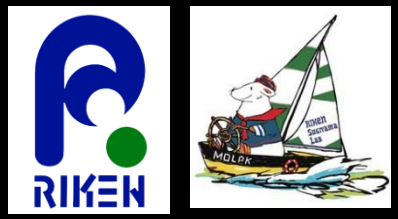
Ki determination in vitro and its impact on modelling and prediction of DDI

Yuichi Sugiyama

Sugiyama Laboratory, RIKEN Innovation Center,
RIKEN, Research Cluster for Innovation,

8th Meet the Experts Transporter Conference in Budapest



April 26-27, 2018
Continental Hotel Budapest

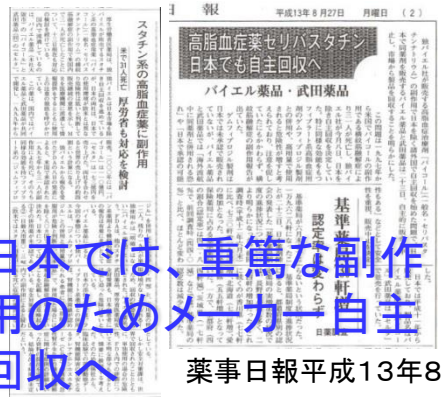
Contents

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

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

3) **Other collaborations**
   Integrated model of rifampicin as a perpetrator
   Time-dependent inhibition
   Substrate-dependent inhibition

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

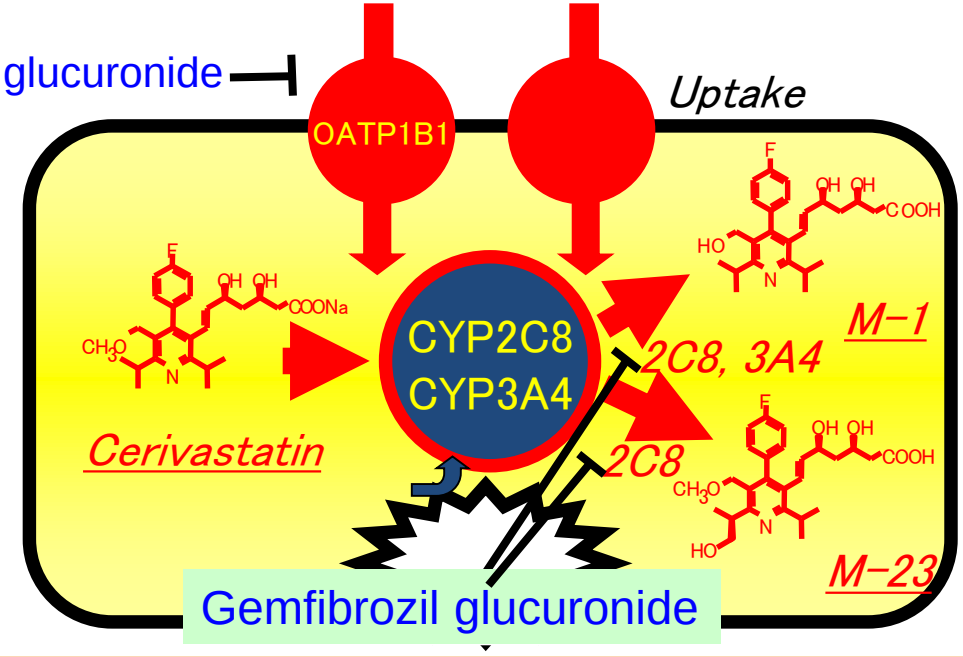
WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

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 In this connection it may be noted that Bayer has withdrawn all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)

Gemfibrozil glucuronide functions as **a dual inhibitor** of OATP1B1 and CYP2C8

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
Others			
Montelukast	OATP2B1	CYP2C8, 2C9, 3A4	-
maraviroc	OATP1B1	CYP3A4	Pgp
fexofenadine	OATPs	-	Pgp

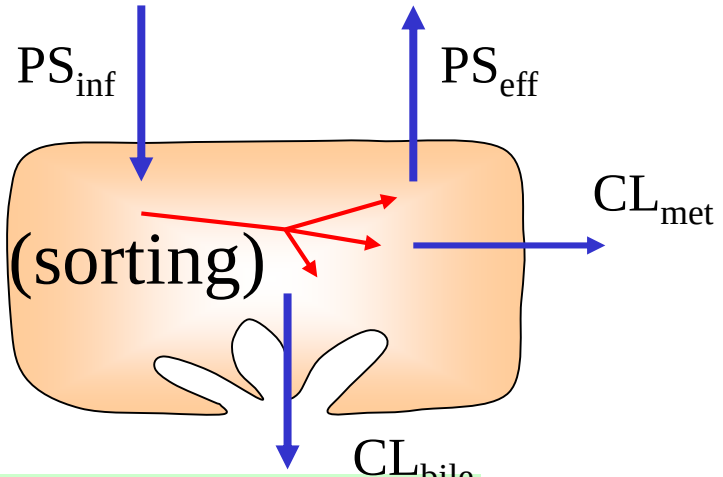
Extended clearance concept

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

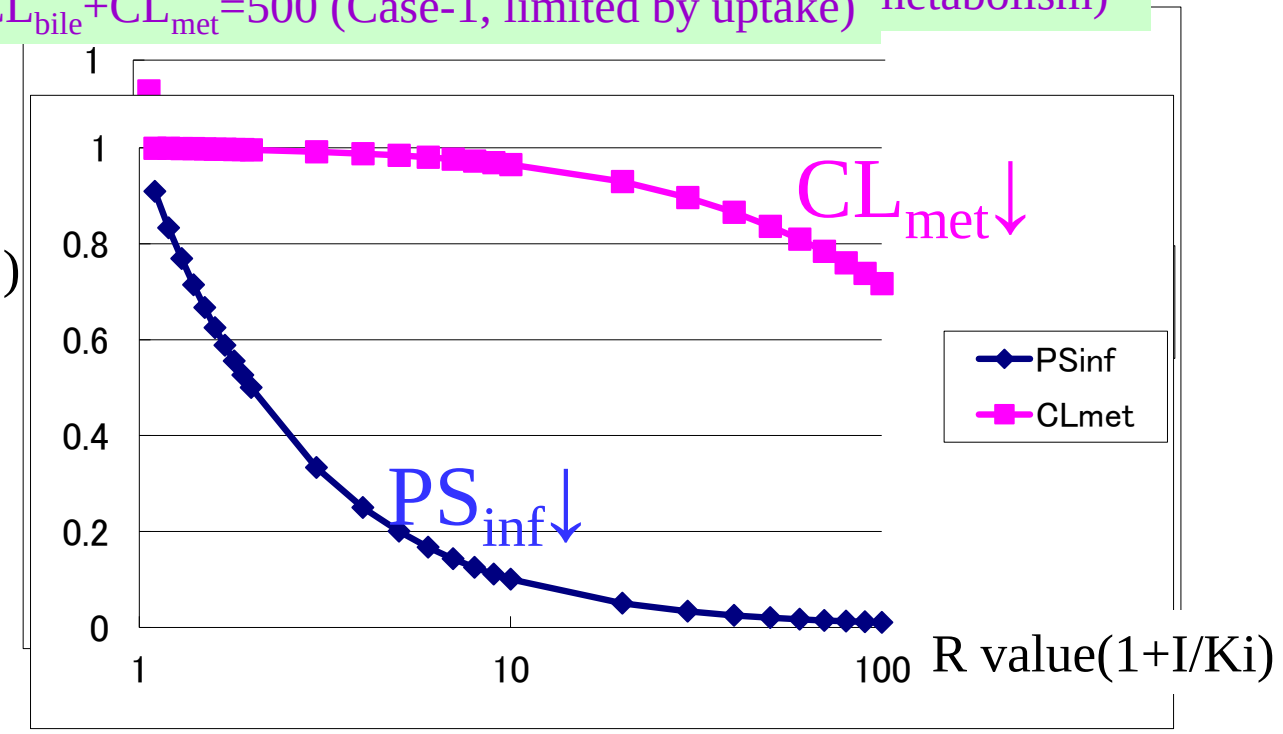
(β value)

R_{dif} values

$=PS_{inf,dif}/PS_{inf,act}$

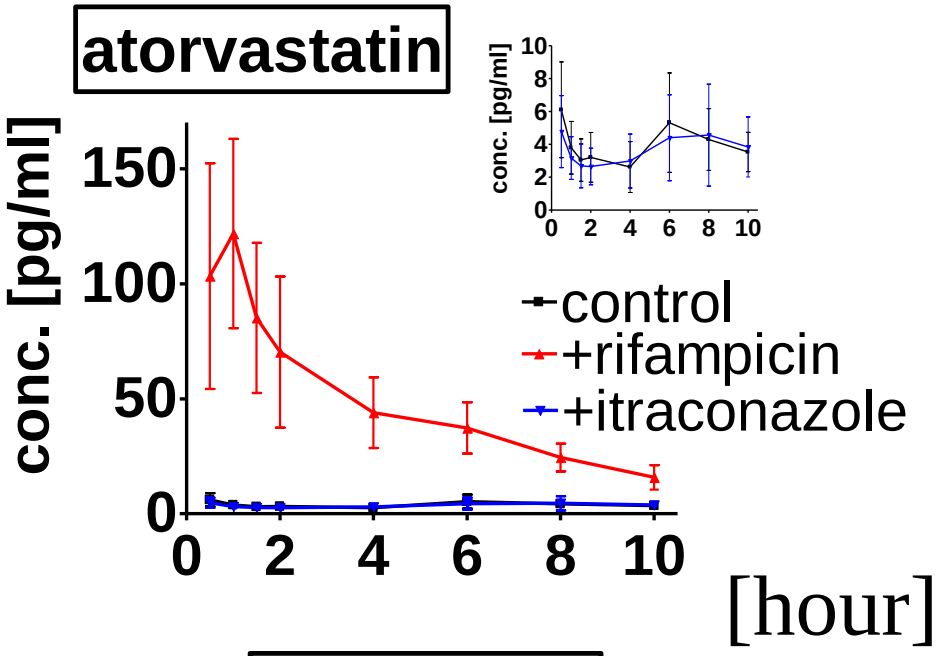


PS_{inf} =100, PS_{eff}=2, CL_{bile}+CL_{met}=500 (Case-1, limited by uptake) netabolism)



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

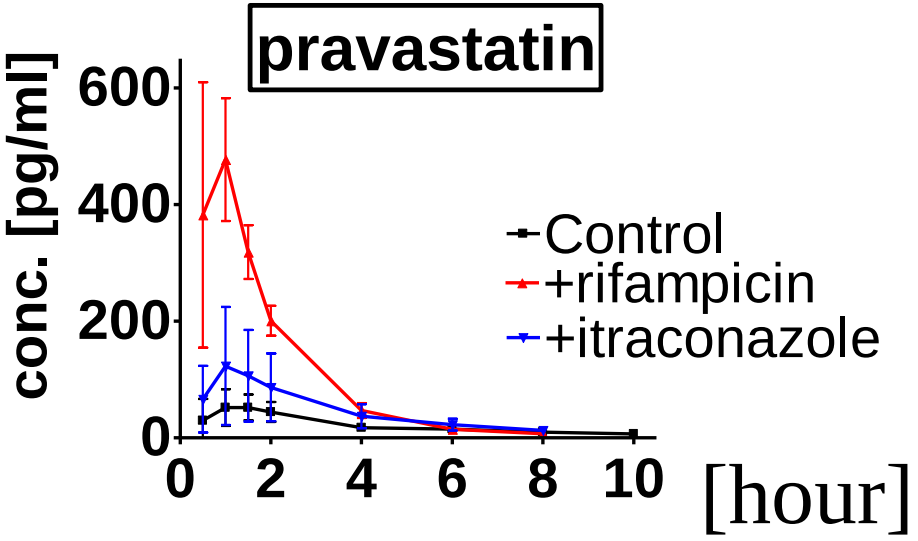
Plasma concentrations of atorvastatin was greatly increased by rifampicin, but not by itraconazole (Maeda K. et al., Clin Pharmacol Ther 90:575-581 (2011).

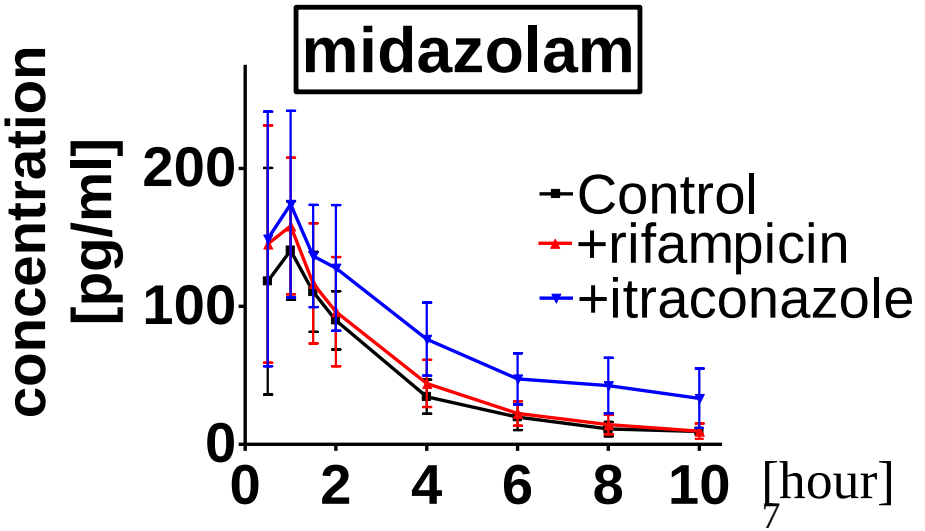


AUC_{0-10} [pg*hr/ml]	ATV	PRV (AUC_{0-8})	MDZ
Cont.	38.5 ±17.5	195 ±78.7	434 ±122
+RIF	439*** ±134	949*** ±179	471 ±168
+ITZ	36.0 ±19.2	386 ±254	755* ±276

***: P<0.0005

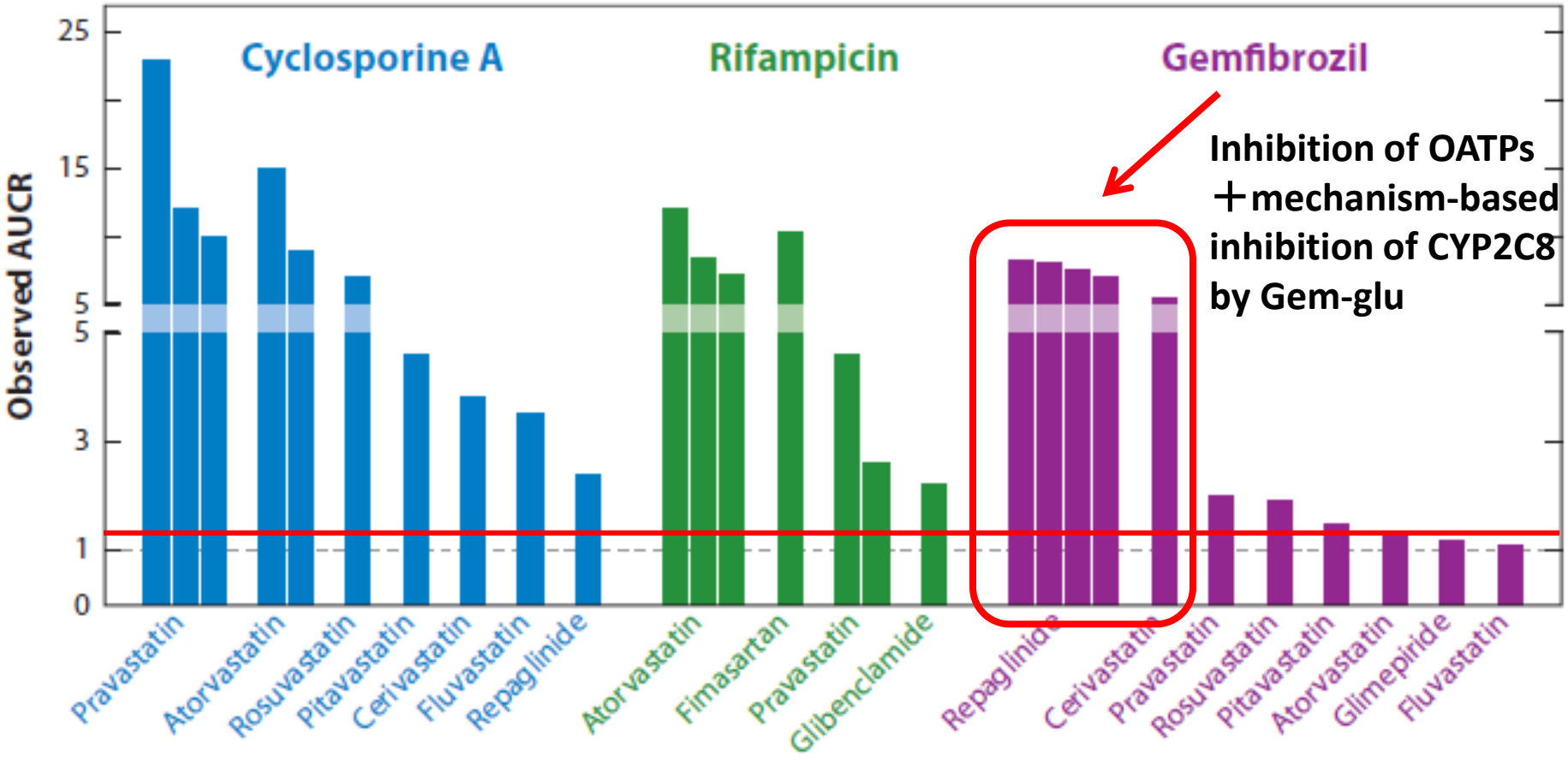
*: P<0.05





*Doses of each substrates are 33μg

OATP1B1/1B3 - mediated DDIs



Atorvastatin, pravastatin, rosuvastatin exhibitied relatively higher AUCR, while fluvastatin, repaglinide, and glibenclamide do lower AUCR.

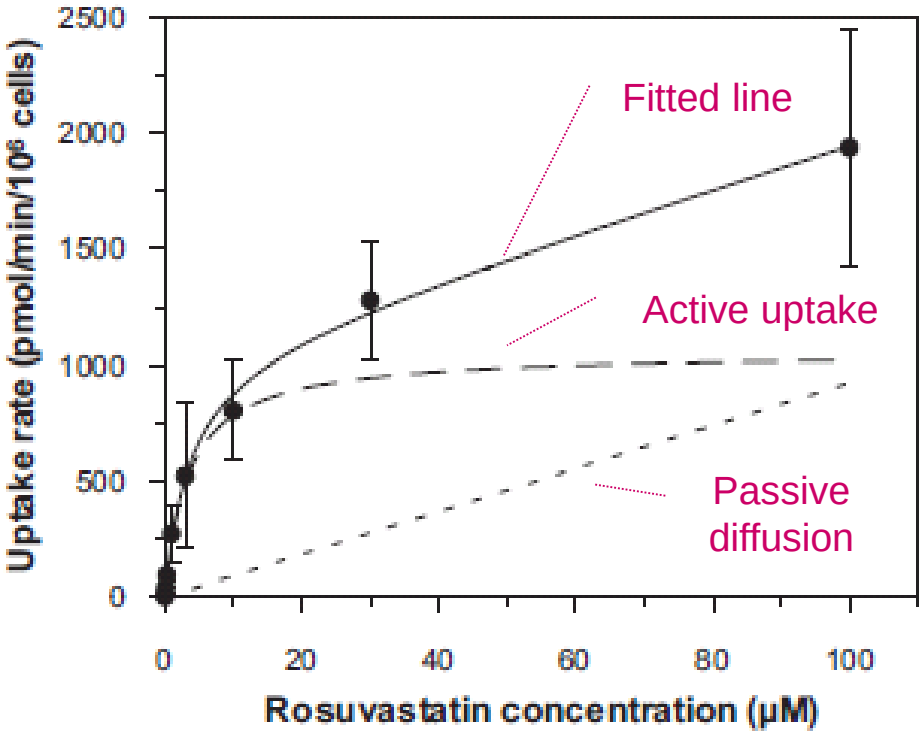
The latter compounds are lipophilic and have higher Rdif and lower foatp values.

（Yoshida K et al., Annu Rev Pharmacol Toxicol, 53, 581-612 (2013)）

Separation of active uptake and passive uptake

Yabe Y et al., DMD (2011) 39: 1808-14.

$$v = \frac{V_{max} \times S}{Km + S} + PS_{dif} \times S$$



R_{dif} values

$=PS_{inf,dif} / PS_{inf,act}$

$=PS_{dif} / (V_{max}/K_m)$

Effect of fraction transported (foatp) by the affected transporter(OATP1Bs)

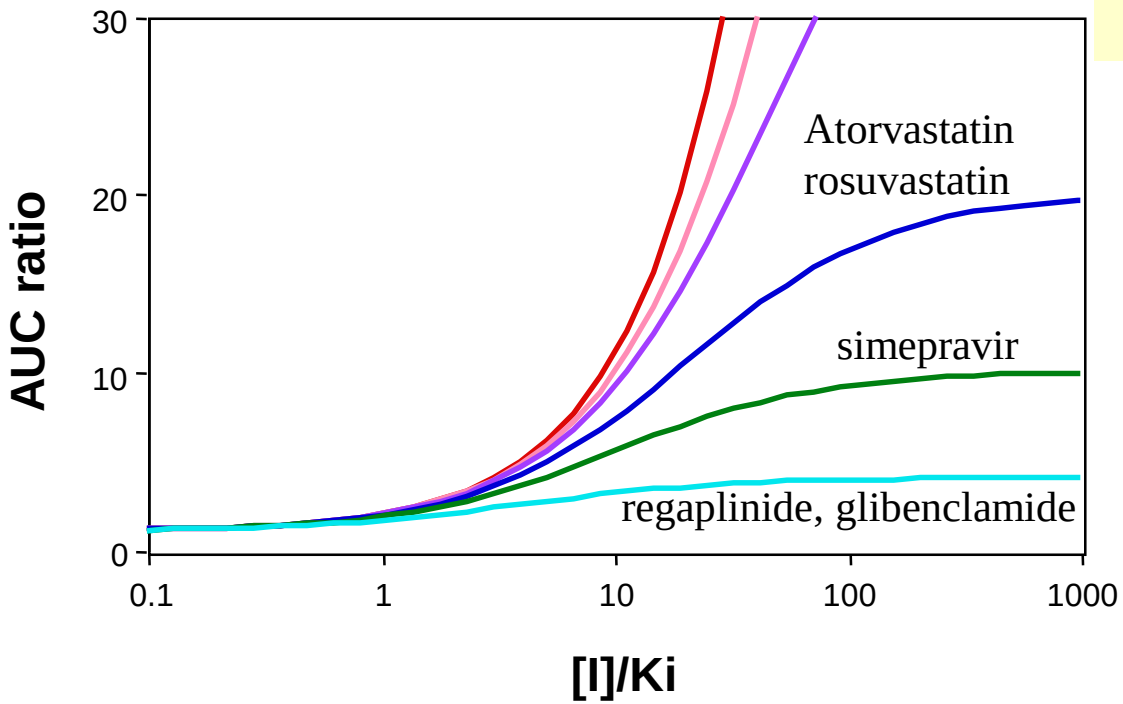
$$\frac{\text{AUC (+inhibitor)}}{\text{AUC (control)}} = \frac{1}{\frac{\text{fm}}{1+[\text{I}]/\text{Ki}} + (1 - \text{fm})}$$

fm ⇒ foatp

Lipophilicity of the substrate ↑

Then

the contribution of passive diffusion increases, and foatp ↓



Ito *et al.*, Drug Metab Dispos 33: 837-844 (2005)

How to obtain the in vivo β value and Rdif values (=PSinf,dif/PSinf,act) from these clinical studies ?

1) Rdif values; Effect of single dose of rifampicin;
Atrovastatin AUCR=12, Rdif is known as 0.024 (in vitro; determined in my lab).
Then, from AUCR for other substrates together with the estimates of foatp(Rifampicin sensitive OATPs) value, in vivo Rdif value of OATPs mediated uptake is estimated

atorvastatin	AUCR=12.0	Rdif = 0.024
simeprevir	AUCR = 7.3	Rdif = 0.07-0.10
bosentan	AUCR=3.2	Rdif = 0.3-0.4
repaglinide	AUCR =2.0	Rdif = 0.7-1.1

2） β values; Effect of iv itraconazole(iv);
Midazolam AUCR=4.0 , fm(3A) is known as 0.9 (in vitro; determined in my lab)
Then, from AUCR for other substrates together with their fm values, in vivo β value of dual substrates of OATP and CYP3A4 is estimated (shown in the next slide)

(Summary) $\beta = \frac{CL_{bile} + CL_{met}}{PS_{eff} + CL_{bile} + CL_{met}}$

 # ATV, Bosentan : Close to Case-1 (β high 0.8~1）

 # CER, REPG, SIMP: （β intermediate 0.3-0.7)

 # DAR (β low < 0.2)

From the clinical DDI studies so far done and also from the I/Ki value of ITZ (CYP3A4 inhibitor), we can estimate the β values of each compound. With high β value of substrate, the inhibition of metabolism and bililary excretion does not affect the blood AUC value of unchanged drug (uptake-limited case)

Yoshikado T et al., A Clinical Cassette Dosing Study for Evaluating the Contribution of Hepatic OATPs and CYP3A to Drug-Drug Interactions. Pharm Res. 34(8):1570-1583 (2017)

Contents

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

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

3) **Other collaborations**
   Integrated model of rifampicin as a perpetrator
   Time-dependent inhibition
   Substrate-dependent inhibition

Quantitative analyses of hepatic OATP-mediated interactions between statins and inhibitors using PBPK modeling with a parameter-optimization method.

Yoshikado T, Yoshida K, Kotani N, Nakada T, Asaumi R, Toshimoto K, Maeda K, Kusuhara H,Sugiyama Y.

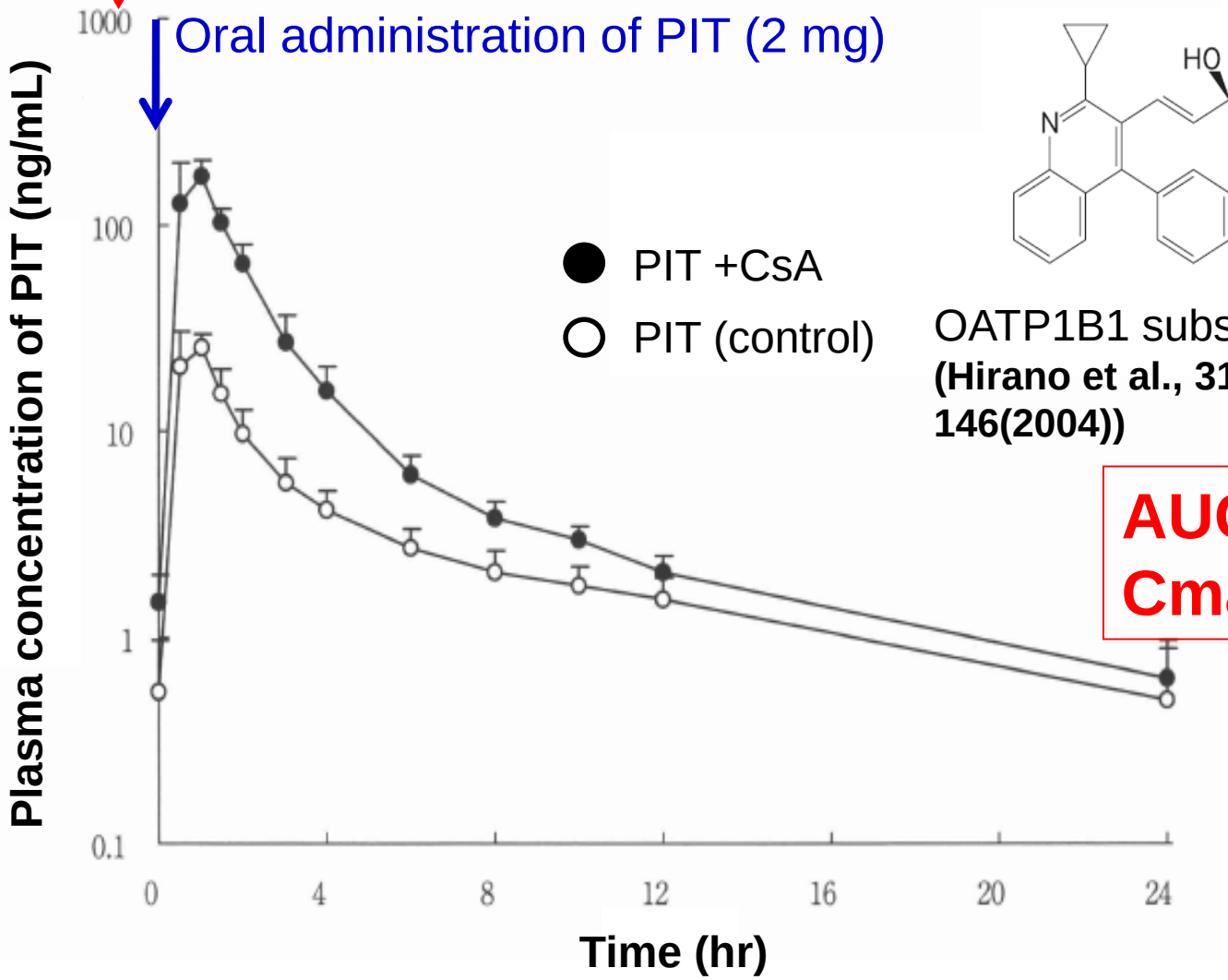
Clin Pharmacol Ther. 100 (5):513-523 (2016)

Elevation of plasma pitavastatin (PIT) concentration by cyclosporine A (CsA)

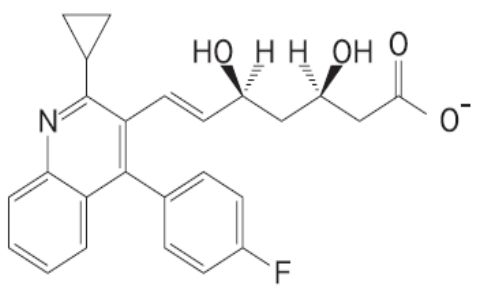
Prediction by dynamic model (PBPK model)

Oral administration of CsA (average 131 mg) 1 hr before PIT

Oral administration of PIT (2 mg)



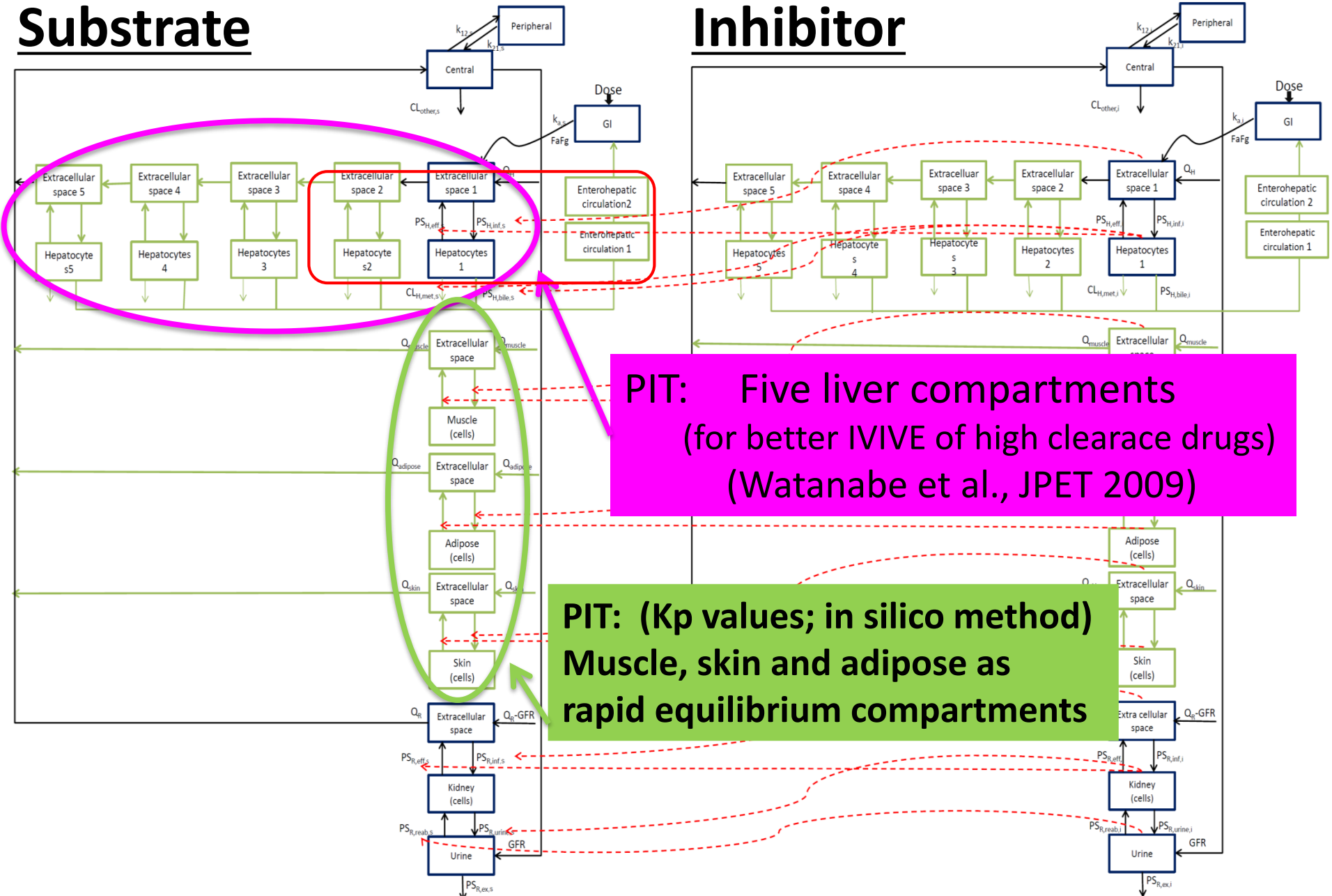
Pitavastatin

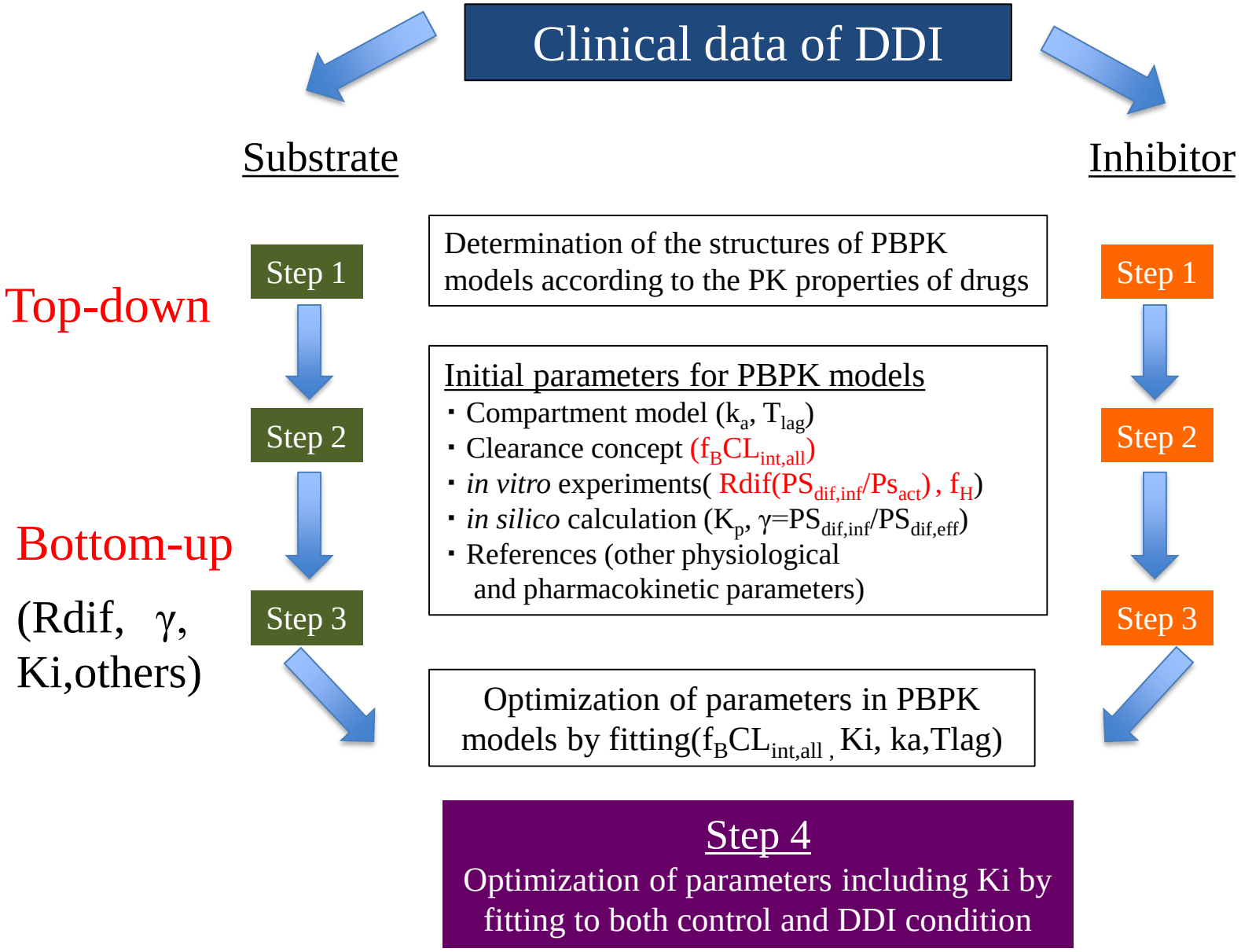


OATP1B1 substrate
(Hirano et al., 311:139-146(2004))

AUC ×4.6
Cmax ×6.5

PBPK model for DDI analyses (PIT, CsA)



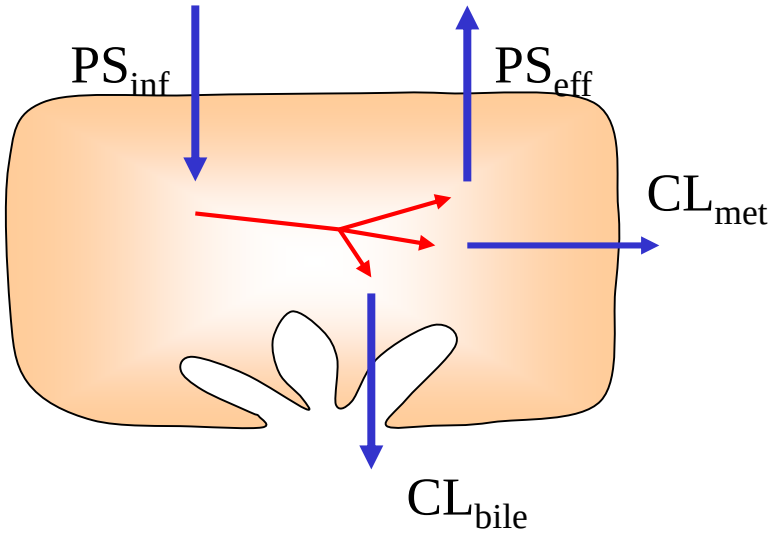


Scheme of the workflow of parameter optimization in the PBPK models to describe hepatic OATP-mediated DDIs.

Extended clearance concept

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

β value



Where $PS_{inf} = PS_{inf,\,act} + PS_{nf,dif}$

PS_{eff} assumed to be $PS_{eff,dif}$

$R_{dif} = PS_{inf,dif} / PSinf,act$

$$K_{p,uu} = \frac{PS_{inf,act} + PS_{inf,dif}}{PS_{\,eff,\,dif}}$$

$\gamma = PS_{inf,dif} / PS_{eff,dif,}$ fbile = CLbile / (CLmet + CLbile)

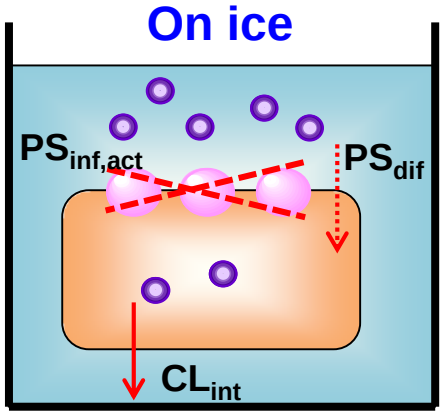
Parameters for elementary steps

$PS_{inf,,act}$, $Ps_{inf,dif}$, $PS_{eff,dif,}$ CL_{bile}, CL_{met}

Hybrid parameters for describing hepatobiliary elimination steps

$CL_{int,all}$, β, K_{puu}, *Rdif*, *fbile*

How to determine $K_{p,uu(true)}$ from in vitro experiment?



$$C/M\ ratio(on\ ice) = \left[\frac{C_{cell}}{C_{medium}}\right]_{on\ ice} = \frac{PS_{dif,inf}}{f_T \cdot PS_{dif,eff}}$$

Assumption: membrane potential is completely lost under on ice condition (recently demonstrated experimentally)

$$PS_{dif,inf} = PS_{dif,eff} \quad \left(\gamma_{on\ ice} = \frac{PS_{dif,inf}}{PS_{dif,eff}} = 1\right)$$

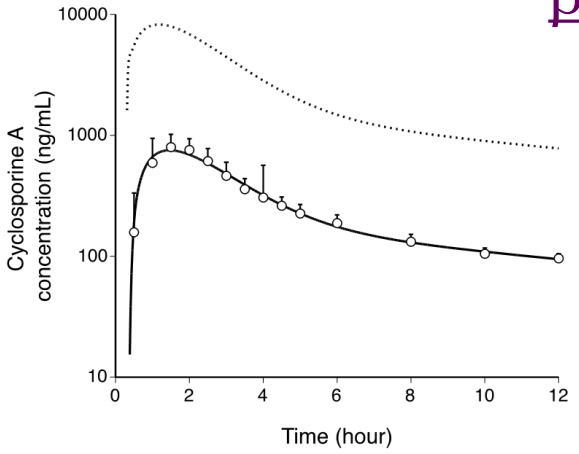
$$\frac{C/M\ ratio(37℃)}{C/M\ ratio(on\ ice)} = \frac{PS_{act,inf} + PS_{dif,inf}}{f_T \cdot \left(PS_{dif,eff} + CL_{int,met}\right)} \cdot f_T = K_{p,uu(true)}$$

Comparison of methods for estimating unbound intracellular-to-medium concentration ratios in rat and human hepatocytes using statins

Yoshikado et al.,Drug Metab Dispos. 45(7):779-789 (2017).

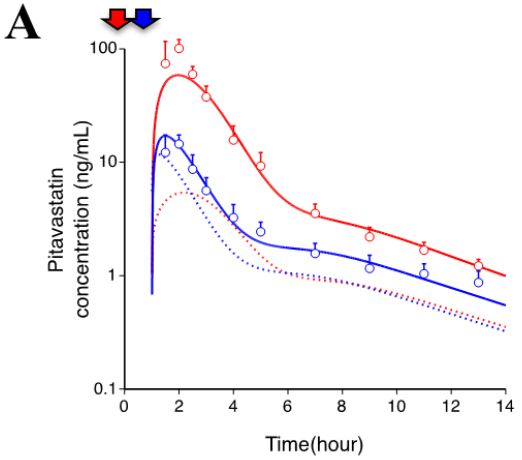
Simulated time course of plasma conc. of cyclosporine A and pitavastatin/fluvastatin

Cyclosporine A

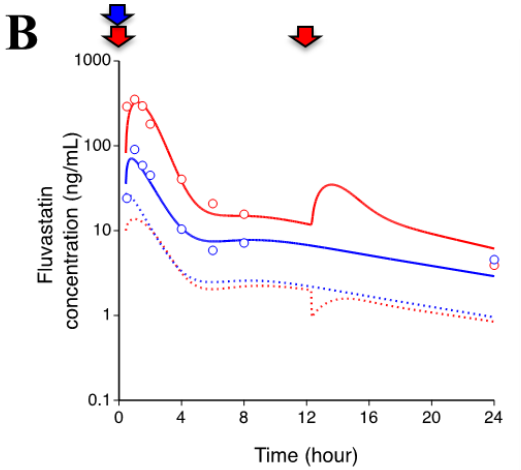


β=0.8

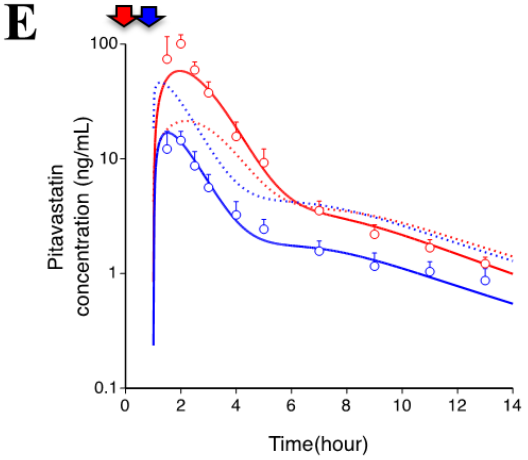
Pitavastatin (EHC model)

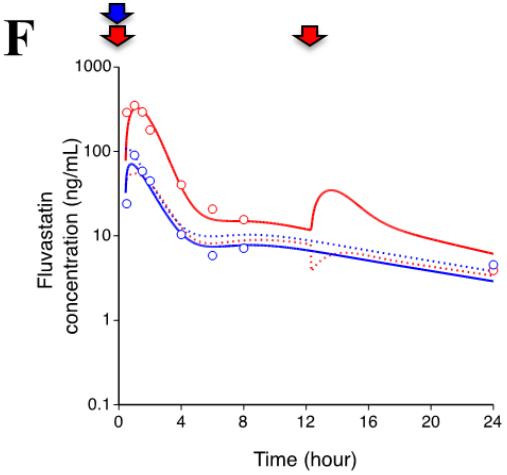


Fluvastatin (EHC model)



β=0.2





Plasma conc..
- control
- +CsA

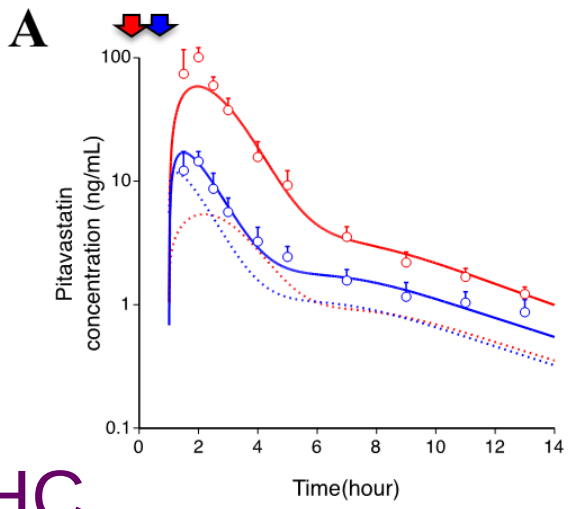
Hepatic conc..
- control
- +CsA

Impact of the consideration of enterohepatic circulation on the simulated time course of plasma conc. of pitavastatin/fluvastatin

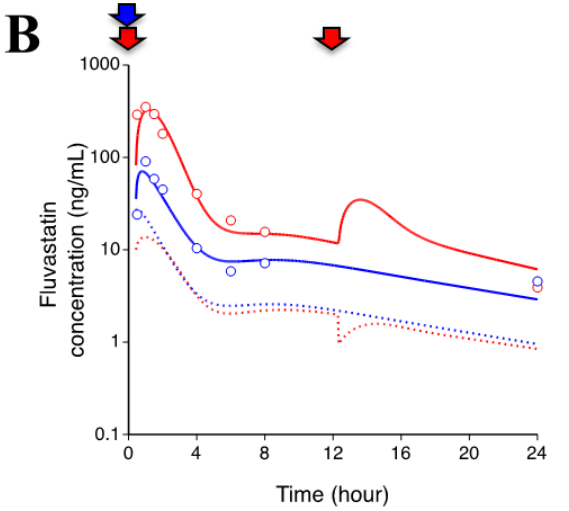
(EHC model gave much better fit to the data)

EHC

Pitavastatin (EHC model)



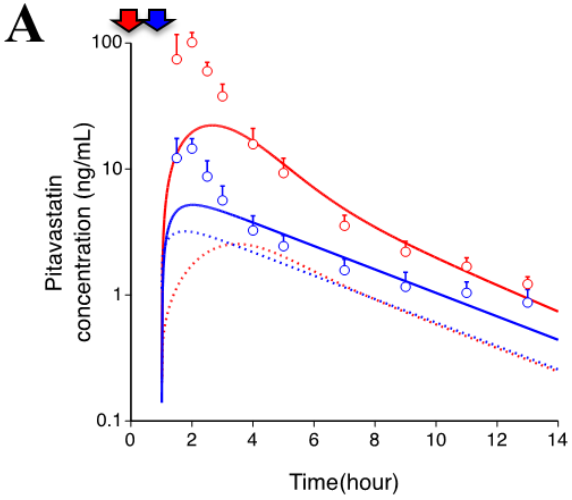
Fluvastatin (EHC model)

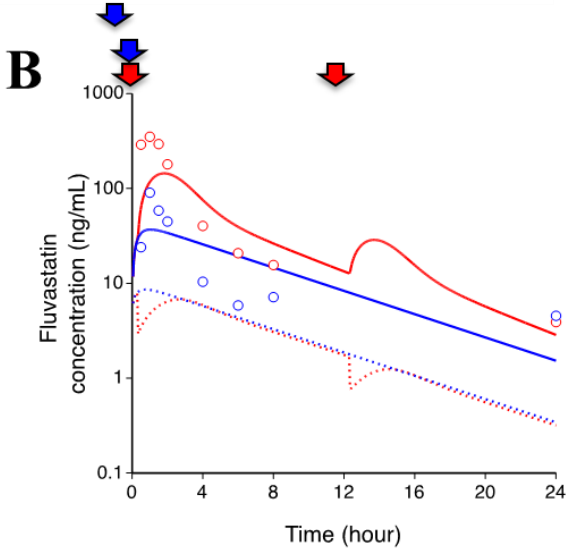


Plasma
control
+CsA

Liver
control
+CsA

Non-EHC





- PBPK models were constructed for pitavastatin, fluvastatin and pravastatin as substrates and cyclosporin A (CsA) and rifampicin (RIF) as inhibitors, where enterohepatic circulations (EHC) of statins were incorporated. Without EHC, good fitting was not obtained for either substrate.
  (In vitro measured Rdif values, γ values were well incorporated into this modeling)

- Similar *in vivo* inhibition constant (K_i) values of each inhibitor against OATPs were obtained, regardless of the substrates.
  CsA: 0.012 uM (pitavastatin) 0.010 uM(fluvastatin)
  Rifampicin; 0.23 uM (pitavastatin) 0.19 uM(pravastatin)

- Estimated K_i values of CsA were comparable to reported *in vitro* values with the preincubation of CsA, while those of RIF were 3-5 folds smaller than reported *in vitro* values .
  CsA(+preincubate) ; 0.014–0.080 uM, Trans-inhibition mechanism
  Rifampicin; 0.65–1.1 uM,
  (Mechanism of lower Ki value in vivo of Rif. compared with in vitro are not known yet.)

Conclusion

* Standardized protocol of top-down analyses of complex DDI (where transporters and enzymes are inhibited) based on PBPK modeling were established The in vivo Ki values were obtained, leading to the prediction of complex DDI of other substrates

* We need some in vitro measured parameters such as Rdif value Kpuu value, γ values(index of the asymmetry of passive diffusion via basolateral membrane) in this model based analyses

* An important parameter, β which determines rate-determining process of drugs is set to different values (0.2, 0.5, 0.8) in the model analyses, and the outcome of analyses are not so much different as far as the plasma-concentration time profiles are analyzed.

* However, this β values should affect the hepatic concentration time profiles. Therefore, this should be estimated in near future from the in vitro experiments (isolated and sandwich cultured hepatocytes, HLMs)

Contents

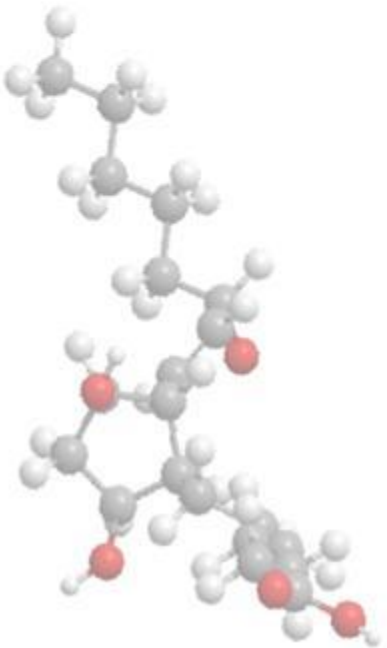
1) **Introduction;**
   Rate-determining process (focusing on the liver)
   (Uptake, efflux, elimination, metabolism)

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

3) **Other collaborations**
   Integrated model of rifampicin as a perpetrator
   Time-dependent inhibition
   Substrate-dependent inhibition

PBPK model of rifampicin incorporating its own hepatic uptake and auto-induction to predict various types of DDIs such as CYP3A/2C9 inductions and/or OATPs inhibitions

Asaumi R, Toshimoto K, Tobe Y, Hashizume K, Nunoya KI, Imawaka H, Lee W, Sugiyama Y. Comprehensive PBPK Model of Rifampicin for Quantitative Prediction of Complex Drug-Drug Interactions: CYP3A/2C9 Induction and OATP Inhibition Effects.
CPT Pharmacometrics Syst Pharmacol. (2018) 7, 186–196



Ryuta Asaumi

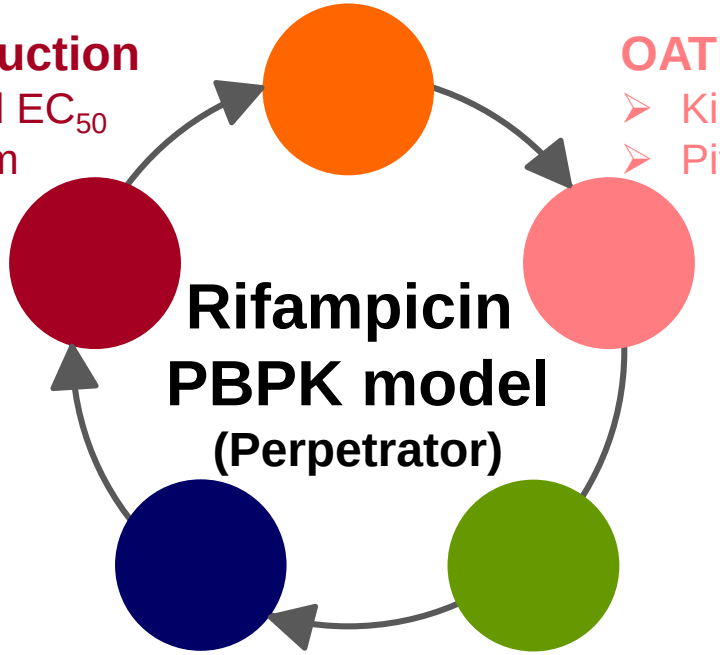
Pharmacokinetic Laboratories, Ono Pharmaceutical Co., Ltd.

Overview

CYP2C9 induction
- Emax and EC_{50}
- Tolbutamide

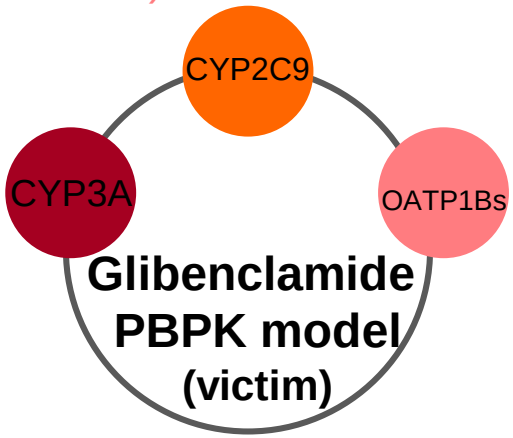
CYP3A induction
- Emax and EC_{50}
- Midazolam

OATP1Bs inhibition
- Ki (reported by yoshikado et al.)
- Pitavastatin



Complex DDIs

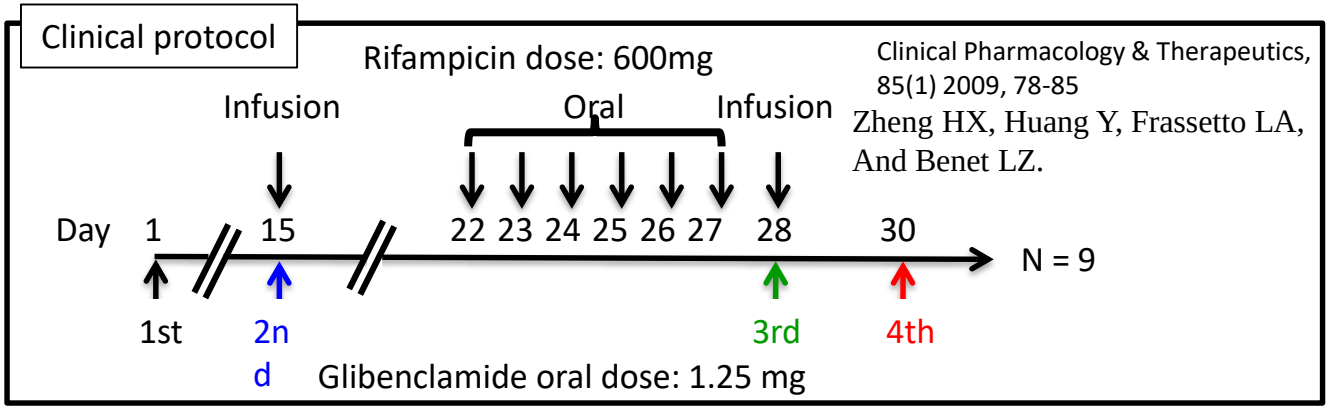
(Verification step)



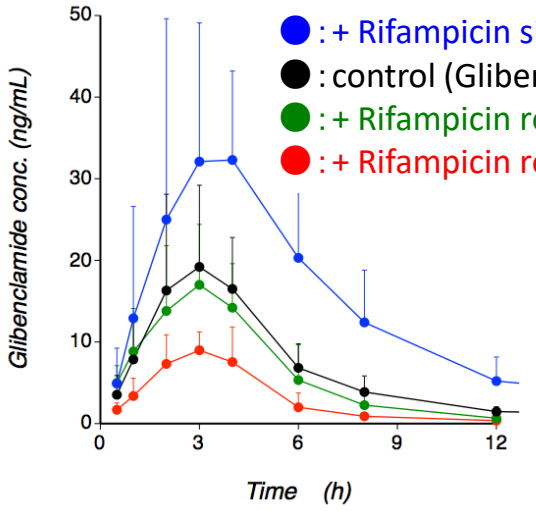
RIF PK profiles
- Non-linearity
- Auto-induction

***In vitro* studies**
- Hepatocyte uptake study
- Protein binding in plasma and intestine homogenate

Complex rifampicin DDI effects on glibenclamide pharmacokinetics

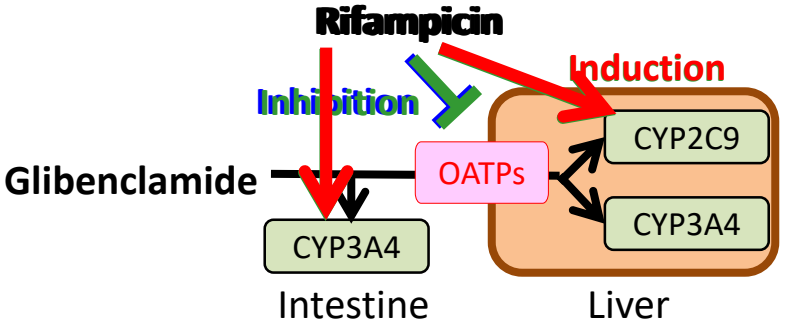


Clinical Pharmacology & Therapeutics, 85(1) 2009, 78-85
Zheng HX, Huang Y, Frassetto LA, And Benet LZ.



● : + Rifampicin single infusion (AUC: 2.25 fold)
● : control (Glibenclamide alone)
● : + Rifampicin repeated oral dose + single infusion (AUC: 0.78 fold)
● : + Rifampicin repeated oral dose (AUC: 0.37 fold)

Collaboration with Asaumi (Ono Pharm)



Further studies recently done on a collaboration base on the OATP-mediated DDIs

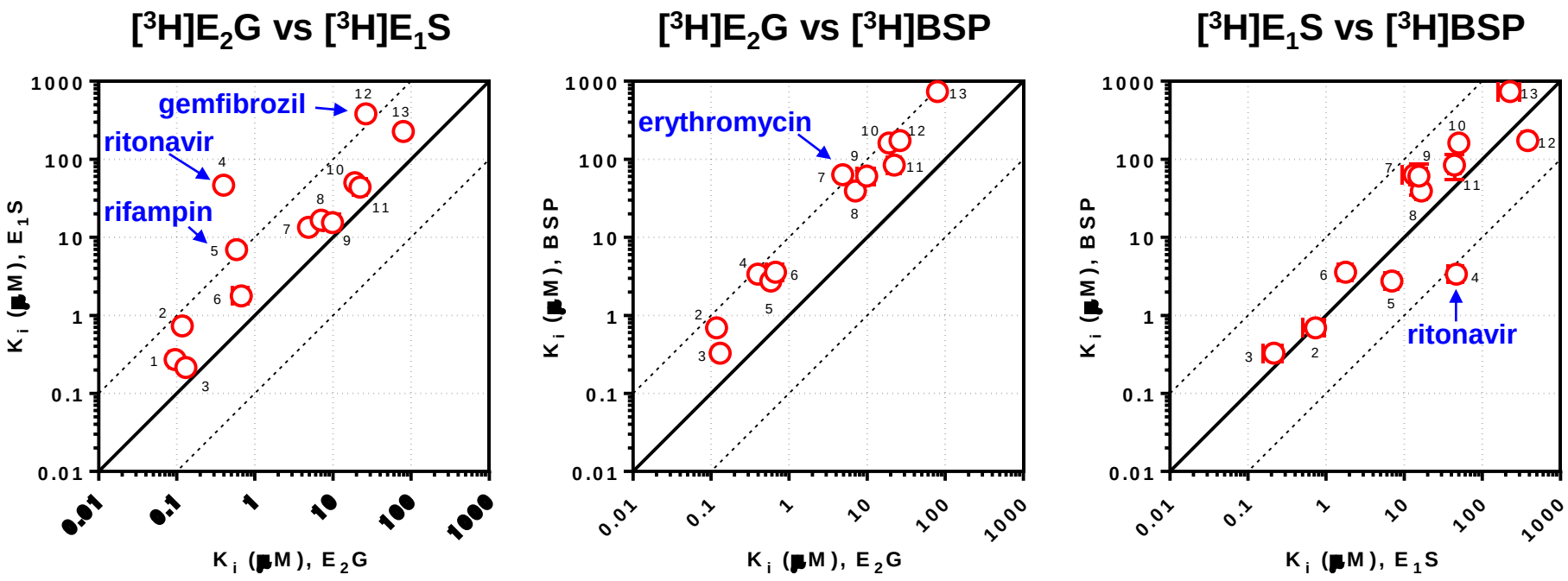
A) Time-dependent inhibition of OATPs by cyclosporine A

Shitara Y et al., (Sanofi) Pharmacol Therap. S0163-7258: 30066-9 (2017)

B) Substrate-dependent inhibition. Collaboration with Eisai

1) **Izumi S, Nozaki** Y, Komori T, Maeda K, Takenaka O, Kusano K, Yoshimura T, Kusuhara H and Sugiyama Y. Substrate-dependent inhibition of organic anion transporting polypeptide 1B1: comparative analysis with prototypical probe substrates estradiol-17beta-glucuronide, estrone-3-sulfate, and sulfobromophthalein. Drug Metab Dispos 41:1859-1866 (2013).
2) Izumi S, Nozaki Y, Maeda K, Komori T, Takenaka O, Kusuhara H and Sugiyama Y. Investigation of the Impact of Substrate Selection on In Vitro Organic Anion Transporting Polypeptide 1B1 Inhibition Profiles for the Prediction of Drug-Drug Interactions. Drug Metab Dispos 43:235-247 (2015).
3) Izumi S, Nozaki Y, Komori T, Takenaka O, Maeda K, Kusuhara H, Sugiyama Y. Investigation of Fluorescein Derivatives as Substrates of Organic Anion Transporting Polypeptide (OATP) 1B1 To Develop Sensitive Fluorescence-Based OATP1B1 Inhibition Assays. Mol Pharm.13: 438-48 (2016)
4) Izumi S, Nozaki Y, Komori T, Takenaka O, Maeda K, Kusuhara H, and Sugiyama Y. Comparison of the Predictability of Human Hepatic Clearance for Organic Anion Transporting Polypeptide (OATP) Substrate Drugs Between Different In Vitro-In Vivo Extrapolation Approaches J.Pharm.Sci., in press

Comparison of K_i values for OATP1B1 between prototypical probe substrates

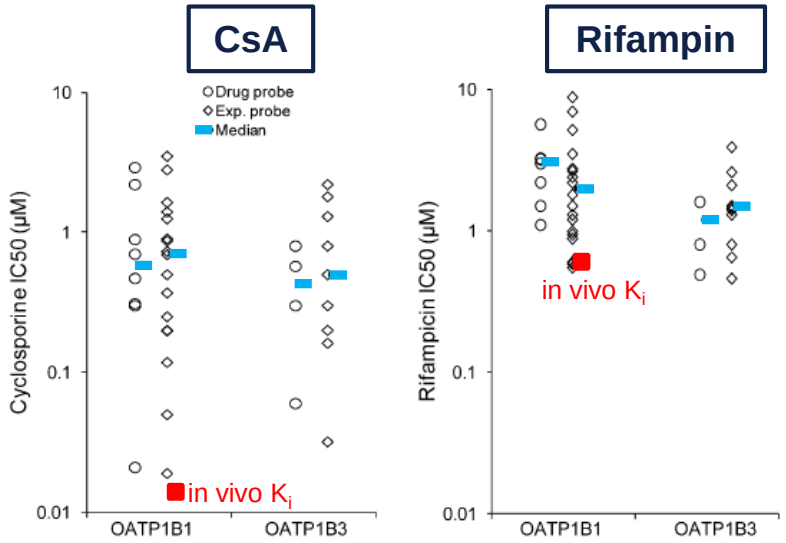


1, E_1S; 2, CsA; 3, BSP; 4, Ritonavir; 5, Rifampin; 6, Tacrolimus; 7, Erythromycin; 8, E_2G; 9, Ketoconazole; 10, TCA; 11, Verapamil; 12, Gemfibrozil; 13, Probenecid.

Izumi et al. (2013) *Drug Metab Dispos* 41: 1859-1866

- **Some inhibitors (eg, ritonavir, gemfibrozil, and rifampin) showed >10-fold (117-fold for ritonavir) variations in the K_i values, depending on the substrates used.**
- **Of the 3 substrates, [^{3}H]E_2G provided the lowest K_i values for all inhibitors examined.**
- **[^{3}H]E_2G can be used as a sensitive probe substrate of OATP1B1, which could offer conservative K_i values and help mitigate the risk of false-negative DDI prediction.**

Comparison of IC_{50} (or K_i) values of CsA and rifampicin obtained in vitro and in vivo (Collaboration with Izumi, Nozaki et al)



IC_{50} values of CsA, rifampin for OATP1B1 and OATP1B3

In vitro IC_{50} values were higher than in vivo K_i values obtained from PBPK model, particularly for CsA.

Li et al. (2014) Clin Pharmacokinet 53: 659-678

Transporters	Substrates	Pre-incubation time (min)	K_i or IC_{50} of CsA		Ratio
			Without CsA	With CsA	
			(μM)	(μM)	
OATP1B1[a]	Atorvastatin	60	0.47 ± 0.34	0.021 ± 0.004	22.4
	[^{3}H]E_2G		0.0458 ± 0.0041	0.0139 ± 0.0066	3.3
	[^{3}H]E_1S		0.134 ± 0.017	0.0264 ± 0.0085	5.1
OATP1B1[b]	[^{3}H]BSP	60	0.252 ± 0.057	0.0799 ± 0.0273	3.2
	Pitavastatin		0.0985 ± 0.0360	0.0252 ± 0.0038	3.9
	Atorvastatin		0.0986 ± 0.0250	0.0229 ± 0.0033	4.3
OATP1B1[c]	[^{3}H]E_2G	30	0.198 ± 0.069	0.019 ± 0.007	10.4
OATP1B3[c]	[^{3}H]E_2G		0.162 ± 0.062	0.032 ± 0.003	2.6

In vitro IC_{50} values of CsA for OATP1B1 and 1B3 obtained w/ or w/o CsA pre-incubation.

K_i (or IC_{50}) = 0.01 ~ 0.08 μM

a) Amundsen et al. (2010) DMD 38: 1499-1504
b) Izumi et al. (2015) DMD 43: 235-247
c) Gertz et al. (2913) Pharm Res 30: 761-780

Experimentally obtained K_i value of CsA after pre-incubation with CsA was comparable to the in vivo K_i value.

2017 AAPS Annual Meeting and Exhibition(Nov 13th 2017)

Dialogue and Debate session

"The unfolded story of Long-Lasting OATP Transporter Inhibition"

Aleksandra Galetin, PhD,
Centre for Applied Pharmacokinetic Research,
University of Manchester, UK

Title: Translation of prolonged OATP1B1 inhibition *in vitro* to clinical DDI risk assessment

Yuichi Sugiyama, PhD,
Head of Sugiyama Laboratory
RIKEN, Yokohama, Japan

Title: Preincubation Time-Dependent and Long-Lasting Inhibition of Organic Anion Transporting Polypeptides (OATPs)

Moderators

Wei Yue, Ph.D.
Assistant Professor of Pharmaceutical Sciences
The University of Oklahoma Health Sciences Center

Dan Bow, Ph.D.
Senior Principal Research Scientist at AbbVie

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

Yoshihisa Shitara [a], Yuichi Sugiyama [b,*]

[a] Pharmacokinetics, Dynamics and Metabolism, Translational Medicine and Early Development, R&D Operations, Sanofi, Tokyo, Japan
[b] Sugiyama Laboratory, RIKEN Innovation Center, RIKEN, Yokohama, Japan

ARTICLE INFO

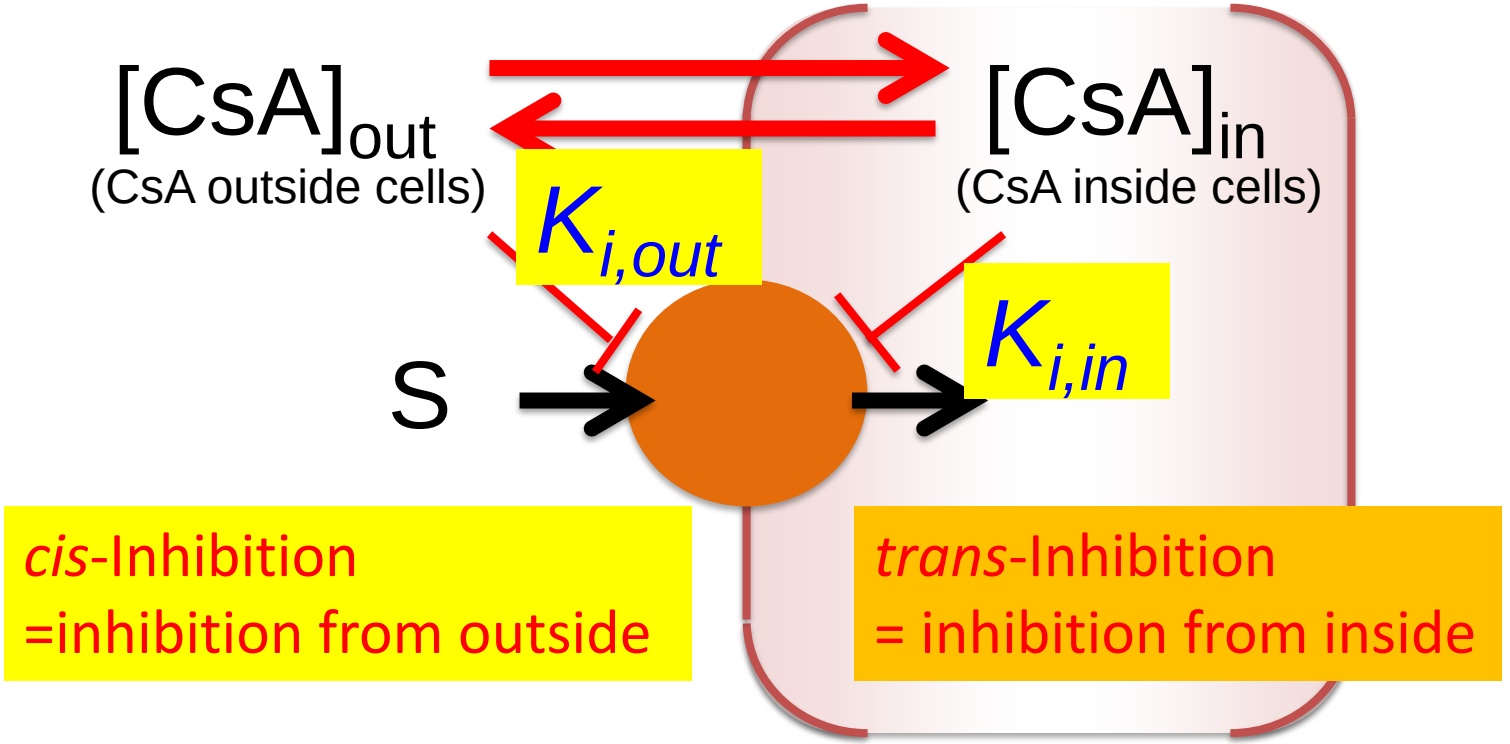
Available online 27 February 2017

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:

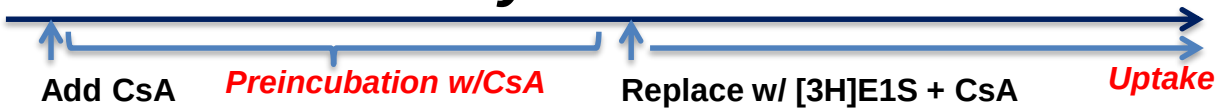
$$CL_{uptake}(+I) = \frac{V_{max}/(1 + f_{u,H}*I_H/K_{i,in})}{K_m*(1 + f_{u,B}*I_{EH}/K_{i,out}) + S}$$

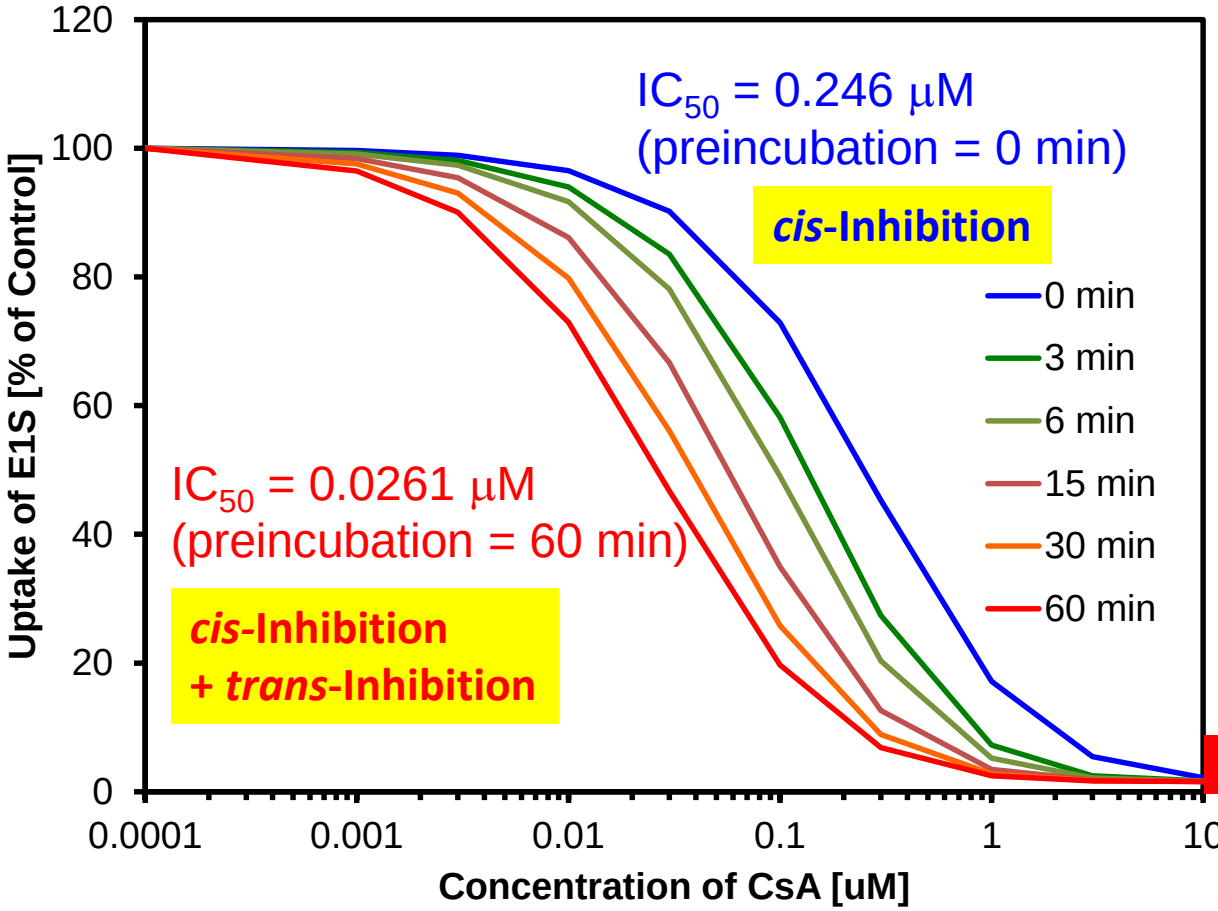
trans-Inhibition (non-competitive)

cis-Inhibition (competitive)

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

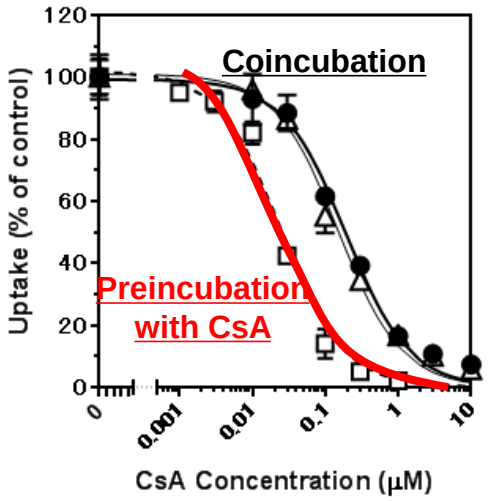
Simulation analysis of time-dependent enhancement effect of inhibition of OATP1B1 by CsA





Observed Data

Inhibition of OATP1B1-mediated uptake of estrone 3-sulfate



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

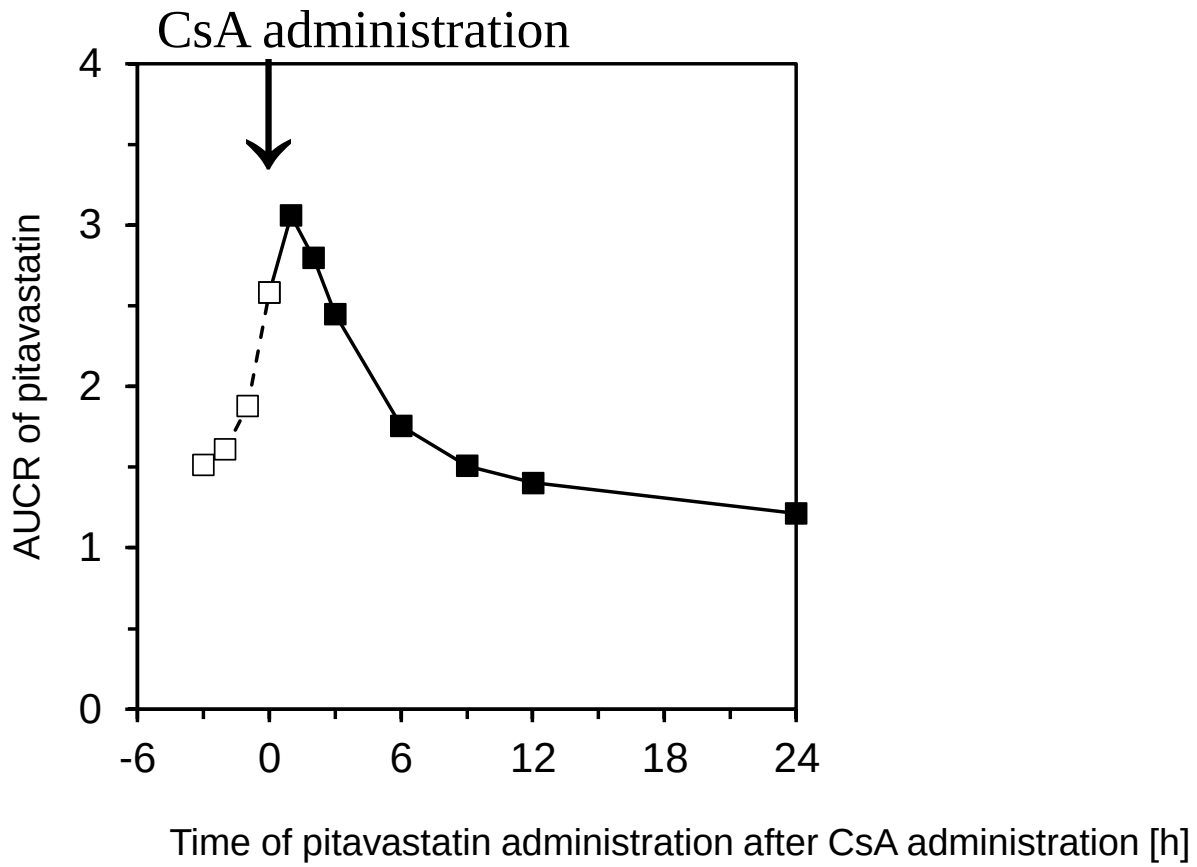
Izumi S et al. (2015)
Drug Metab Dispos 43, 235

$K_{i,out}$: 0.296 (μM), $K_{i,in}$: 0.0119 (μM): fitted values

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

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

When pitavastatin is administered one hour after the CsA administration, AUCR of pitavastatin exhibited the maximum value



Estimation of pitavastatin AUCR by coadministration with CsA for different time interval between two drugs.

AUCR values of pitavastatin by coadministration with CsA with several intervals were estimated from the PBPK modeling considering trans-inhibition mechanism.

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?

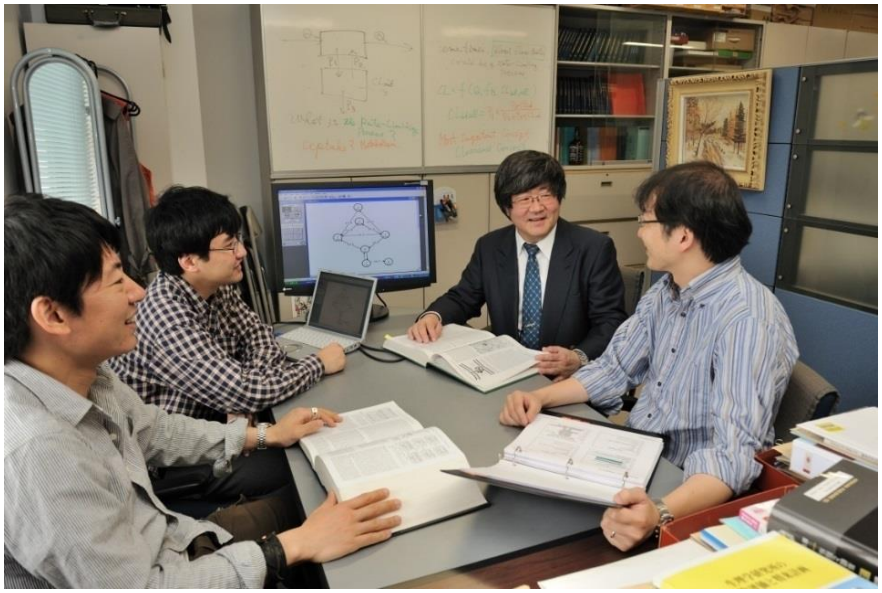
2) More mechanism based PBPK modeling; transfer of inhibitor to intracellular sites ⇒ estimation of on/off rate of inhibitors ⇒ estimation of intracellular kinetics of inhibitors

COI

I am a scientific advisory board member of the following companies.

1) SimCYP
2) SEKISUI Medical

I am and have been a consultant of and collaborating with 30 domestic and global pharmaceutical industries



RIKEN

Kazuya Maeda, Hiroyuki Kusuhara (Univ of Tokyo)

Acknowledgement

Sugiyama Lab Main Members

Takashi Yoshikado（wet +dry, IVIVE DDI）
Kota Toshimoto（dry,VCT(Virtual clinical study）
Kim, Soo-Jin： (DDI, PGx, IVIVE)
Lee, Kyeong Ryoon（Daewoong） (DDI, IVIVE)
Kim, Sae Hee （Daewoong） (DDI, IVIVE)
Atsuko Tomaru (IVIVE, Bioanalysis wth LC/MS/MS)
Aya Kiriake (IVIVE, transporter expression systems)
Kiyoe Morita (IVIVE, isolated hepatocyte (suspension, plated)
In-Soo Yoon (DDI, isolated hepatocytes (suspension, plated)

Azusa Futatsugi (DDI, PGx)
Keiko Ishigame (IVIVE, Bioanalysis)
Hisako Motokawa(IVIVE, Bioanalysis)

Secretaries
Sachie Sato
Chinami Yamada
Rie Abe
Aya Miyamoto

Acknowledgement

The members of PKPD seminar

PKPD seminar held once a month (18:30 – 22:00)
Headed by Yuichi Sugiyama