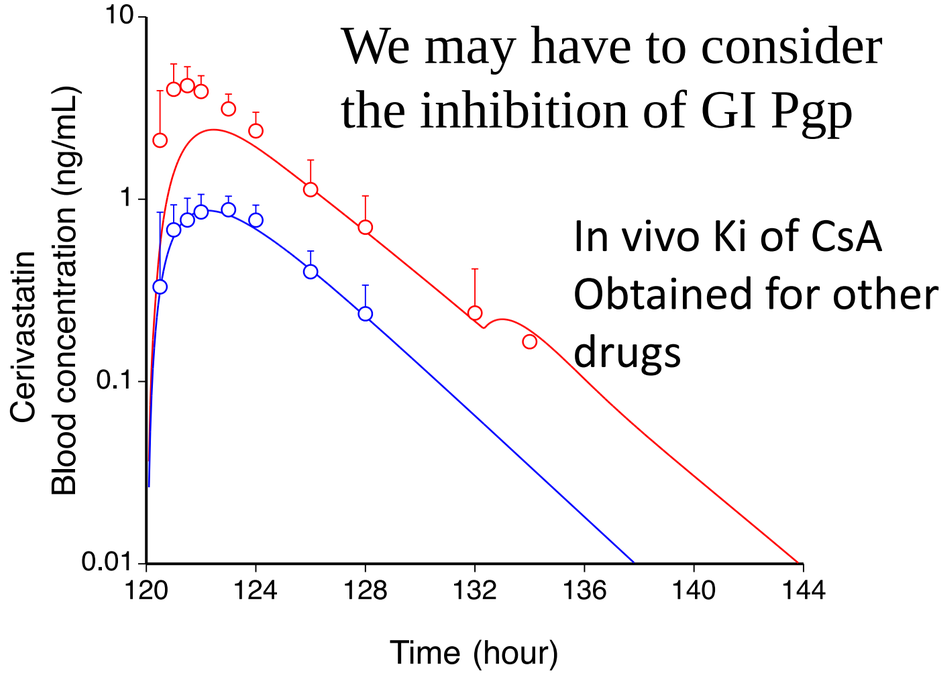


Integration of bottom-up approach
And top-down approach is important

Yoshikado T et al.,
Clin Pharmacol Ther., (2016)

Best simulation of CER vs CsA / CER vs GEM

CER vs CsA

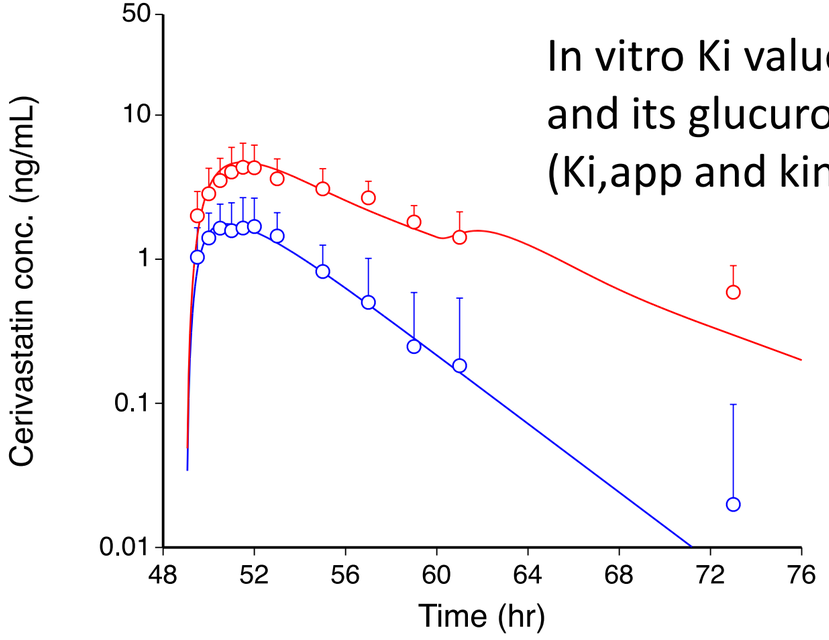


We may have to consider the inhibition of GI Pgp

In vivo Ki of CsA Obtained for other drugs

○ : Observed Data
Mück W et al. *Clin Pharmacol Ther.* (1999)

CER vs GEM



In vitro Ki value of GEM and its glucuronide (Ki,app and kinact) MBI

○ : Observed Data
Backman JT et al., *Clin Pharmacol Ther.* (2002)

Present PBPK models were able to well reproduce the clinical DDIs

Yao Y, Toshimoto K, Kim SJ, Yoshikado T, Sugiyama Y. Quantitative Analysis of Complex Drug-Drug Interactions between Cerivastatin and Metabolism/Transport Inhibitors Using Physiologically Based Pharmacokinetic Modeling. Drug Metab Dispos. 46:924-933. (2018)

Summary

- **The concentration-time profiles for CER and GEM/GEM-glu described by PBPK models were well agreed with the clinically observed data.**

- **The present PBPK models were able to capture the clinical DDIs**
  - **<u>CER and CsA :</u> using x1/2 *in vivo* Ki value for OATP1B1 which is previously reported (substrate-dependent Ki). We may have to take into account the inhibition of intestinal Pgp to better describe this DDI**
  - **<u>CER and GEM:</u> using reported *in vitro kiact value (GEM-glu) and* Ki value for OATP1B1 or CYP2C8 when fm_2C8 = 0.85 value was used**

Complex DDIs involving both transporters and metabolic enzymes could be quantitatively predicted by PBPK modeling (Bottm-up approach) based on the in vitro parameters ($K_{i,}$ k_{inact})

We now know some cases where simple bottom up prediction (IVIVE) cannot be applied.

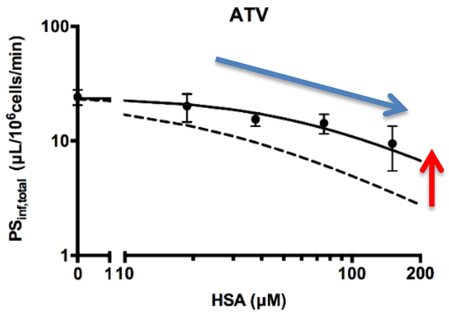
1) **Albumin-mediated hepatic uptake observed for highly protein bound drugs (OATP1B, OAT2 substrates)**

2) **Time-dependent inhibition constant (Ki,app value) observed for some OATP1B inhibitors and OCT1 inhibitors**

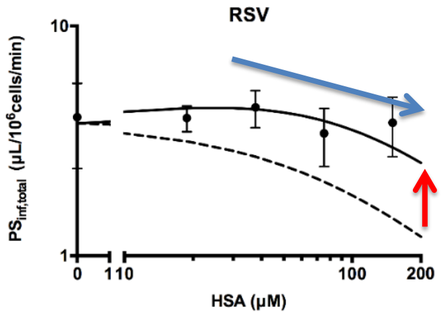
Albumin-mediated uptake of 10 OATPs substrates

Uptake clearance for total drug in various HSA concentrations

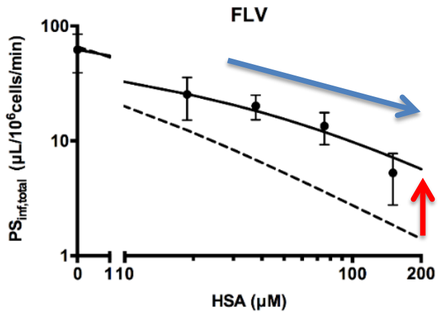
fu,p: 0.0281



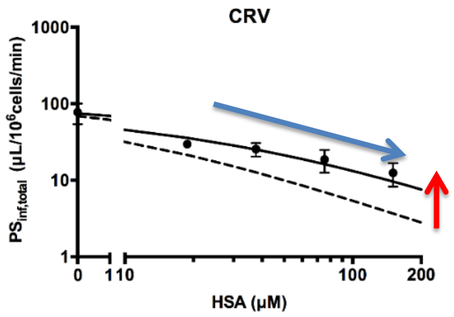
fu,p: 0.0988



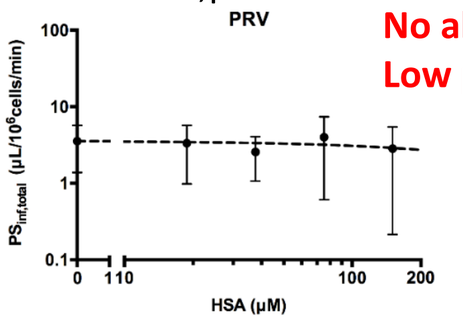
fu,p: 0.00405



fu,p: 0.00961



fu,p: 0.502



No albumin effect,
Low protein binding drug

Solid line: fitted data by Taso's model
Broken line: free theoretical line

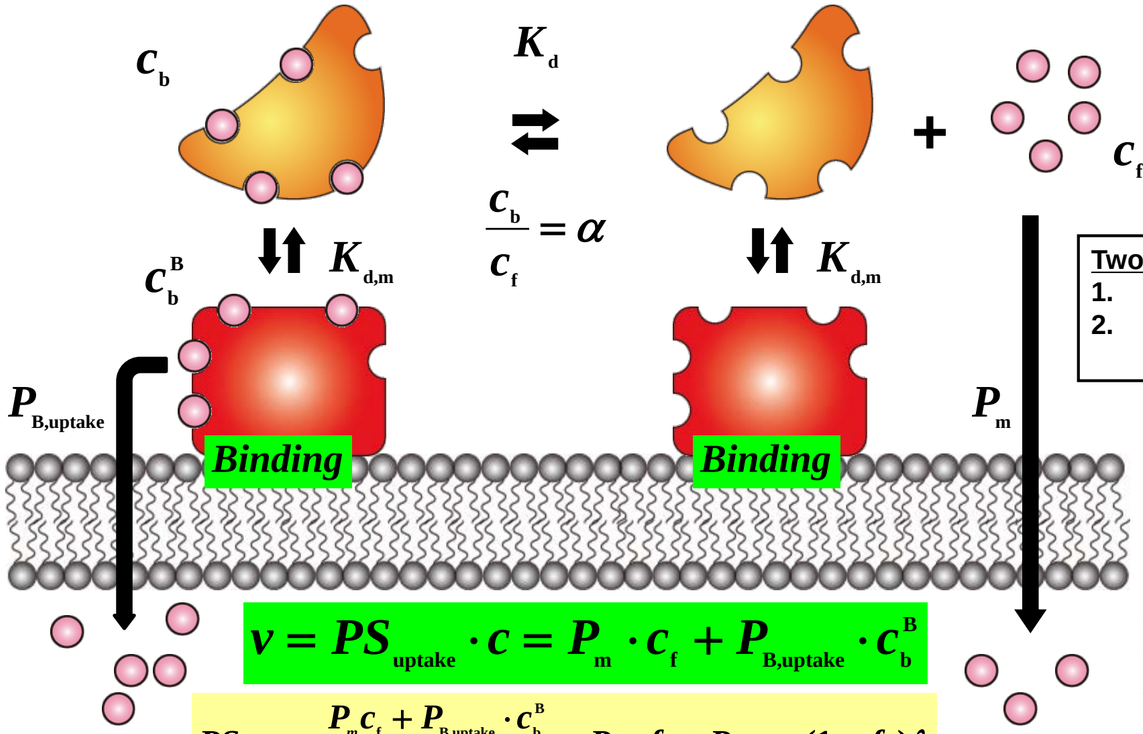
Soo-JinKim, Kyeong-RyoonLee, Seiji Miyauchi, and Yuichi Sugiyama

Extrapolation of In Vivo Hepatic Uptake Clearance from In Vitro Uptake Clearance by Suspended Human Hepatocytes (IVIVE) for Anionic Drugs with High Binding to Human Albumin: Improvement of IVIVE by Considering the "Albumin-Mediated" Hepatic Uptake Mechanism Based on the Facilitated-Dissociation Model

Drug Metab Dispos. 47(2):94-103 (2019).

The interaction of the albumin-ligand complex with the surface of hepatocytes enhances the dissociation of the ligand from albumin

Tsao SC, Sugiyama Y, Sawada Y, Iga T and Hanano M. Kinetic analysis of albumin-mediated uptake of warfarin by perfused rat liver. J Pharmacokinet Biopharm 16:165-181 (1988).



Two pathway
1. Unbound ligand pathway
2. Dissociated ligand pathway from ligand-albumin complex

$$\lambda = \frac{[Alb]_B}{[Alb]_t} = \frac{B_{max}}{K_{d,m} + [Alb]}$$

λ : the ratio of bound albumin concentration to total albumin concentration;
B_{max} is the binding capacity of albumin to the cell surface.

$$v = PS_{uptake} \cdot c = P_m \cdot c_f + P_{B,uptake} \cdot c_b^B$$

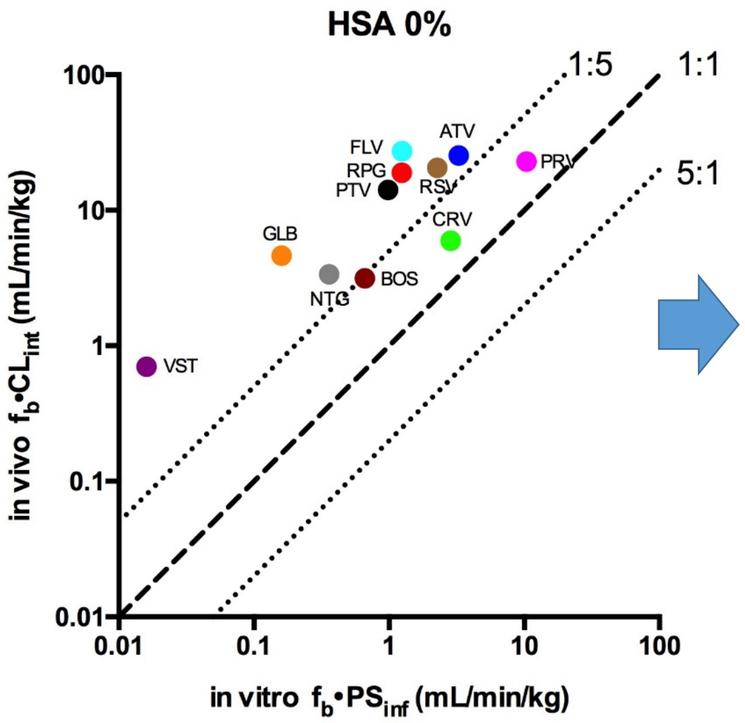
$$PS_{uptake} = \frac{P_m c_f + P_{B,uptake} \cdot c_b^B}{c} = P_m \cdot f_u + P_{B,uptake} \cdot (1 - f_u)\lambda$$

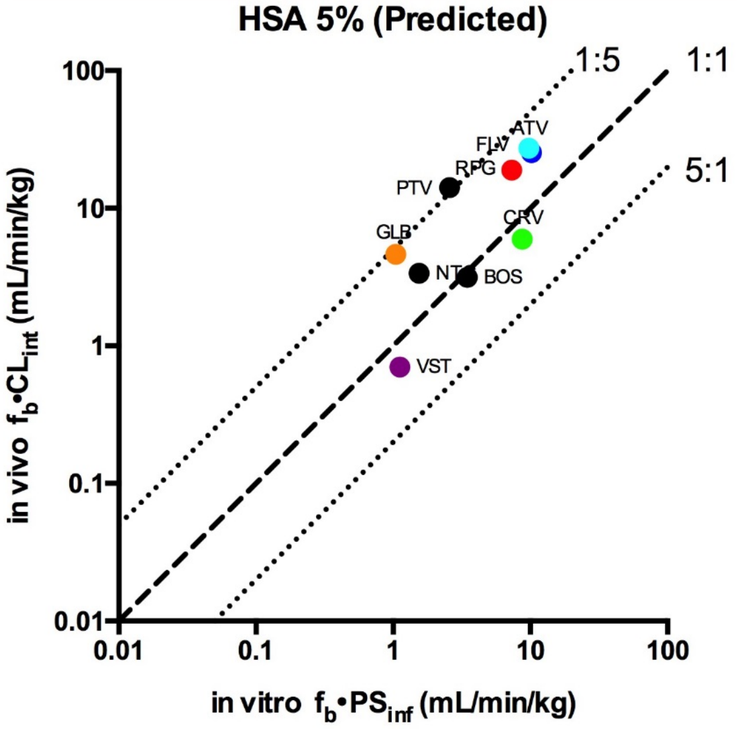
$$PS_{uptake,u} = P_m + P_{B,uptake} \cdot (\frac{1}{f_u} - 1)\lambda = P_m + P_{B,uptake} \cdot \frac{B_{max}[Alb] \cdot \frac{n}{K_d}}{K_m + [Alb]}$$

$$f_u = \frac{1}{[Alb] \cdot \frac{n}{K_d} + 1}$$

Improvement of IVIVE of hepatic uptake clearance by taking into account of albumin-mediated hepatic uptake mechanism

IVIVE was improved by taking into account of the albumin-mediated hepatic uptake, though not perfect.

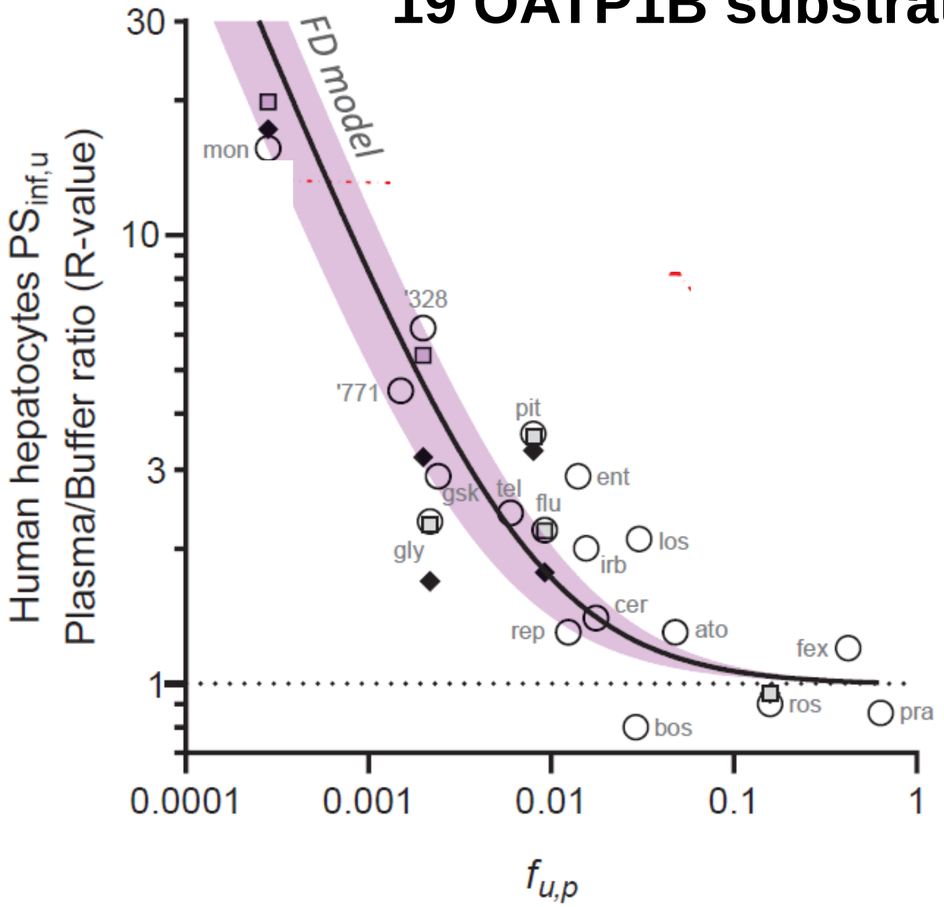




9 compounds

The $CL_{uptake,u}$ (at 5% HSA) predicted by fitting with Taso model was used.

19 OATP1B substrates



Facilitated-dissociation (FD) model

$$R = \frac{PS_{inf,u,plasma}}{PS_{inf,u,buffer}} = 1 + \left(\frac{1}{f_{u,p}} - 1\right) \cdot \frac{r \cdot B_{max}}{K_{d,m} + [Alb]}$$

The parameter 'r' represents a ratio of uptake clearance of the unbound ligand dissociated from the ligand-albumin complex at cell surface to the uptake clearance of the unbound ligand dissociated in the plasma away from cell surface. For data fitting, 'r · Bmax' was considered as a hybrid constant as they were individually un-identifiable.

Yi-an Bi, Sangwoo Ryu, David A. Tess, A. David Rodrigues, Manthena V. S. Varma
Effect of Human Plasma on Hepatic Uptake of Organic Anion-Transporting Polypeptide 1B Substrates: Studies using Transfected Cells and Primary Human Hepatocytes
DMD Fast Forward. Published on November 2, 2020 as DOI: 10.1124/dmd.

(24)

We now know some cased where simple IVIVE cannot be applied.

1) Albumin-mediated hepatic uptake observed for highly protein bound drugs (OATP1B, OAT2 substrates)

2) Time-dependent inhibition constant (Ki,app value) observed for some OATP1B inhibitors and OCT1 inhibitors

Pharmacology & Therapeutics 177 (2017) 67–80

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Preincubation-dependent and long-lasting inhibition of organic anion transporting polypeptide (OATP) and its impact on drug-drug interactions

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[a] Pharmacokinetics, Dynamics and Metabolism, Translational Medicine and Early Development, R&D Operations, Sanofi, Tokyo, Japan
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ARTICLE INFO

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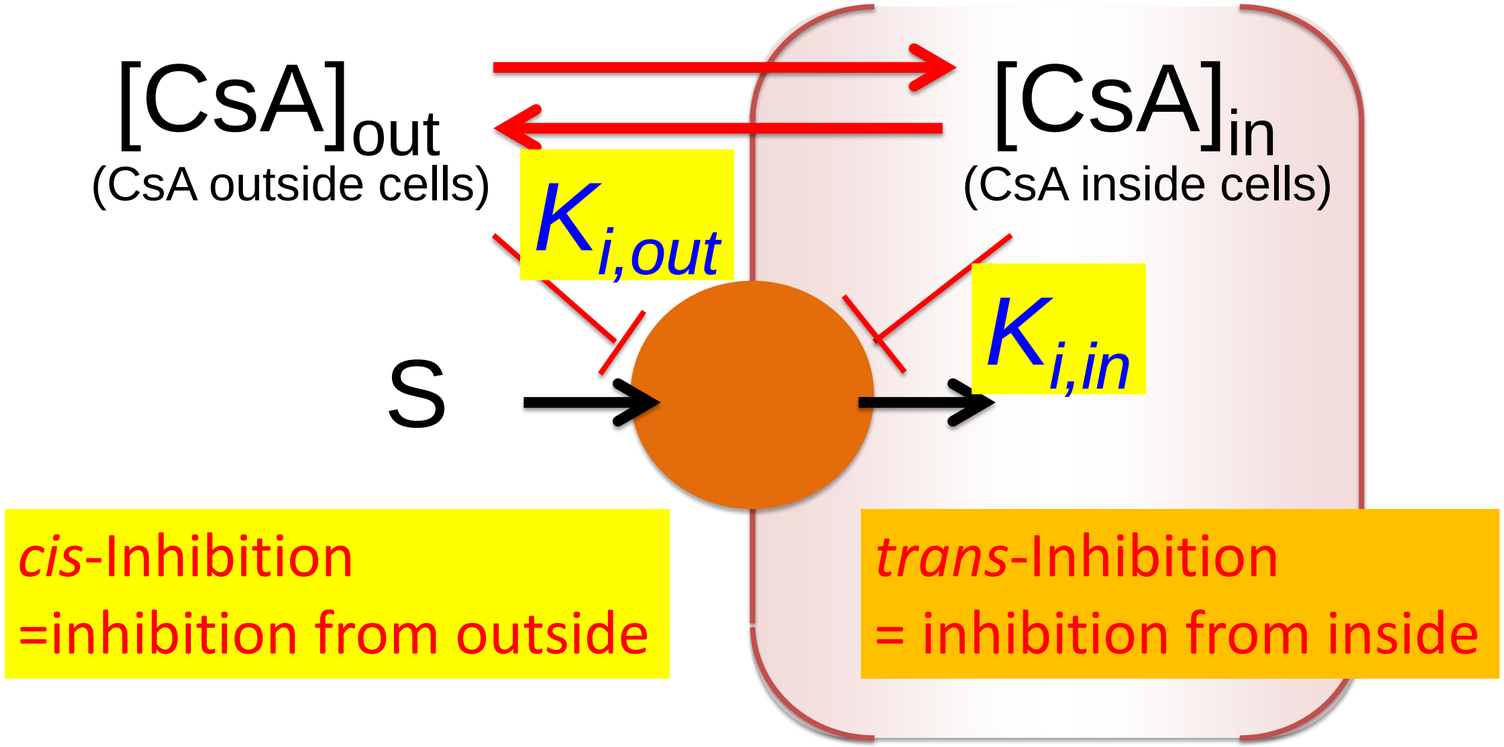
Keywords:
OATP1B1
Drug–drug interactions
Hepatic uptake
Time-dependent inhibition
Long-lasting inhibition
Physiologically based pharmacokinetic model
Modeling & simulation

ABSTRACT

Preincubation with cyclosporin A (CsA), a potent inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3, enhanced its inhibitory effects on these transporters *in vitro*. A similar effect was observed upon preincubation with some other inhibitors. Removing these from the incubation media did not readily reverse the inhibition on OATP1B1 and OATP1B3. This preincubation-dependent long-lasting inhibition appeared to be related to CsA concentration in the cells in addition to that in the incubation media. Thus, we hypothesized that CsA inhibits OATP1B1 and OATP1B3 from inside (*trans*-inhibition) as well as outside (*cis*-inhibition) the cells and constructed the *cis*- and *trans*-inhibition model. The enhanced inhibitory effect of CsA on OATP1B1 observed after preincubation was quantitatively described using $K_{i,out}$ and $K_{i,in}$ as inhibition constants for *cis*- and *trans*-inhibitions, respectively. In addition, a long-lasting inhibition was also described by this model. Additional factors taken into consideration when simulating *in vivo* pharmacokinetic alterations by CsA are potential inhibition by AM1, a major metabolite of CsA, which has been reported to inhibit OATP1B1 and OATP1B3. Based on the physiologically based pharmacokinetic model incorporating *trans*- and *cis*-inhibition of OATP1B1 by CsA, the simulation showed that OATP1B1-mediated drug–drug interaction with CsA was suggested to be time-dependent also *in vivo* although further clinical studies are required for confirmation.

Cis- and trans-inhibition of CsA on OATP1B1



Uptake clearance of OATP1B1 substrates in the liver when co-administered with CsA:

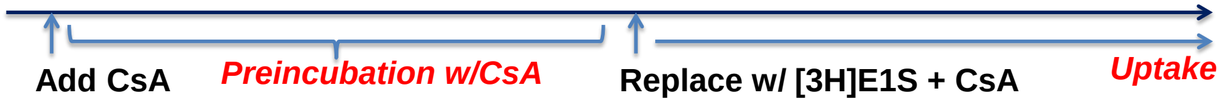
$$CL_{uptake}(+I) = \frac{V_{max}/(1 + f_{u,H}*I_H/K_{i,in})}{K_m*(1 + f_{u,B}*I_{EH}/K_{i,out}) + S}$$

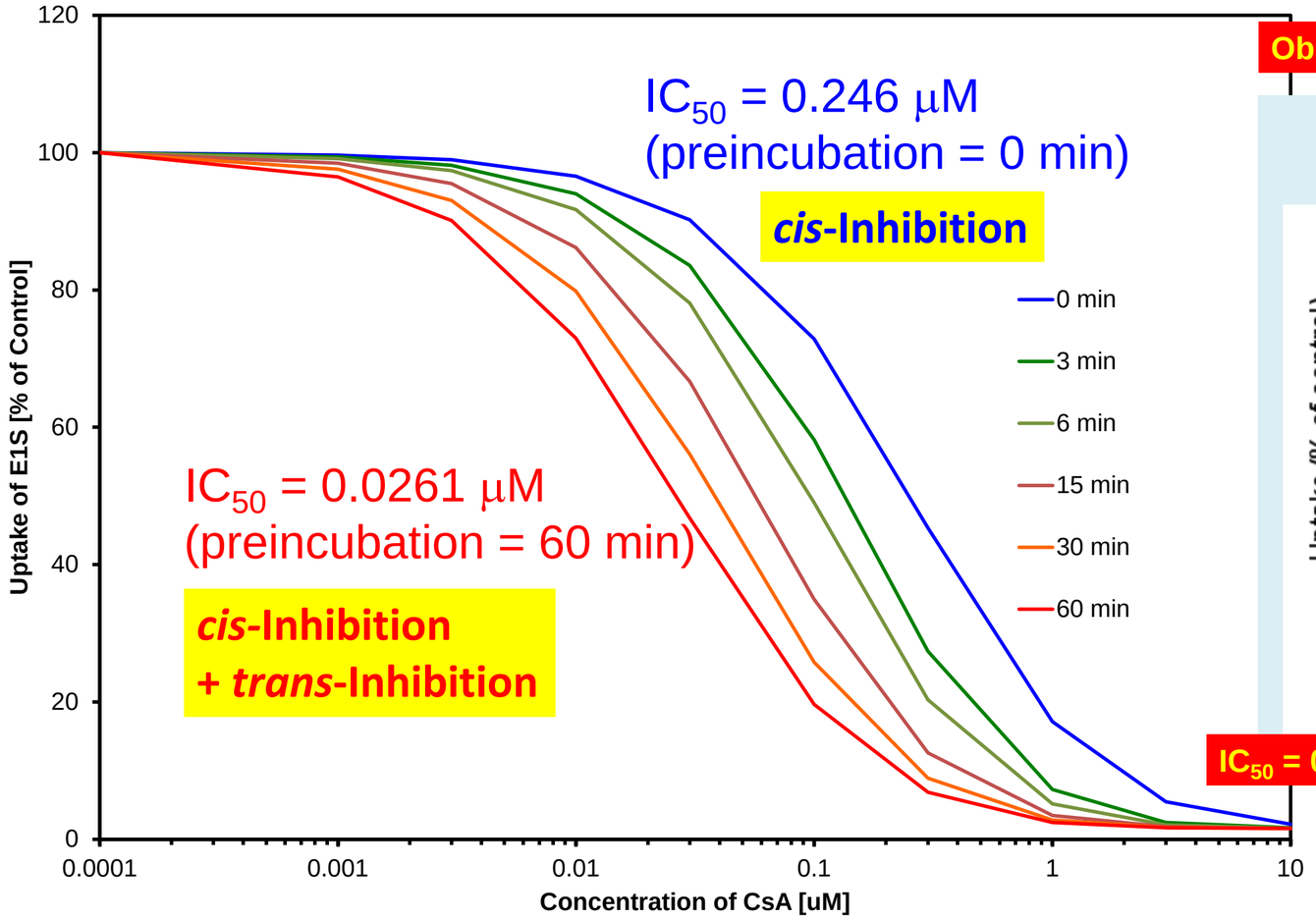
trans-Inhibition (non-competitive)

cis-Inhibition (competitive)

*I_H, I_{EH}: inhibitor (CsA) concentrations in the liver and at the extracellular space of the liver, respectively

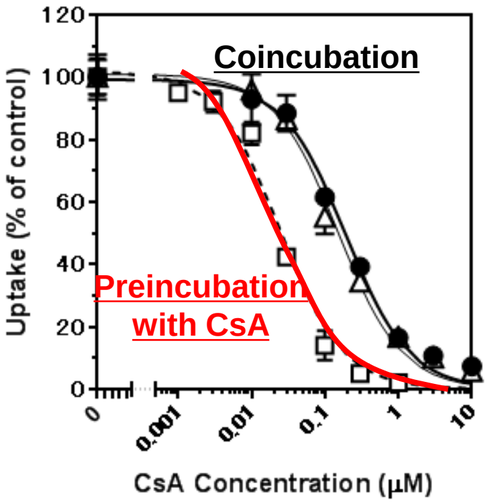
Simulation analysis of time-dependent enhancement effect of inhibition of OATP1B1 by CsA





Observed Data

Inhibition of OATP1B1-mediated uptake of estrone 3-sulfate



IC_{50} = 0.0264 μM ← IC_{50} = 0.253 μM

Izumi S et al. (2015)
Drug Metab Dispos 43, 235

$$1/(1 + I_{out}/IC_{50,app}) = 1/[(1 + I_{out}/K_{i,out})x(1 + I_{u,in,unbound}/K_{i,in})]$$

:with respect to time $I_{u,in}\uparrow$, $K_{i,in}\rightarrow$ $\Rightarrow IC_{50,app}\downarrow$

(1) A Systematic In Vitro Investigation of the Inhibitor Preincubation Effect on Multiple Classes of Clinically Relevant Transporters

Péter Tátrai, Patrick Schweigler, Birk Poller, Norbert Domange, Roelof de Wilde, Imad Hanna,

Zsuzsanna Gáborik, and Felix Huth

Solvo Biotechnology, Budapest, Hungary; Novartis Institutes for Biomedical Research, Basel, Switzerland and Novartis Institutes for Biomedical Research, East Hanover, New Jersey

Drug Metab Dispos 47:768–778, 2019

OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K

(Some inhibitors exhibited more than 200 folds decrease in apparent IC50 value by pre-incubation)

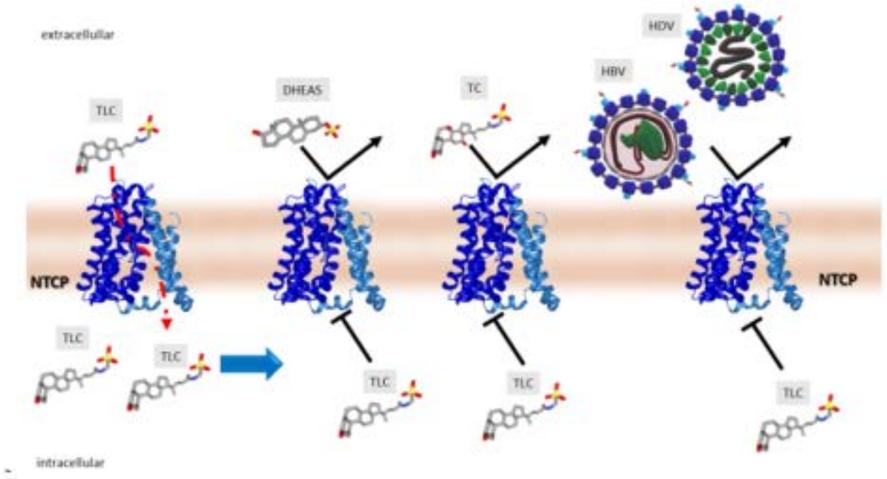
(2) Long-term *trans*-inhibition of the hepatitis B and D virus receptor NTCP by taurolithocholic acid

Long-term *trans*-inhibition of the hepatitis B and D virus receptor NTCP by taurolithocholic acid

Kira AAT Lowjaga, Michael Kirstgen, Simon F Müller, Nora Goldmann, Felix Lehmann, Dieter Glebe, Joachim Geyer

Institute of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Justus Liebig University Giessen, Germany

Am J Physiol Gastrointest Liver Physiol 320: G66–G80, 2021.



What is the best translational approach until the mechanism is fully elucidated?

1) Benefit in using ‘shifted’ IC50 in the PBPK models as conservative approach?
   (Current recommendation by regulations)

2) More mechanism based PBPK modeling; distribution of inhibitor from extracellular space to intracellular sites ⇒ estimation of Permeability clearance, tissue binding, Ki,in, Ki,out⇒ estimation of inhibiting effects which are changed with preincubation-time

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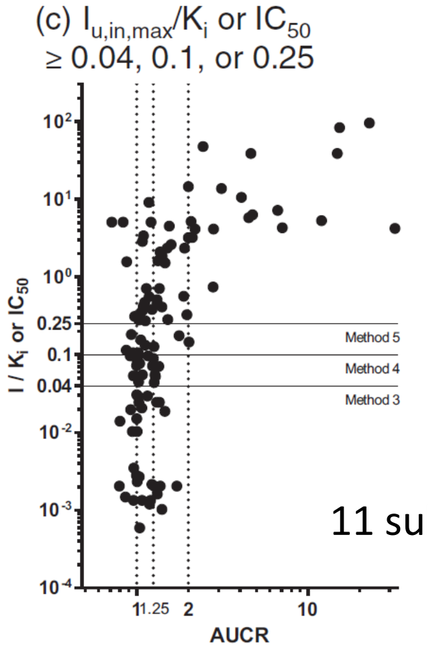
Concerns about the clinical DDI assessment: R-value



$$\text{R-value} = 1 + I_{u,\,in,\,max} / K_i \text{ or } IC_{50}$$

$$I_{u,\,in,\,max} = f_u{}^* I_{max} + (k_a \times \text{Dose} \times F_a{}^* F_g / Q_h)$$

If $F_a{}^* F_g$ values and k_a values are unknown, use 1 and 0.1 min^{-1}
If fu values are <0.1 or undetermined, assume f_u =0.01

11 substrates and 61 inhibitors (total 106 studies)

Many false positive prediction

Method	I: $I_{max}/K_i \geq 0.1$	2: $I_{u,max}/K_i \geq 0.02$	EMA R ≧ 1.04	4: R ≥ 1.1	PMDA R ≧ 1.25	FDA R ≧ 1.25 $I_{max}/Ki \geqq$ 0.1
FN	12	17	8	12	15	17
FP	27	16	33	22	16	13
TN	28	39	22	33	39	42
TP	40	35	44	40	37	35
True positive rate	60%	69%	57%	65%	70%	73%
True negative rate	70%	70%	73%	73%	72%	71%

Vaidyanathan J et al., *J. Clin. Pharmacol.* 2016

Current criteria may request pharmaceutical industry to conduct false positive DDI study, and overlook DDI risk.

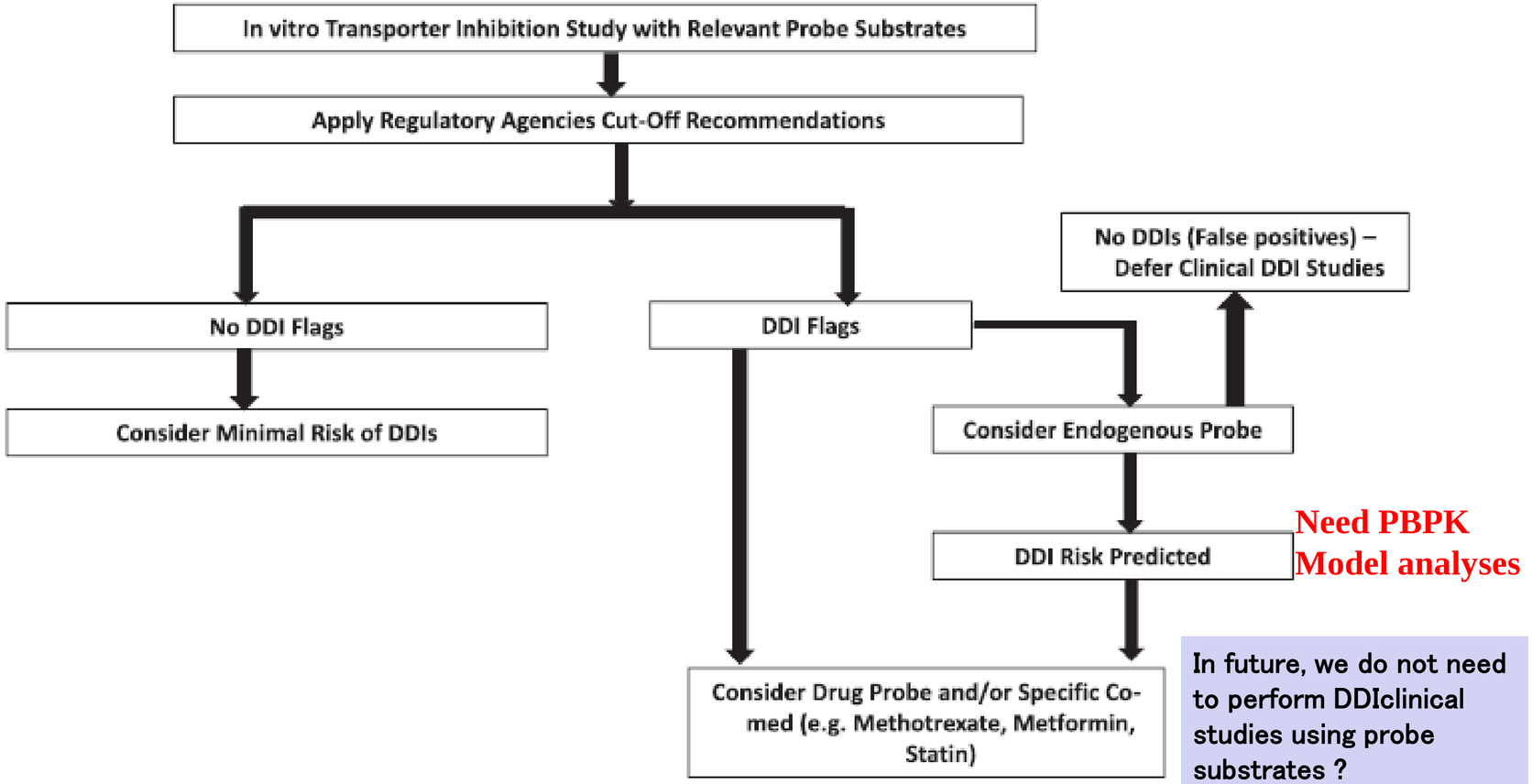
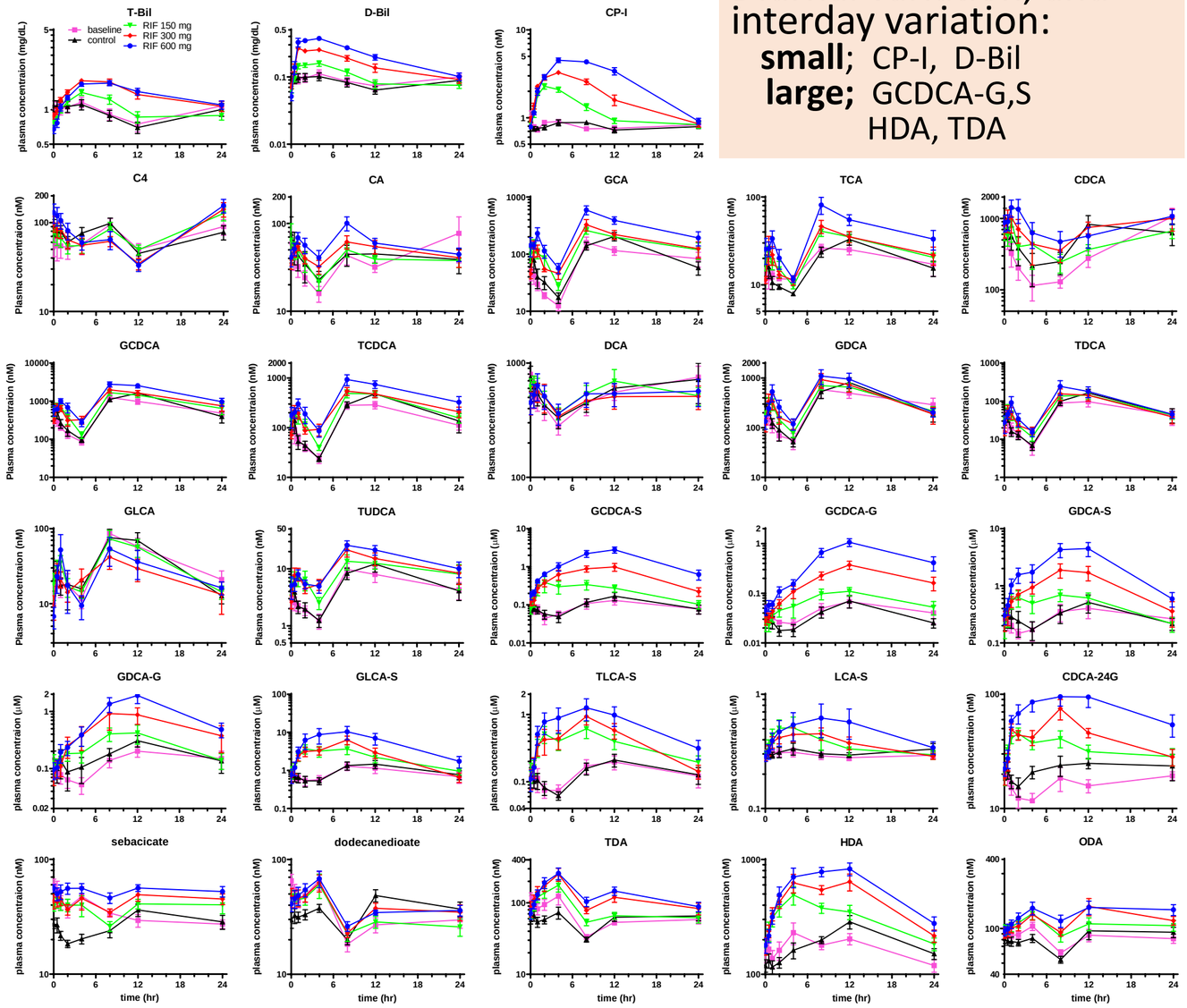


Figure 6 Potential inclusion of endogenous transporter markers in a regulatory decision tree. DDI, drug–drug interaction.

Rodrigues AD, Taskar KS, Kusuhara H, Sugiyama Y.
Clin Pharmacol Ther.103(3):434-448(2018)



Diurnal variation, and interday variation:

small; CP-I, D-Bil

large; GCDCA-G,S

HDA, TDA

C4, 7-hydroxy-4-cholesten-3-one;
CA, cholate; CDCA, chenodeoxycholate; CDCA-24G, chenodeoxycholate-24-glucuronide;
CP-I, coproporphyrin I;
D-Bil, direct bilirubins; DCA, deoxycholate;
GCDCA-G, glycochenodeoxycholate-3-glucuronide;
GCDCA-S, glycochenodeoxycholate-3-sulfate;
GDCA-G, glycodeoxycholate-3-glucuronide;
GDCA-S, glycodeoxycholate-3- sulfate;

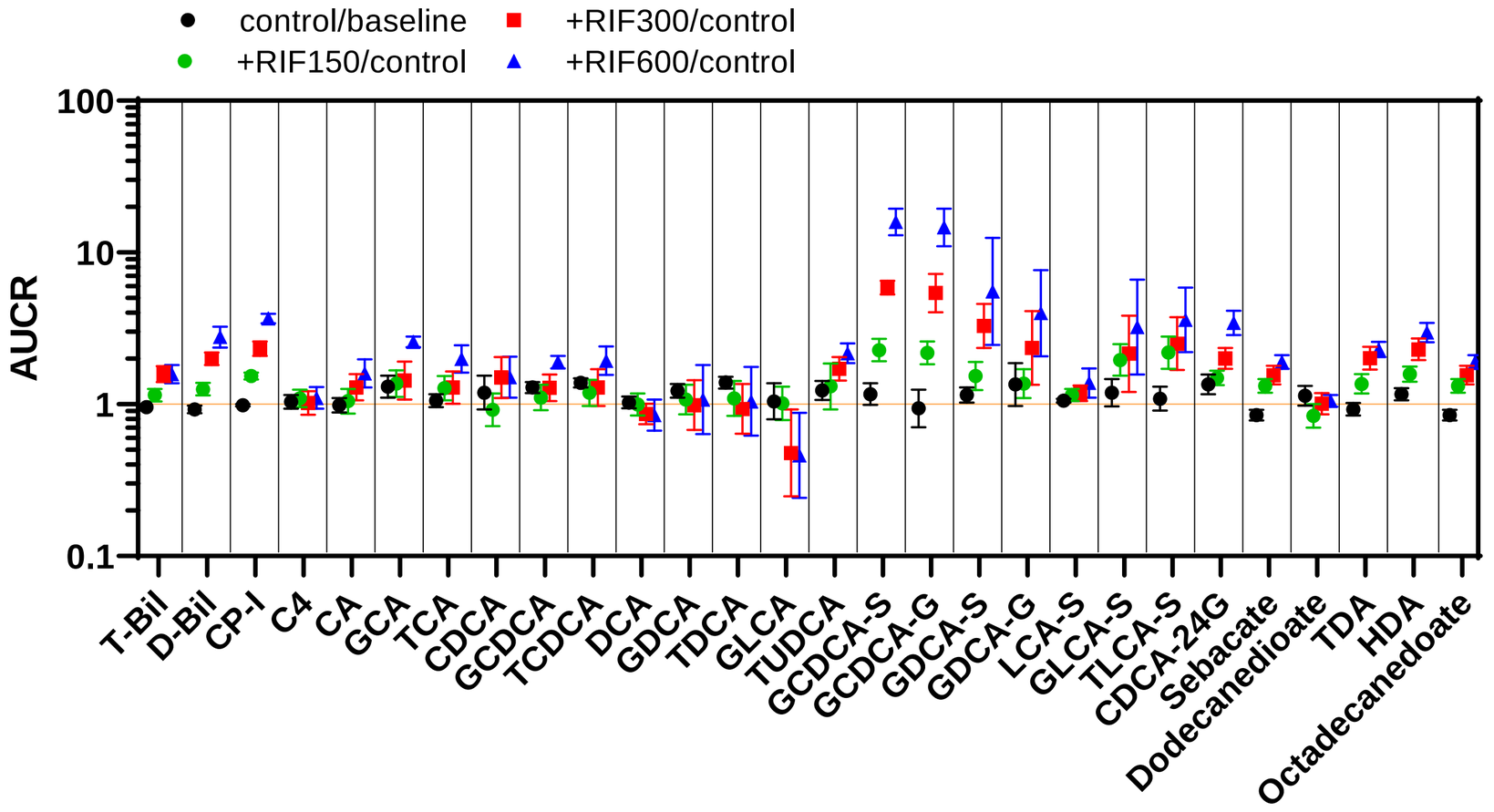
HDA, hexadecanedioic acid;
LCA-S, lithocholate-3-sulfate; RIF, rifampicin;
T-Bil, total bilirubins

Mori D, Kimoto E, Rago B, Kondo Y, King-Ahmad A, Ramanathan R, Wood LS, Johnson JG, Le VH, Vourvahis M, Rodrigues AD, Muto C, Furihata K, Sugiyama Y, Kusuhara H.

Dose-Dependent Inhibition of OATP1B by Rifampicin in Healthy Volunteers: Comprehensive Evaluation of Candidate Biomarkers and OATP1B Probe Drugs.
Clin Pharmacol Ther. 107(4):1004-1013 (2020).

Effect of rifampicin on the plasma concentration time profiles of 4 probe drugs and 28 endogenous substrates

Plasma concentrations of the endogenous substrates were determined at designated times in healthy volunteers treated with or without an oral dose of rifampicin (150, 300 and 600 mg).

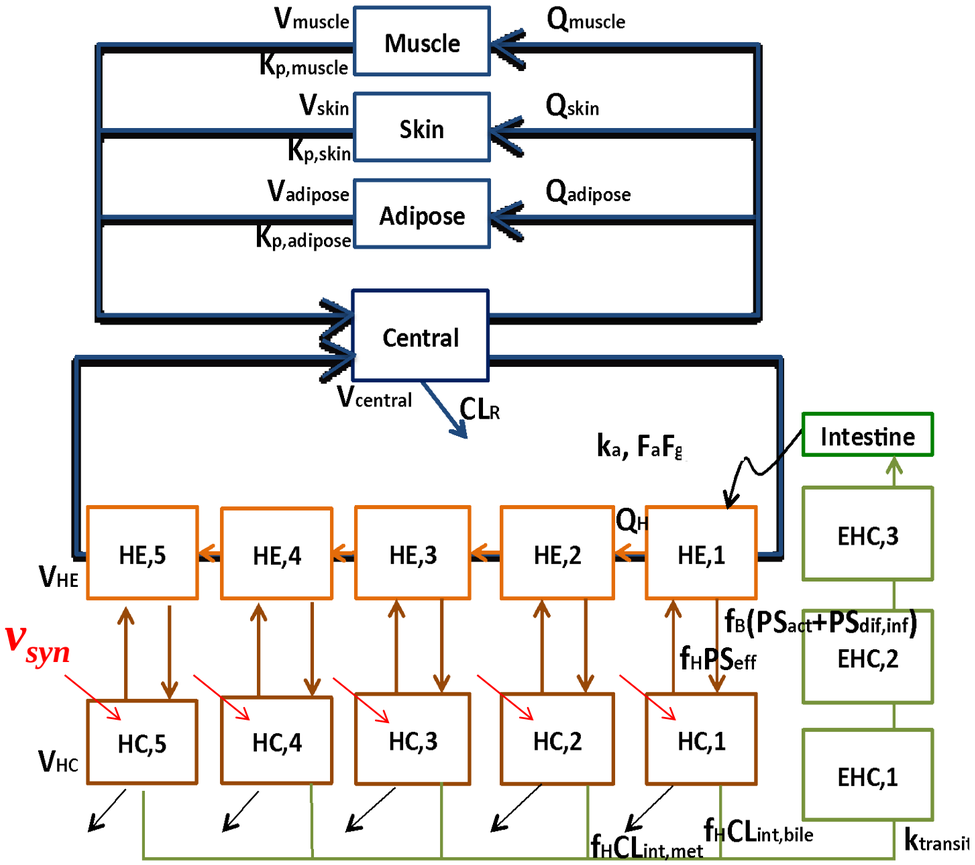


AUCR with 90% confidence interval assuming log normal distribution of various endogenous substrates with increasing dose of rifampicin. AUC0-24h was used to calculate AUCR.

Mori D, Kimoto E, Rago B, Kondo Y, King-Ahmad A, Ramanathan R, Wood LS, Johnson JG, Le VH, Vourvahis M, Rodrigues AD, Muto C, Furihata K, Sugiyama Y, Kusuhara H.
Dose-Dependent Inhibition of OATP1B by Rifampicin in Healthy Volunteers: Comprehensive Evaluation of Candidate Biomarkers and OATP1B Probe Drugs. Clin Pharmacol Ther. 107(4):1004-1013 (2020).

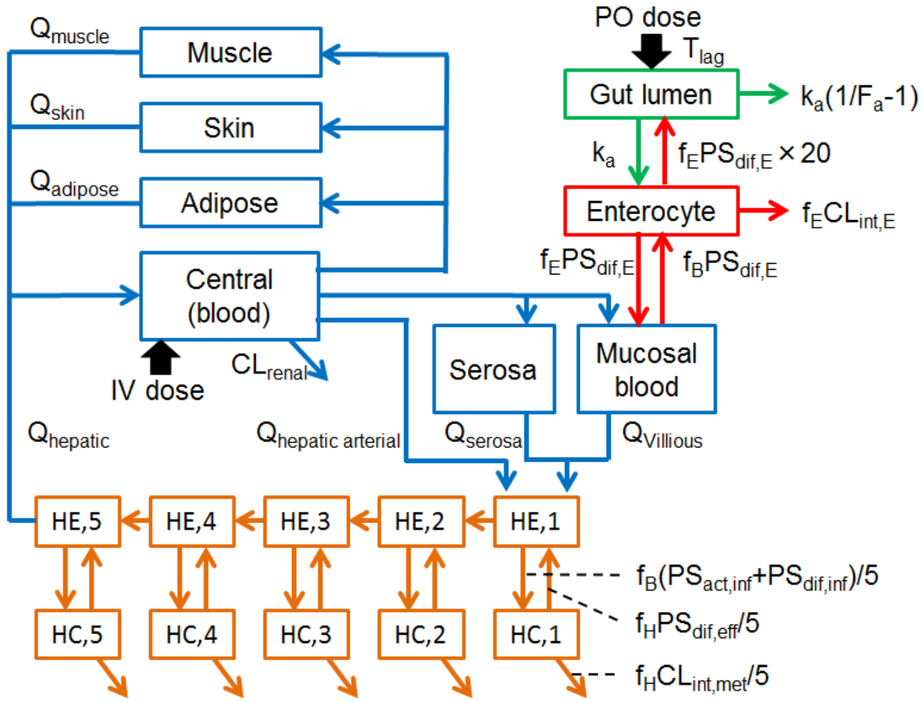
Structure of PBPK models for CP-I and rifampicin

CP-I



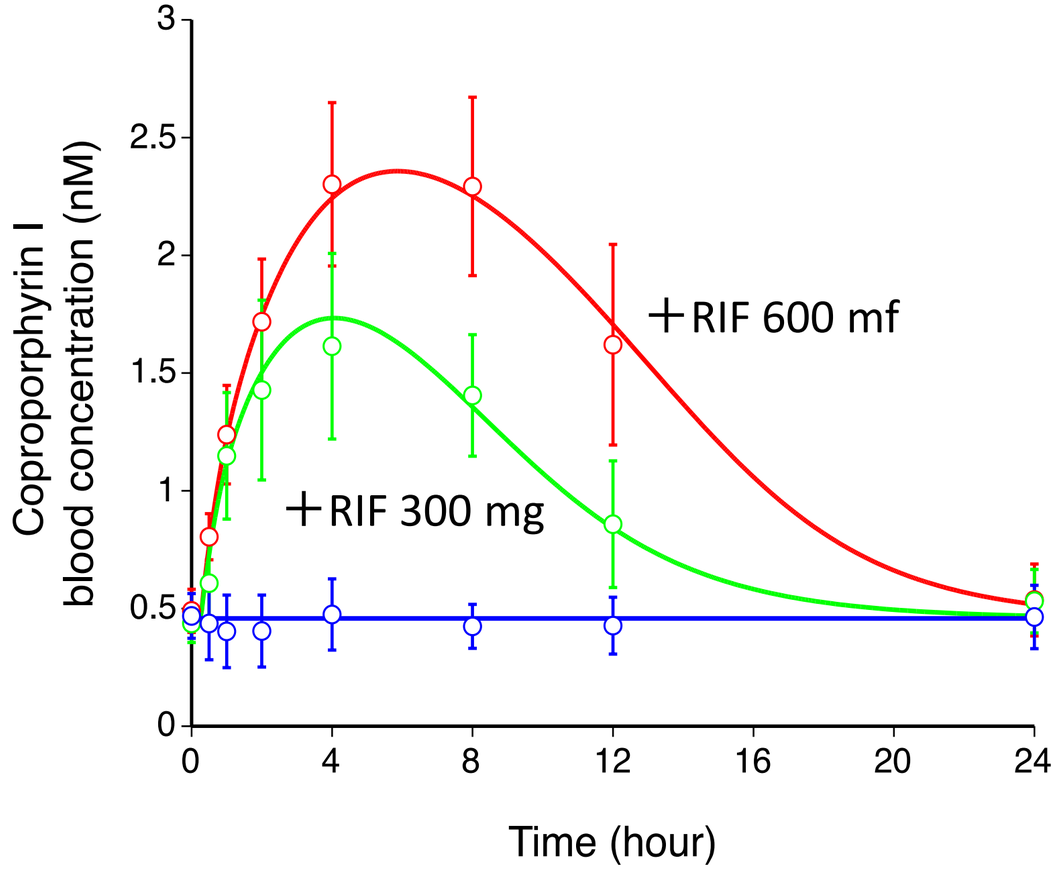
Rifampicin

Asaumi et al., CPT-PSP 7:186-196, 2018



☑ The basic model structure for OATP1Bs substrates was reported previously *(Yoshikado et al., Clin Pharmacol Ther 100:513-523, 2016).*

☑ The biosynthesis rate (v_{syn}) of CP-I is incorporated.



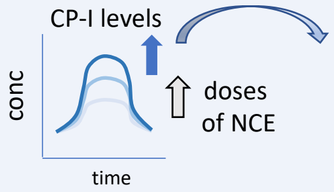
Simultaneously fitted blood concentration–time profiles of CP-I in the absence and presence of RIF after parameter optimization using the PBPK model incorporating the inhibition of OATP1Bs and MRP2.

Yoshikado T, Toshimoto K, Maeda K, Kusuhara H, Kimoto E, Rodrigues AD, Chiba K, Sugiyama Y. PBPK Modeling of Coproporphyrin I as an Endogenous Biomarker for Drug Interactions Involving Inhibition of Hepatic OATP1B1 and OATP1B3. CPT Pharmacometrics Syst Pharmacol. 7(11):739-747 (2018).

Strategy to predict DDI for a probe substrate using CP-I as an endogenous biomarker

Step 1

phase I trial of New Chemical Entity (NCE)



Obtain ***in vivo*** $K_{i,OATP1Bs\ (CP\text{-}I)}$ using CP-I (an endogenous probe)

Step 2

***in vitro* transport study** to obtain inhibitory potency of NCE using CP-I and a probe drug

in vitro $K_{i,OATP1Bs\ (CP\text{-}I)}$

in vitro $K_{i,OATP1Bs\ (Drug)}$

Obtain

in vivo $K_{i,OATP1Bs\ (Drug)}$ = ***in vivo*** $K_{i,OATP1Bs\ (CP\text{-}I)}$ X $\frac{\textit{in vitro}\ K_{i,OATP1Bs\ (Drug)}}{\textit{in vitro}\ K_{i,OATP1Bs\ (CP\text{-}I)}}$

Step 3

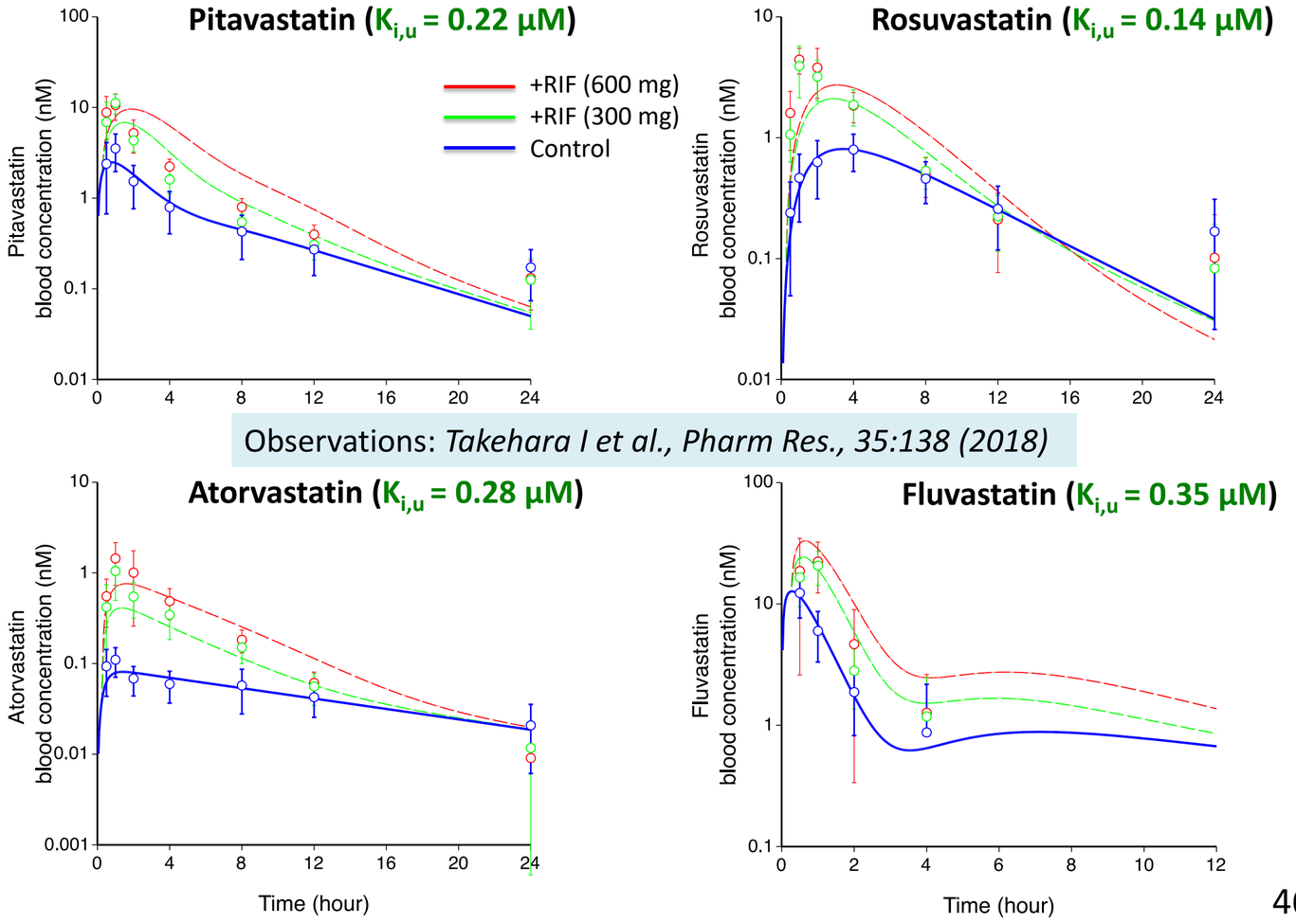
PBPK modeling-based simulations

Quantitative prediction of the impact of NCE on the pharmacokinetics of a probe drug (concentration-time profiles, AUC, C_{max})

Yoshikado T, Toshimoto K, Maeda K, Kusuhara H, Kimoto E, Rodrigues AD, Chiba K,Sugiyama Y. PBPK Modeling of Coproporphyrin I as an Endogenous Biomarker for Drug Interactions Involving Inhibition of Hepatic OATP1B1 and OATP1B3.
CPT Pharmacometrics Syst Pharmacol. 7:739-747 (2018)

Flowchart: Thanks to Dr. Wooin Lee

Prediction of the effect of RIF on blood concentration-time profiles of statins
(Correction of in vivo $K_{i,uOATP1Bs}$ based on substrate-dependent difference of in vitro $K_{i,u}$)



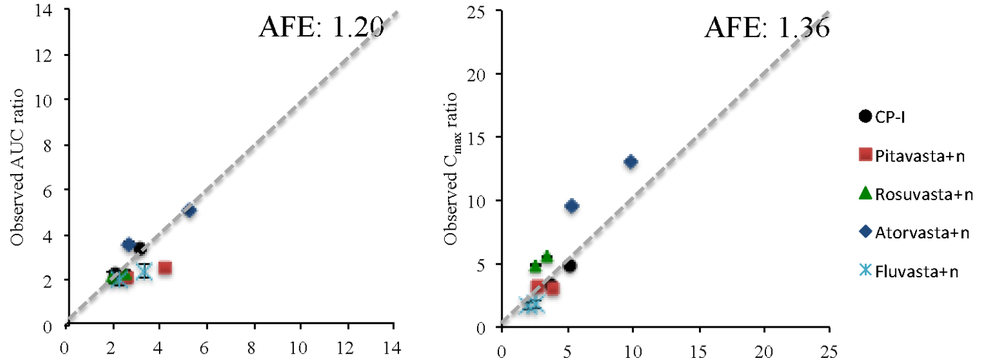
Observations: *Takehara I et al., Pharm Res., 35:138 (2018)*

Predicted and observed AUC ratios and C_{max} ratios for statins using our PBPK models

With Taking substrate-dependent $K_{i,u,OATP1Bs}$ into consideration

Upper panel

Ki(CP-I)
≠ Ki (statins)



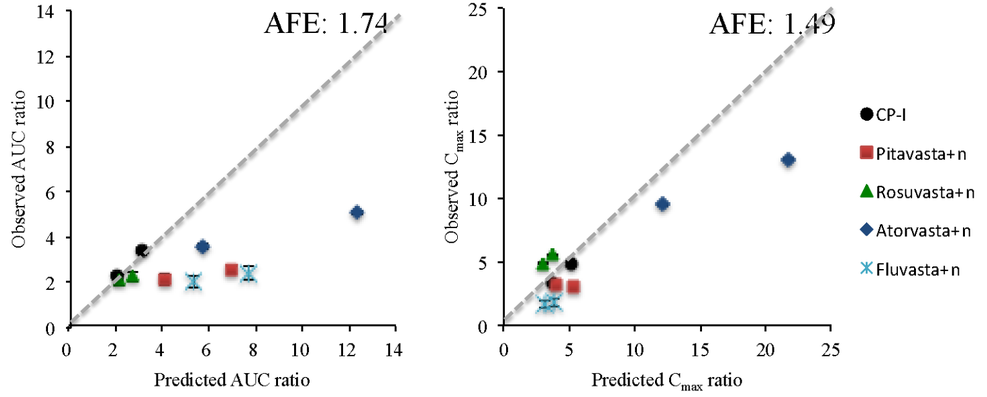
Observations: *Takehara I et al., Pharm Res., 35:138 (2018)*

AFE:
Average fold errors

Without taking substrate-dependent $K_{i,u,OATP1Bs}$ into consideration

Lower panel

Ki(CP-I)
= Ki (statins)



Summary

The PBPK modeling approach provides an insightful understanding of the mechanisms governing changes in the plasma conc. of an endogenous biomarker (CP-I) for OATP1Bs and MRP2 (CP-I) and enables complex analyses of the dose-dependent inhibitory effects of RIF on the hepatic OATP1Bs/MRP2-mediated transport of CP-I.

It also lead to the successful prediction of RIF interaction with several probe substrates (statins) for OATP1Bs.

Ki value for MRP2 (as a biliary excretion transporter of CP-I) cannot be determined only from the top-down analyses, and the value obtained by PET imaging analyses of different probe (TIC-Me (PGI2 receptor imaging in the brain)) was used to obtain Ki,MRP2 (0.87 uM).

Perspective

Emphasize the importance of the use of multiple biomarkers (coproporphyline I, bilirubin glucuronide and glycochenodeoxycholic acid sulfate) to assess the OATP1Bs mediated interaction of new NCE as perpetrators in their phase 1 clinical studies.

Some of recent manuscripts indicate the advantage and validity of the use of coproporphyline I as a biomarker of OATP1Bs function in vivo. However, it is not so easy to confirm that your NCE does not modulate other transporters and enzymes which will be responsible for the biosynthesis, intestinal absorption and biliary excretion and renal clearance of this biomarker. In fact, rifampicin and cyclosporine which are well known to inhibit OATP1Bs mediated hepatic uptake are also known to affect P-gp/BCRP in the intestine, BSEP and MRP2/BCRP in the liver.

Use of multiple biomarkers will ultimately increase the confidence in our prediction of clinical DDI using biomarkers from pharmaceutical and regulatory perspectives.

Contents

1) Introduction;
Rate-determining process (focusing on the liver)
(Uptake, efflux, elimination, metabolism) DDI

2) PGx of OATP1B1: PBPK model based analysis

3-1) PBPK model based analysis of OATPs mediated drug-drug interaction
(Top down + Bottom-up)

(i) victim drugs-perpetrator drugs
(ii)endogenous biomarker (CP-I) – rifampicin

3-2) Simple bottom-up predictions dot not always work well.
(i) prediction of hepatic clearance of highly protein bound drugs
(albumin-mediated hepatic uptake mechanisms should be considered)
(ii) Time-dependent inhibition (inhibitors for OATP1B and OCTs)

4) Target-mediated drug disposition (TMDD); To obtain dose-dependent change in molecular target occupancies only from the plasma concentration time-profile

Target-mediated Drug Disposition (TMDD)

- ✓Introduced by Dr. Gerhard Levy (1994)
- ✓Type of **nonlinear PK**
- ✓**When drugs bind to a target with high affinity and to a significant extent (relative to dose),** part of the initial dose is rapidly acquired by the target sites and only then the drug will distribute to other tissues.

Pharmacologic target-mediated drug disposition

Gerhard Levy, PharmD *Amherst, N.Y.*

(Clin Pharmacol Ther, 1994)

Well-recognized with biologics (e,g, monoclonal antibodies),

but earliest examples were in fact small-molecule drugs

(more cases being reported/identified lately)

Gerhard Levy, PharmD (1928-2017)

Courtesy from Wooin Lee

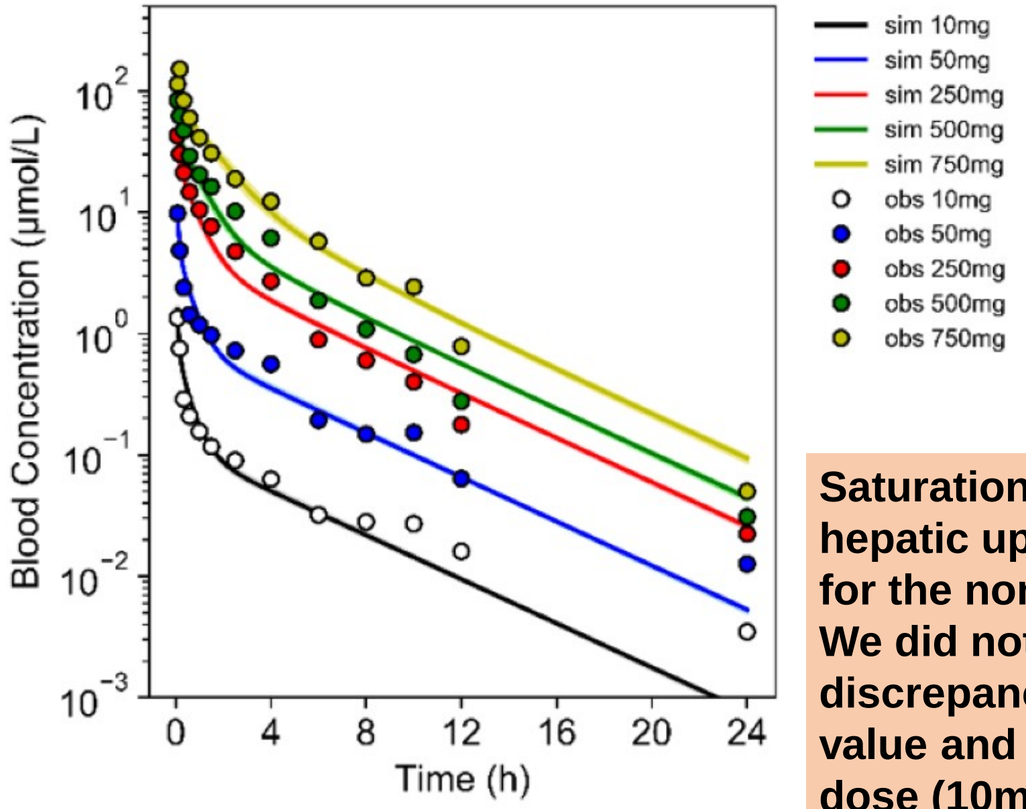
Can the prediction of dose-dependent molecular target occupancy be possible from the phase-1 clinical studies ?

Just measuring the blood concentration of drugs over a wide range of dose without measuring the tissue concentration such as PET imaging

This is the methodology presented in a recent NRDD review(1) and in a recent original article on bosentan (2)

(1) Burt T, Young G, Lee W, Kusuhara H, Langer O, Rowland M, Sugiyama Y.
Phase 0/microdosing approaches: time for mainstream application in drug development?
Nat Rev Drug Discov. 19(11):801-818 (2020).

(2) Koyama S, Toshimoto K, Lee W, Aoki Y, and Sugiyama Y.
Revisiting nonlinear bosentan pharmacokinetics by PBPK modeling: Target binding, albeit not a major contributor to nonlinearity, can offer prediction of target occupancy
Drug Metab Dispos., in press



Volz A-K, Dingemanse J, Krause A, and Lehr T (2019) Target-mediated population pharmacokinetic modeling of endothelin receptor antagonists. *Pharm Res* **37**:2.

Saturation of OATP1B mediated hepatic uptake mostly accounted for the non-linear PK of bosentan. We did not analyze such a discrepancy between observed value and fitted line at the lowest dose (10mg)

Our previous publication

Sato M, Toshimoto K, Tomaru A, Yoshikado T, Tanaka Y, Hisaka A, Lee W, Sugiyama Y.
Physiologically Based Pharmacokinetic Modeling of Bosentan Identifies the Saturable Hepatic Uptake as A Major Contributor to Its Nonlinear Pharmacokinetics. Drug Metab Dispos. 46(5):740-748 (2018).

(44)

26

Recent studies on the analyses of non-linear PK of bosentan

Sato M, Toshimoto K, Tomaru A, Yoshikado T, Tanaka Y, Hisaka A, Lee W, and Sugiyama Y
Physiologically based pharmacokinetic modeling of bosentan identifies the saturable hepatic uptake as a major contributor to its nonlinear pharmacokinetics.
Drug Metab Dispos 46: 740–748 (2018)

(Major mechanism for non-linear PK: Hepatic uptake (OATP1B)

Li R, Niosi M, Johnson N, Tess DA, Kimoto E, Lin J, Yang X, Riccardi KA, Ryu S, El-Kattan AF, et al.
A study on pharmacokinetics of bosentan with systems modeling, part 1: translating systemic plasma concentration to liver exposure in healthy subjects.
Drug Metab Dispos 46: 346–356 (2018).

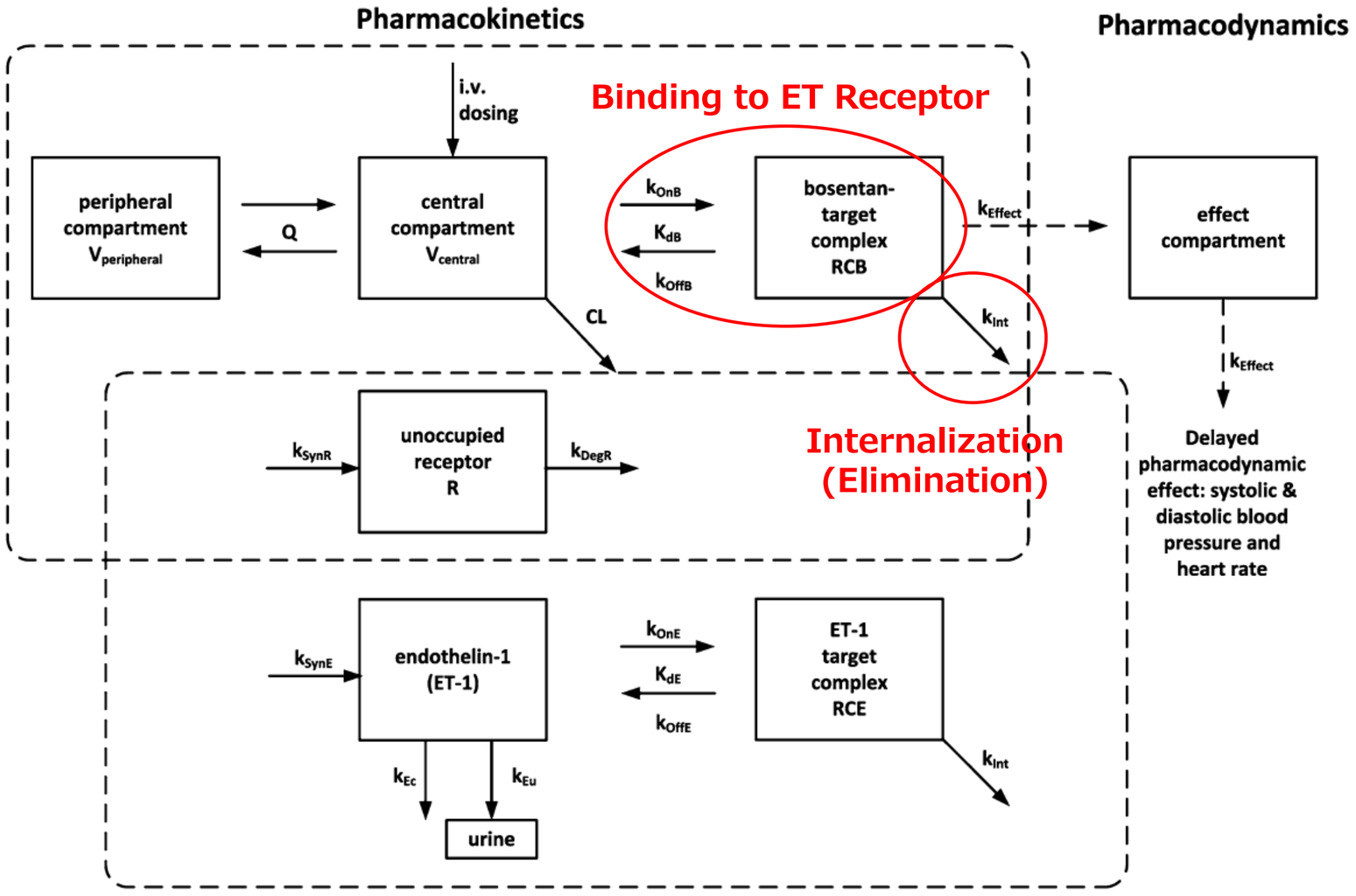
(Major mechanism for non-linear PK:Multiple mechanism, OATP1B, CYPs, TMDD)

Volz A-K, Krause A, Haefeli WE, Dingemanse J, and Lehr T:
Target-mediated drug disposition pharmacokinetic–pharmacodynamic model of bosentan and endothelin-1.
Clin Pharmacokinetics 56:1499–1511 (2017).

Volz A-K, Dingemanse J, Krause A, and Lehr T :
Target-mediated population pharmacokinetic modeling of endothelin receptor antagonists.
Pharm Res **37**:2 (2019) .

(Major mechanism for non-linear PK: Target binding followed by the internalization(TMDD))

Volz A. *et al.*, ClinPhamacokinet. 2017

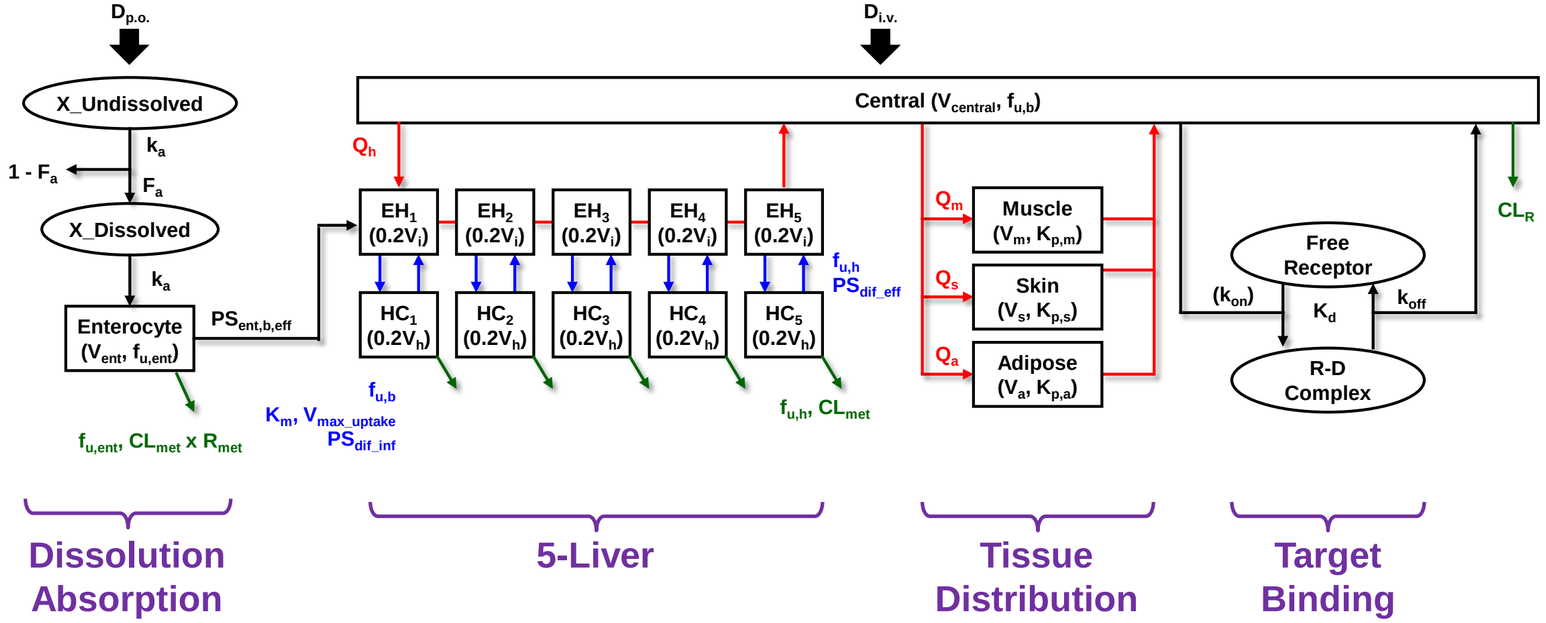


- Population PK/PD Model considering only TMDD.
- There is no evidence that bosentan can be internalized and eliminated after binding to ET receptor. (Endothelin can be interenalized and degradated.)

(45)

PBPK Model Structure of Bosentan

Koyama S, Toshimoto K, Lee W, Aoki Y, and Sugiyama Y.
Revisiting nonlinear bosentan pharmacokinetics by PBPK modeling:
Target binding, albeit not a major contributor to nonlinearity, can offer prediction of target occupancy
Drug Metab Dispos., 49:298-304 (2021)



- Combined dissolution/absorption, 5 liver, tissue distribution, and target binding.
- Target binding is directly connected to central compartement.

- Considered saturable hepatic uptake and target binding, and non-saturable metabolism.
- Assuming linear and dissolution-rate limited absorption.

(48)

Cluster Gauss-Newton method in comparison to conventional methods

Conventional methods

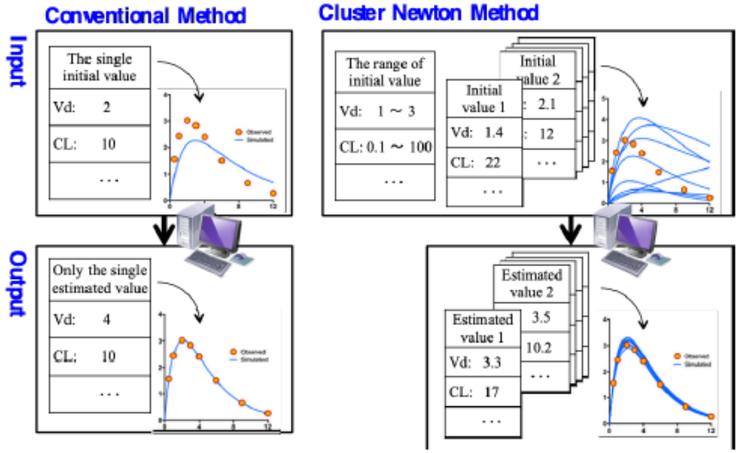
- Requires **appropriate initial iterate** for the parameters.
- Obtains **only a single set** of optimised solutions.
- Computationally **expensive**.
  - Need extra model evaluations (e.g. for derivative computation)
  - Need to restart with different initial parameters

Requires a lot of experience!

Cluster Gauss-Newton method

- Only requires **setting wide ranges** of initial iterates.
- Obtains **multiple sets** of optimised solutions.
- Computationally **cheap and robust**.
  - No need for extra model evaluation.
  - Can estimate many unknown parameters in a complex model

Requires less experience.



Aoki, Y., Hayami, K., Toshimoto, K., & Sugiyama, Y. (2020). Cluster Gauss–Newton method. *Optimization and Engineering*, 1-31.

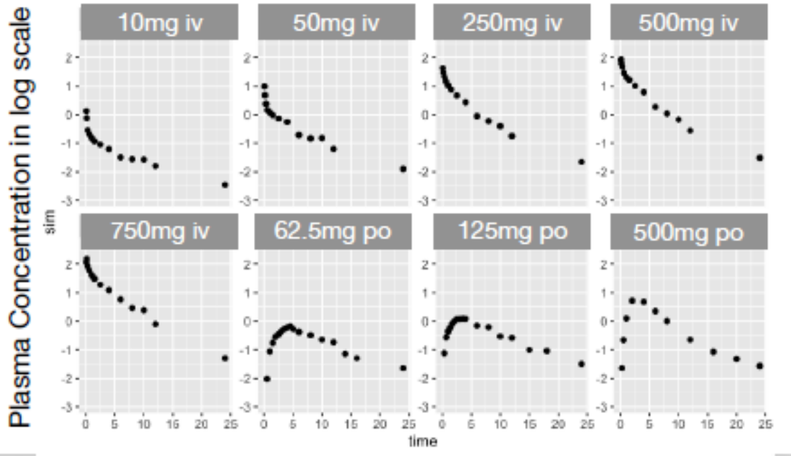
Aoki Y, Hayami K, Toshimoto K, Sugiyama Y. (2020)
Cluster Gauss–Newton method; An algorithm for finding multiple approximate minimisers of nonlinear least squares problems with applications to parameter estimation of pharmacokinetic models.
Optimization and Engineering https://doi.org/10.1007/s11081-020-09571-2

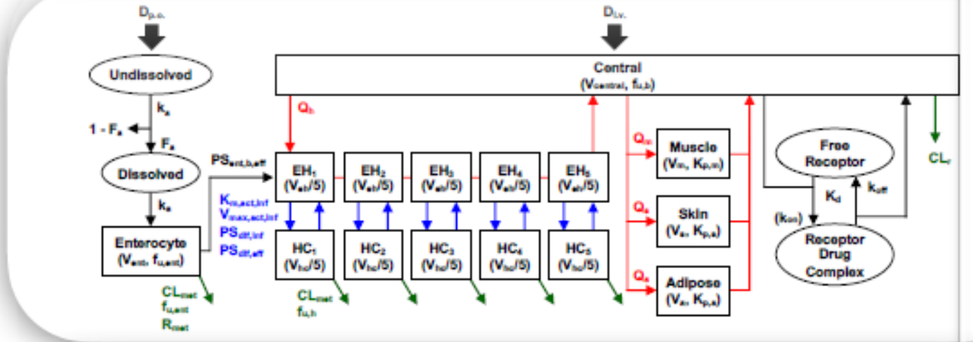
Estimating the receptor occupancy of bosentan with top-down approach

Drug Concentration **Measurements**

Physiology based model

Estimate Unknown PK parameters





CL_{met}=? **k_{off}=?** k_{on}=? **Kd=?**

$PS_{ent\ b\ efflux}$=? $PS_{dif\ inf}$=?

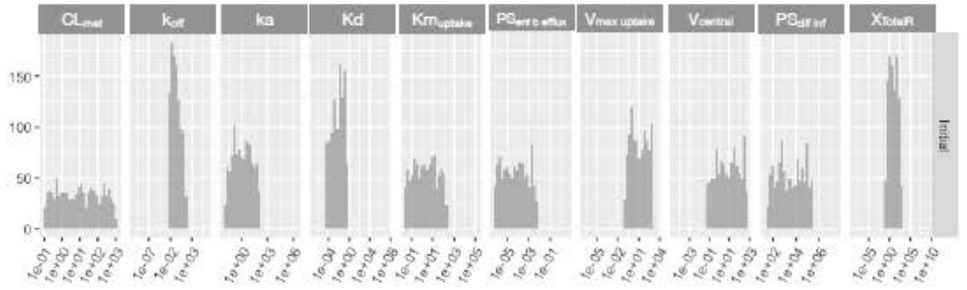
$V_{central}$=?

Km_{uptake}=? $V_{max\ uptake}$=? **X_{TotalR}=?**

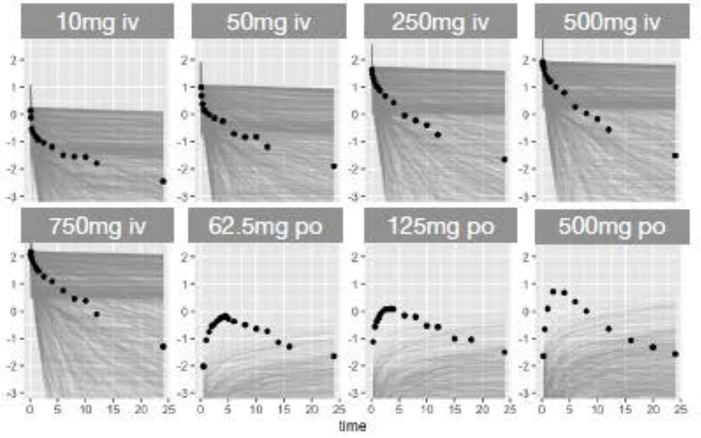
Koyama, Satoshi, et al. "Revisiting nonlinear bosentan pharmacokinetics by PBPK modeling: Target binding, albeit not a major contributor to nonlinearity, can offer prediction of target occupancy." *Drug Metabolism and Disposition (accepted for publication)*.

Estimating the receptor occupancy of bosentan with top-down approach

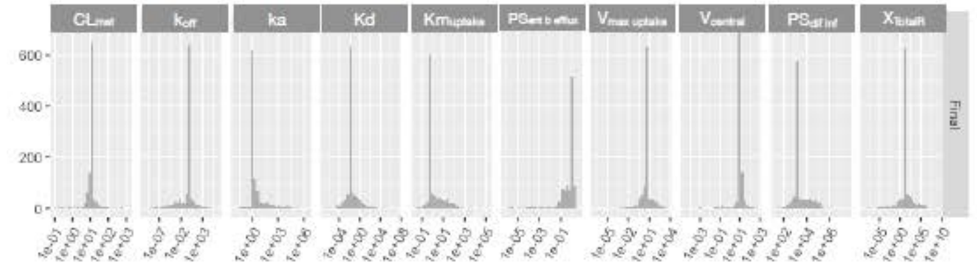
Initial Parameter Distribution



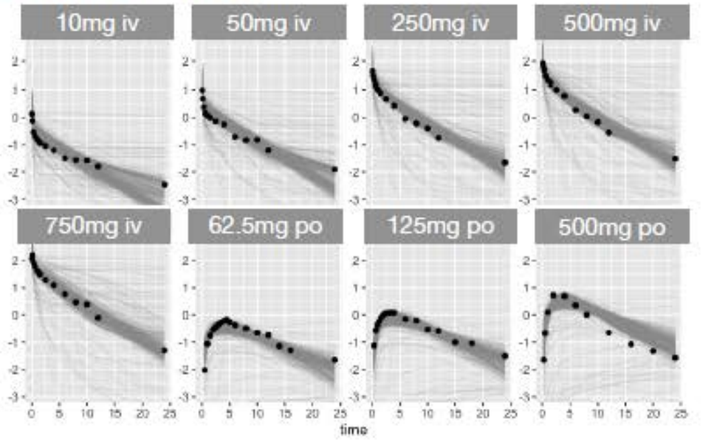
Initial model fit



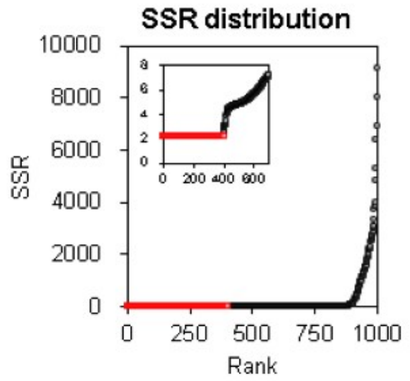
Final Parameter Distribution



Final model fit

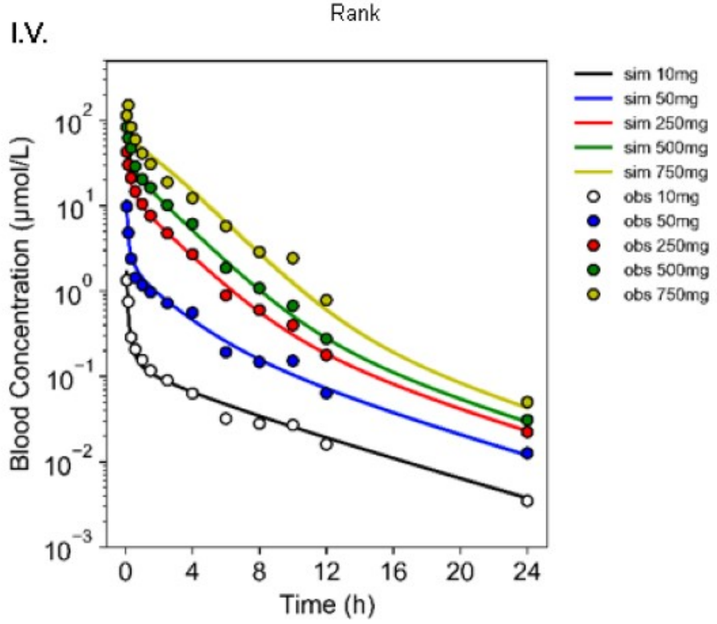


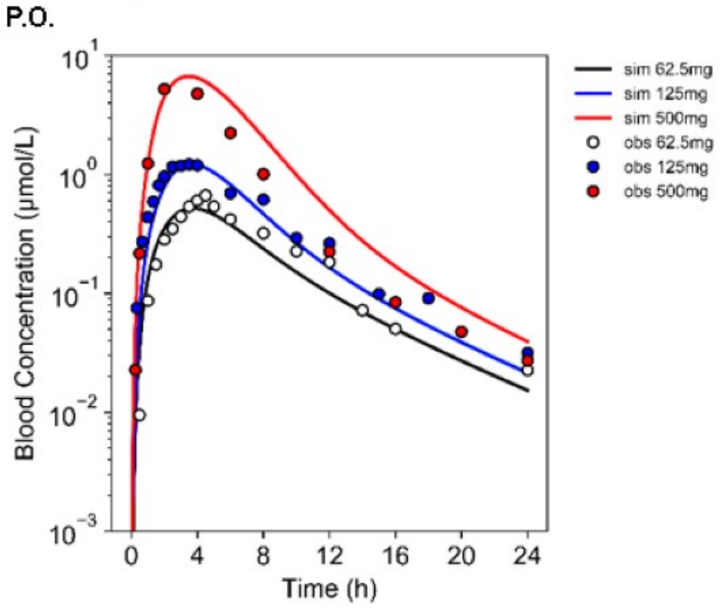
Fitted Line and Observed Data of I.V. and P.O. of Bosentan



1st: SSR=2.20948
red: SSR < 2.3 (rank 1 - 401)

Lines of **rank1-401** are shown.
Deep-colored lines indicate calculated reuslt of rank 1.
Light-colored lines indicate calculated results of from 2 to 401.

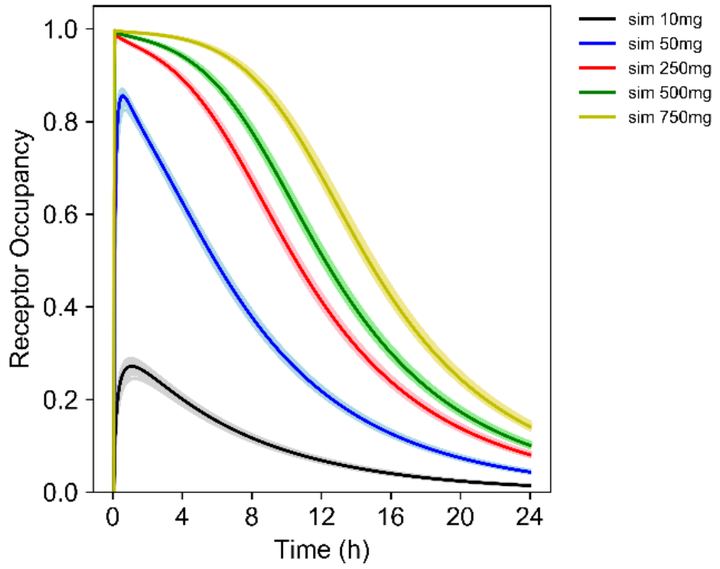




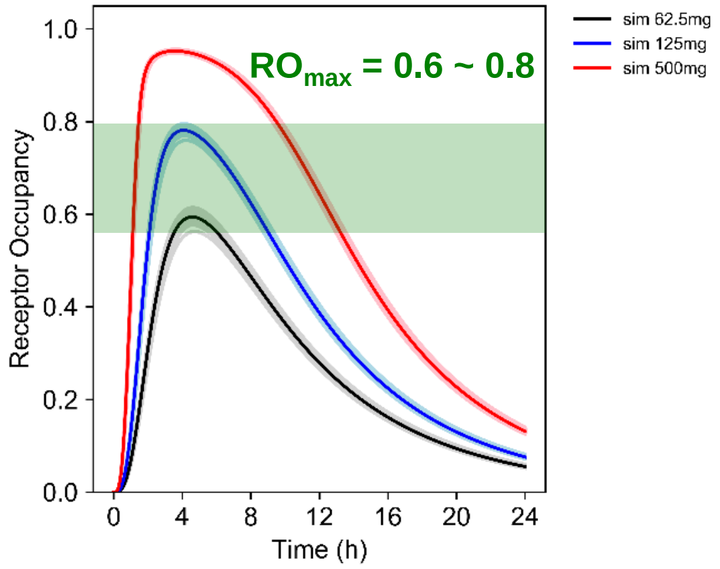
Now the data at all the doses are well captured by the model including target binding and saturable hepatic uptake.

Calculated Time-Course of Receptor Occupancy

(A) I.V.



(B) P.O.



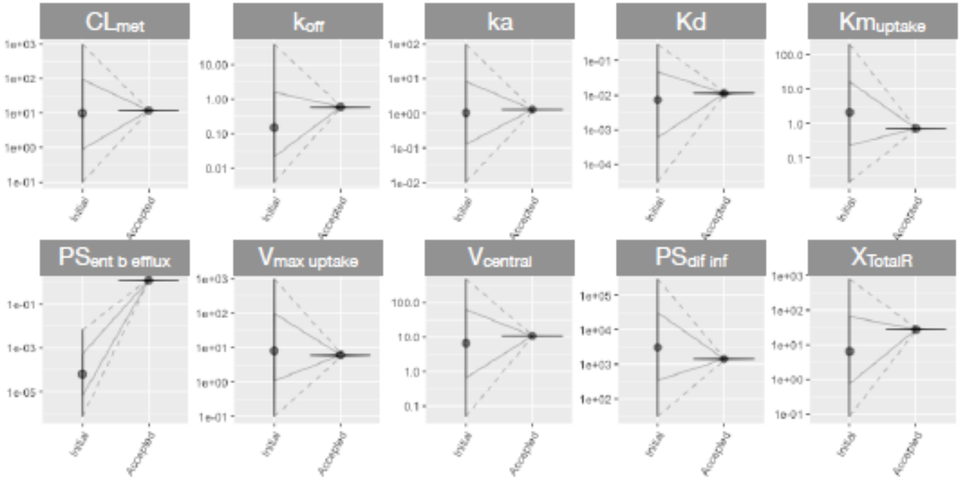
Lines of r**ank1-401** are shown.
Deep-colored lines indicate calculated reuslt of rank 1.
Light-colored lines indicate calculated results of from 2 to 401.

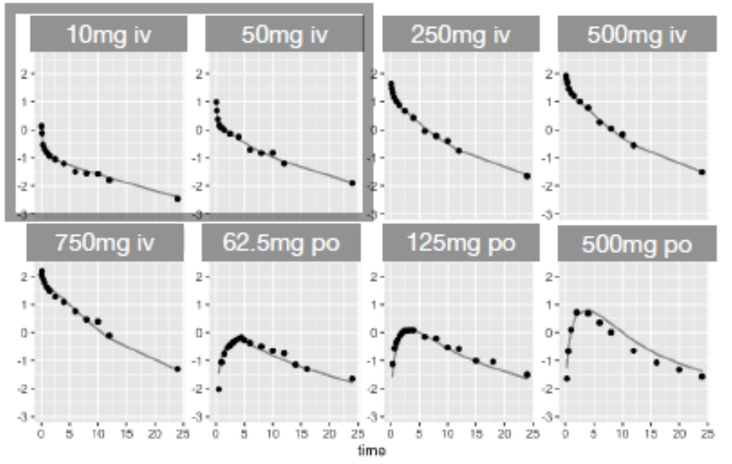
◆Receptor occupancy was calculated 0.6-0.8 when clinical dose of Bosentan (62.5, 125 mg P.O.) was administered.

(50)

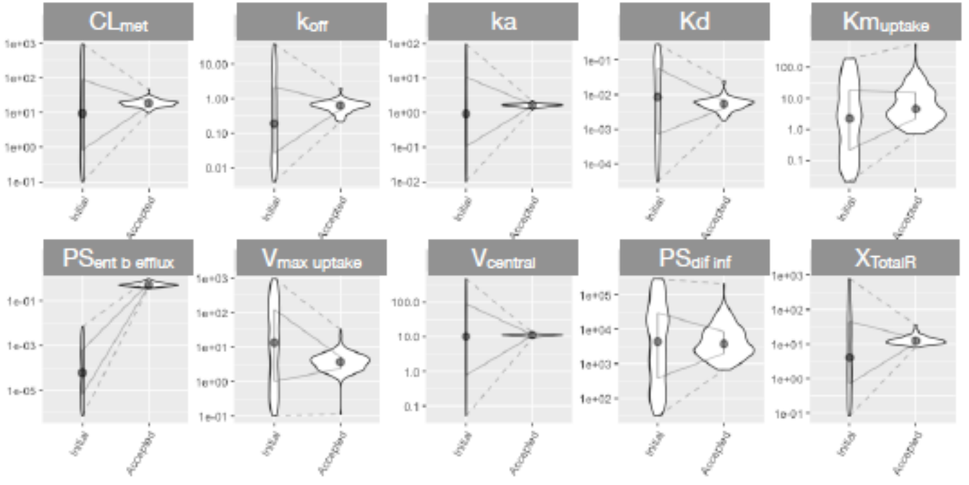
Estimating the receptor occupancy of bosentan with top-down approach

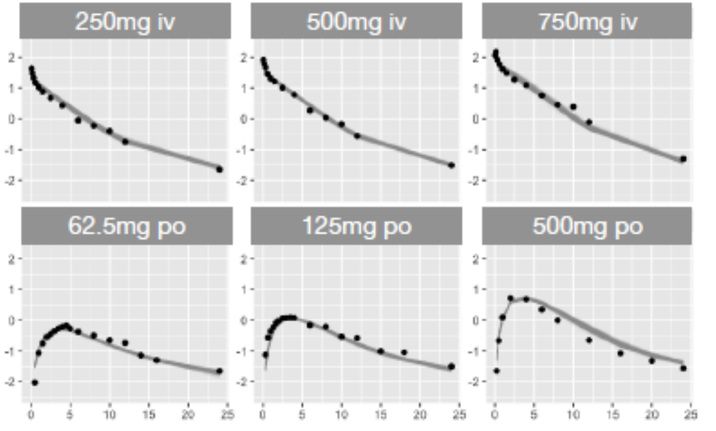
Parameters found though topdown approach **including low-dose**



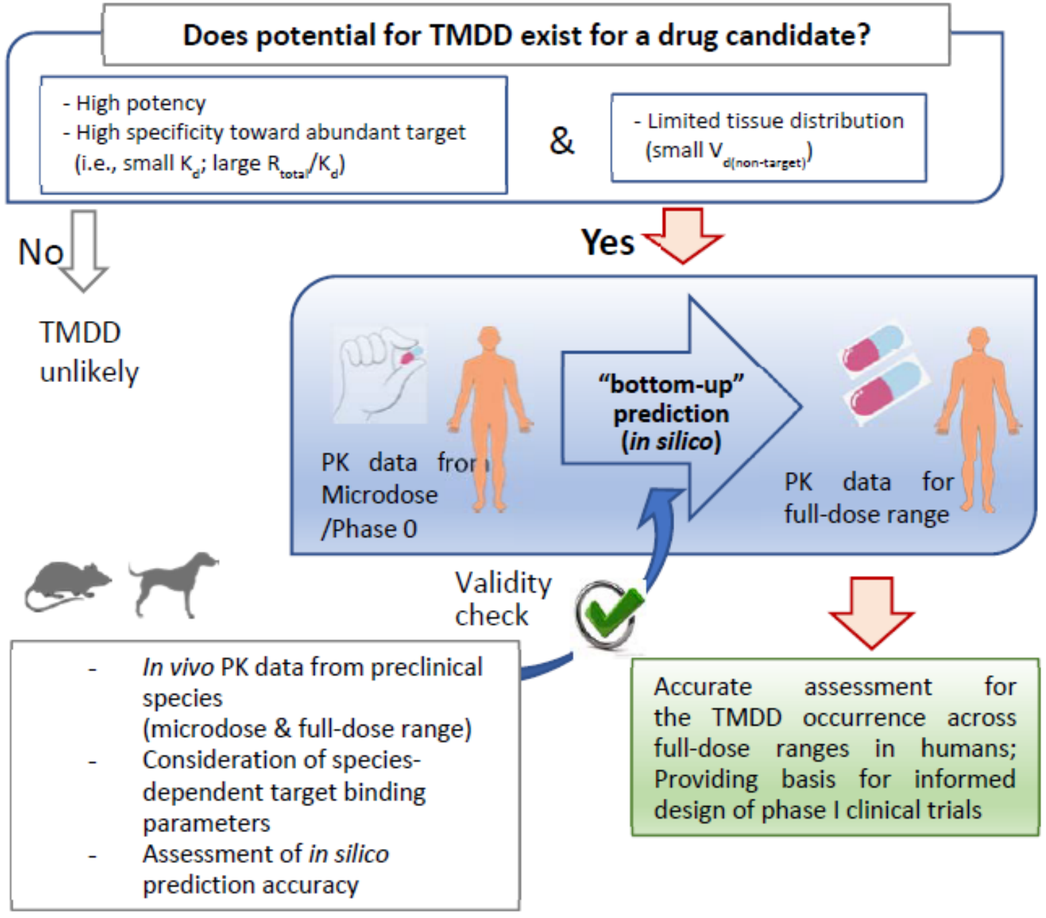


Parameters found though topdown approach **<u>not</u> including low-dose**





Workflow for assessment of drug candidates with possible TMDD.
PBPK modeling-based prediction with target considerations can be combined with PK data analysis from a microdose analysis in human subjects.



If a small dose (e.g., microdose) PK data is included in Phase 1 clinical dose escalation study, we may be able to detect the TMDD and predict the doses which exhibit the appropriate target occupancy (therapeutic dose)

Burt T, Young G, Lee W, Kusuhara H, Langer O, Rowland M, Sugiyama Y.

Phase 0/microdosing approaches: time for mainstream application in drug development?
Nat Rev Drug Discov. 19::801-818 (2020).

Our efforts for PBPK modeling to analyze TMDD will continue

To assess how the inclusion of microdosing(small dosing) data improves the prediction accuracy of overall target occupancy based on blood PK profiles

We may be able to estimate the therapeutic dose during the phase 1 clinical studies once the starting dose is microdose or relevant small dose.

Disclosure for COI

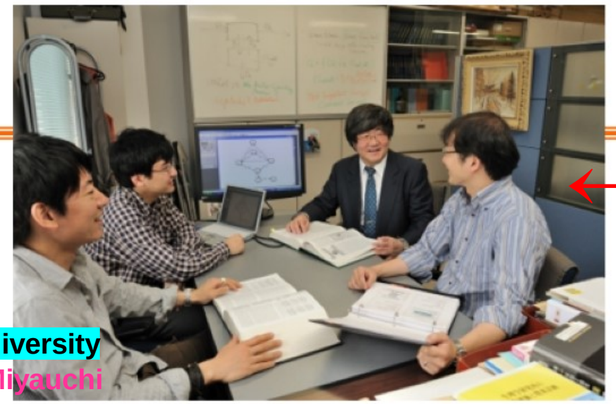
I am a scientific advisory board member of SimCYP.

I have been serving as a chair and a vice-chair of the global consortia of Pharma Industries:

(i) PET-IVIVE (6 companies) as a chair

(ii) Endogenous biomarker-DDI prediction (8 companies)

Acknowldgement



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