The 34th Annual Meeting of JSSX in Tsukuba
Kitagawa memorial Award

Promotion of investigations for drug discovery＆development using pharmacokinetic modeling ＆simulation

「Pharmacokinetic modeling ＆ simulationを活用した創薬・開発研究の推進」

Motohiro Kato, Ph.D

Research History

Hiroshima Univ.
Chugai

1987
1990 Erythropoetin
1991 G-CSF
1995
1997
1998

PK/PD for EPO and G-CSF

Univ. of Tokyo

Mechanism based inhibition
Human clearance prediction
CYP induction

Prof. Sugiyama's monthly seminar (since 1998)

DDI
Intestinal metabolism
CYP induction

2005 Young scientist award

PK/PD for tofogliflozin and anti-cancer drugs
Transcellular transport
Pharmacokinetics of antibody

Intestinal inhibition
P-gp kinetics
Virtual clinical trial

2014 tofogliflozin

2016 Dr. Yamaguchi
Young scientist award

2017 Dr. Tachibana
Young scientist award

2019 Early Retirement

2019 Dr. Haraya
Young scientist award

Major research since 2005

1. **CYP inhibition**
2. **CYP induction**
3. Human prediction using CYP3A tgm and monkey
4. PK/PD for tofogliflozin and anti-cancer drugs
5. Transcellular transport
6. Elimination mechanism of antibody in CSF
7. Intestinal metabolism(inhibition, nonlinear kinetics)
8. Inter-individual difference for pharmacokinetics

(PKPD seminar)

Modeling & Simulation is a powerful tool.

High throughput screening
Simple prediction
easy understanding

More accurate
Detailed prediction

Static model — simple, 1 - 3 parameters

Dynamic model — complex, many parameters

Static model (DDI guideline (Japan))

CYP inhibition

$$R = 1 + \frac{[I]}{Ki}$$ Competitive inhibition

Tim dependent inhibition(mechanism based inhibition)

$$R = \frac{(k_{obs} + k_{deg})}{k_{deg}} \qquad k_{obs} = k_{inact} \times [I]/(K_I + [I])$$ 2013

$$R = \frac{(k_{obs} + k_{deg})}{k_{deg}} \qquad k_{obs} = k_{inact} \times 50 \times [I]/(K_I + 50 \times [I])$$ 2018

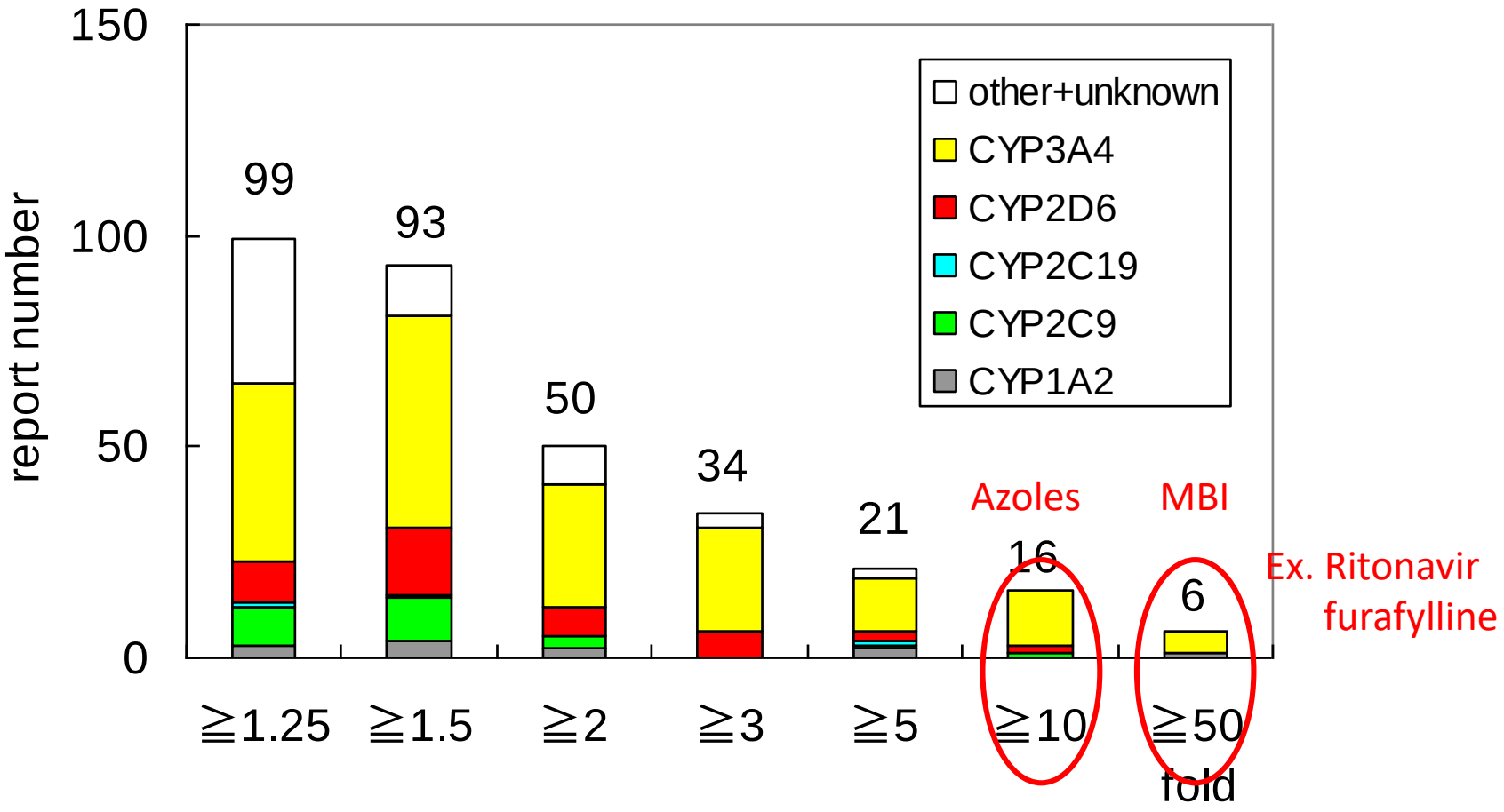
CYP induction

$$R = \frac{1}{\left(1 + \frac{d \times E_{max}}{EC_{50} + [I]}\right)}$$ 2013

$$R = \frac{1}{\left(1 + \frac{d \times 10 \times E_{max}}{EC_{50} + 10 \times [I]}\right)}$$ 2018

CYP inhibition

Increase of AUC mediated by CYP inhibition



(Kato etal. Pharm Res 25: 1891-1901, 2008)

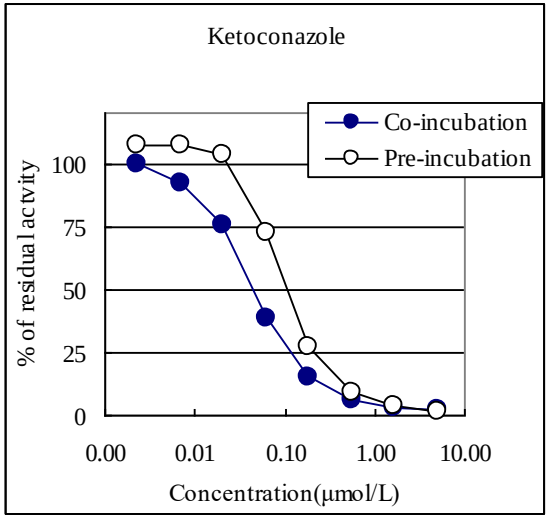
CYP inhibition

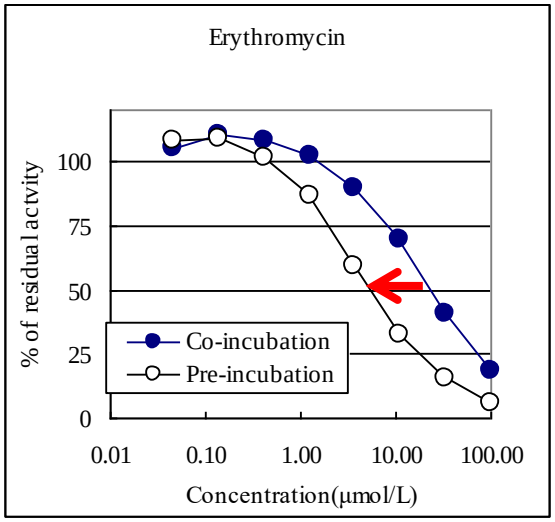
Competitive inhibition
reversible inhibition

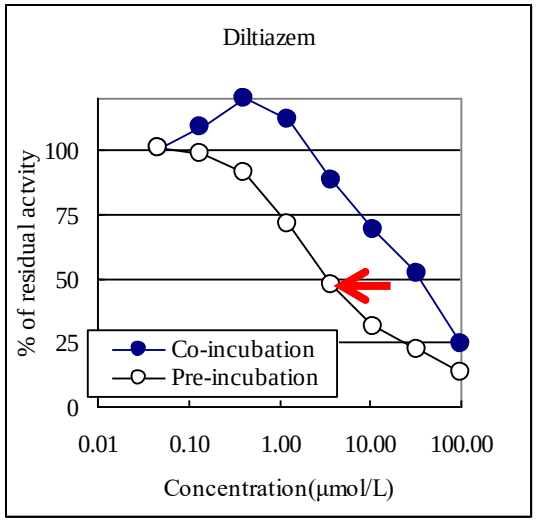
Mechanism-based inhibition(Time dependent inhibition)
irreversible inhibition

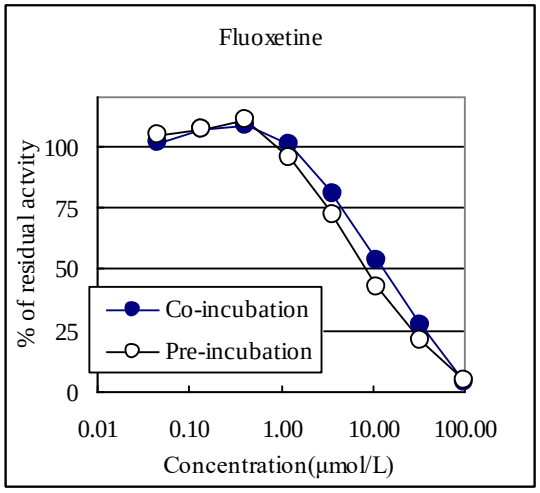
Fluorometric enzyme inhibition assay including TDI evaluation
96-well microtiter plates

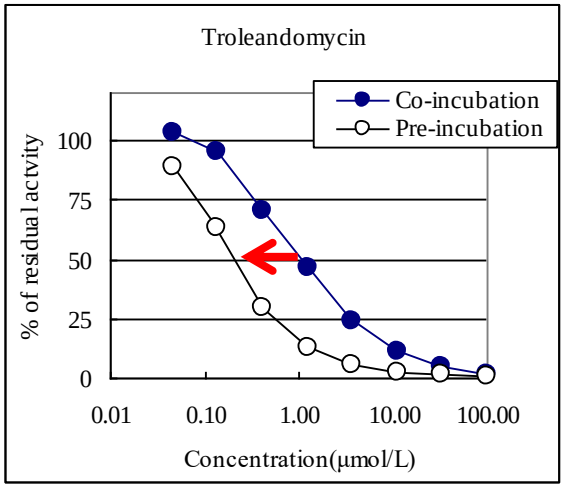
Shift assay

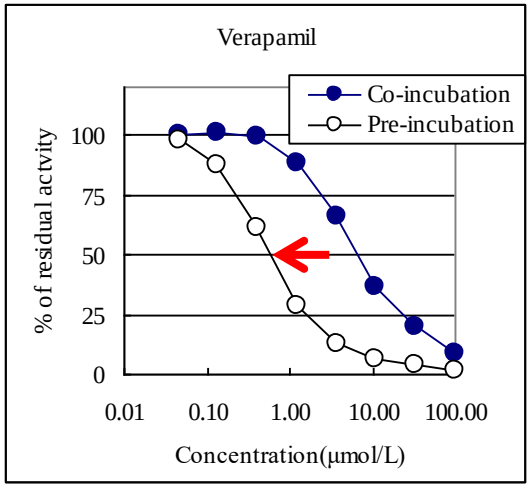








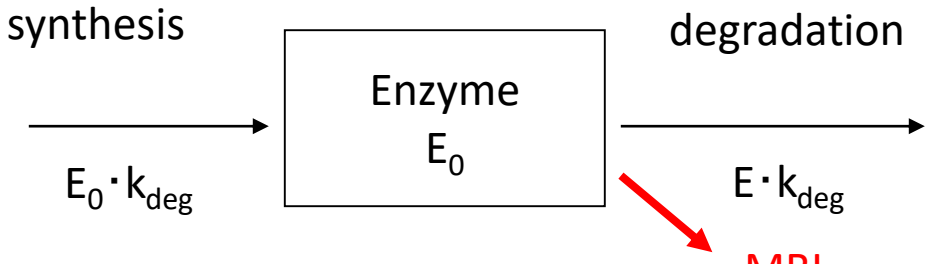




Concentration and time-dependent inhibition of BFC dealkylation activity

Sekiguchi N etal., Drug Metab Pharmacokinet 24:500–510, 2009

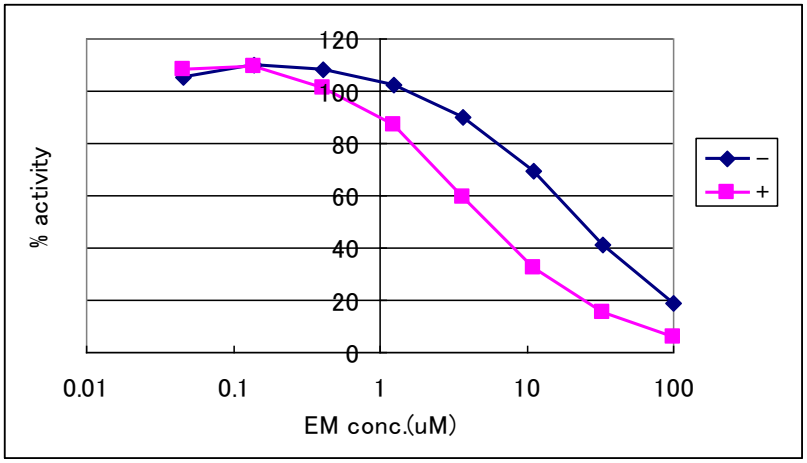
Model for mechanism based inhibition



$$\frac{dEact}{dt} = -\frac{kinact \cdot Eact \cdot Iu}{Ki,app + Iu} + k\,\mathrm{deg} \cdot E0 - k\,\mathrm{deg} \cdot Eact$$

At steady state

$$\frac{E_{act}}{E_0} = -\frac{K_{i,app} + I_u}{K_I + \left(\frac{k_{inact}}{k_{deg}} + 1\right) \cdot I_u} = \frac{1 + {I_u}/{K_{i,app}}}{1 + \left(\frac{k_{inact}}{k_{deg}} + 1\right) \cdot {I_u}/{K_{i,app}}} = \frac{AUC(control)}{AUC(inhibitor)}$$

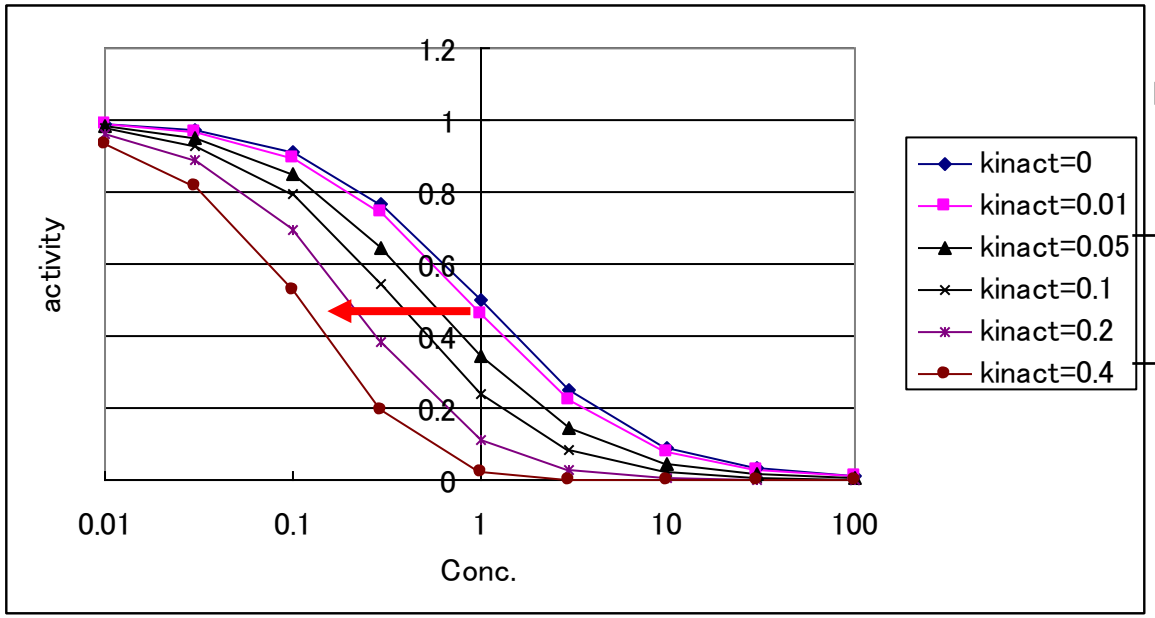


Can we estimate k_{inact}, $K_{i,app}$ from our assay?

Estimation of k_{inact}

Assumption

An Inhibior concentration does not change.
IC50(-) equal to Ki,app.



IC50(intact)/IC50(preincubation)

IC50(-)/IC50(+)
=1.56

IC50(-)/IC50(+)
=10

$$k_{inact} = \frac{\left(1 + \frac{IC_{50(-)}}{IC_{50(+)}}\right)}{t} \cdot ln\left(\frac{2}{\left(1 + \frac{IC_{50(+)}}{IC_{50(-)}}\right)}\right)$$

AUC change

$$\frac{\mathrm{AUC}(+)}{\mathrm{AUC}(-)} = \frac{1 + \left(1 + \frac{1 + \frac{IC_{50(-)}}{IC_{50(+)}}}{k_{deg} \cdot t} \cdot ln\left(\frac{2}{\left(1 + \frac{IC_{50(-)}}{IC_{50(+)}} \right)} \right) \right) \cdot \frac{I_u}{IC_{50(-)}}}{\left(1 + \frac{I_u}{IC_{50(-)}} \right)}$$

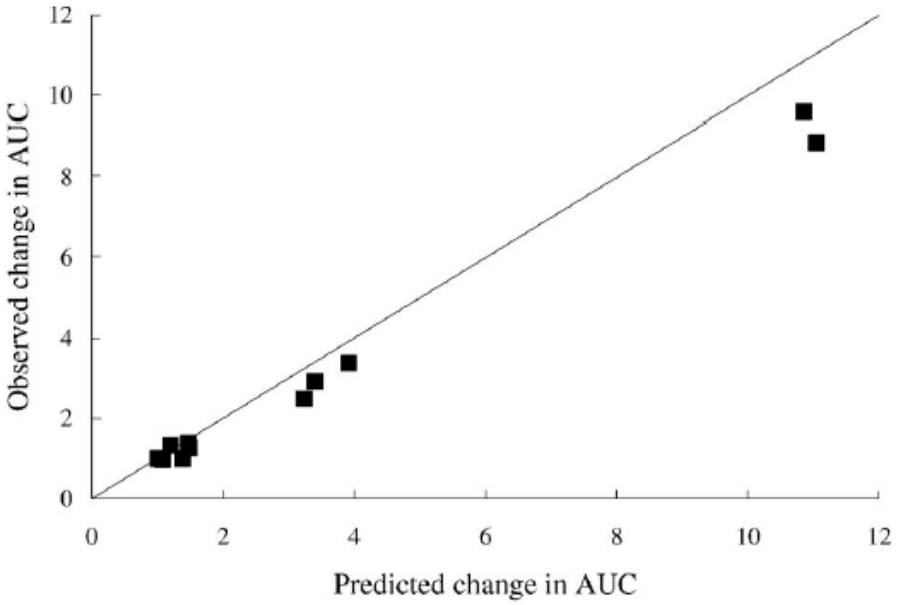
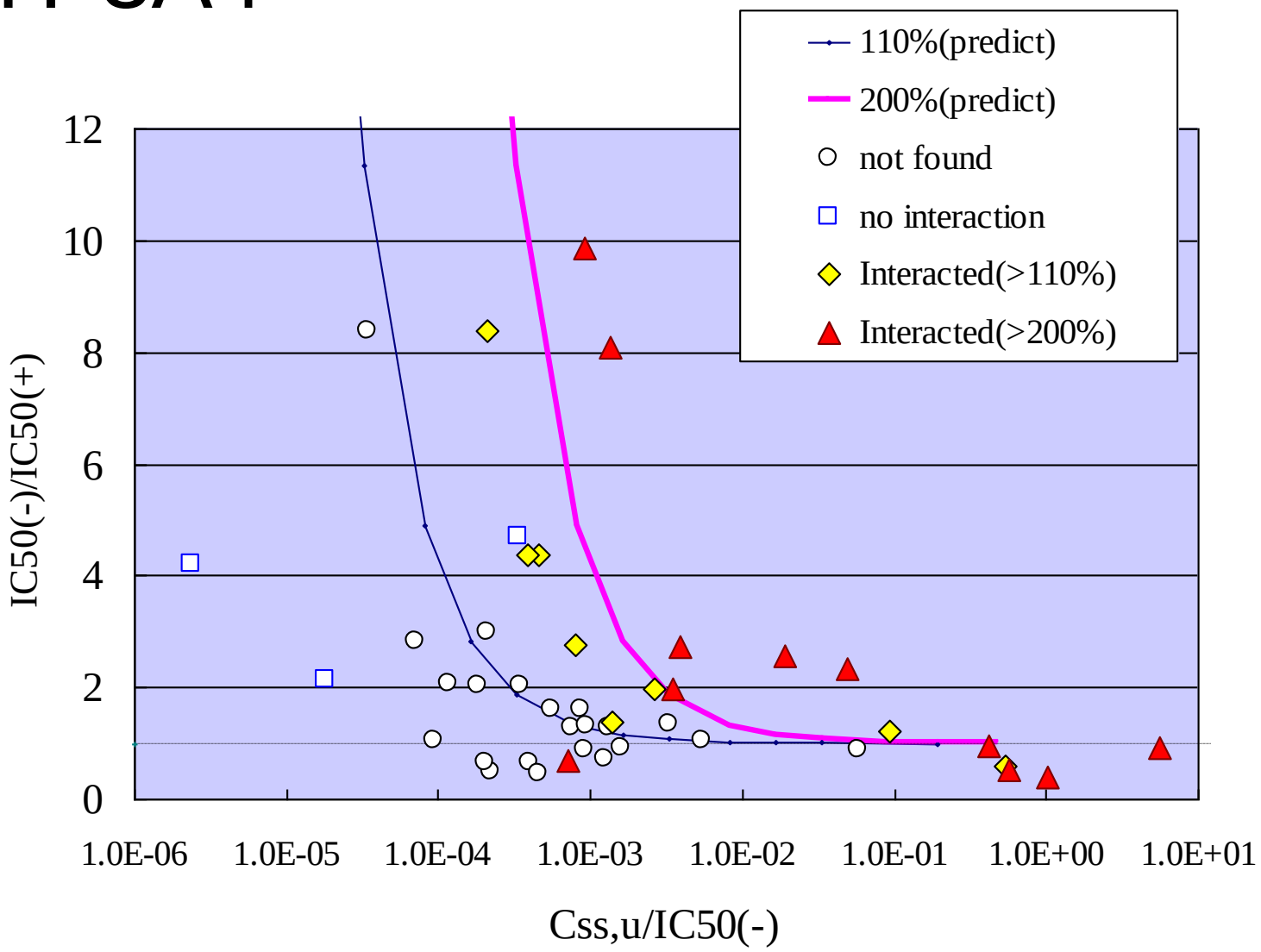


Fig. 3. Relationship between the predicted ratios of AUC change of co-administrated drugs and the ratios reported in clinic from mechanism-based inhibitors
Prediction of the change in AUC was calculated using equation 10. The line represents the 1:1 correlation.

Sekiguchi N etal., Drug Metab Pharmacokinet 24:500–510, 2009

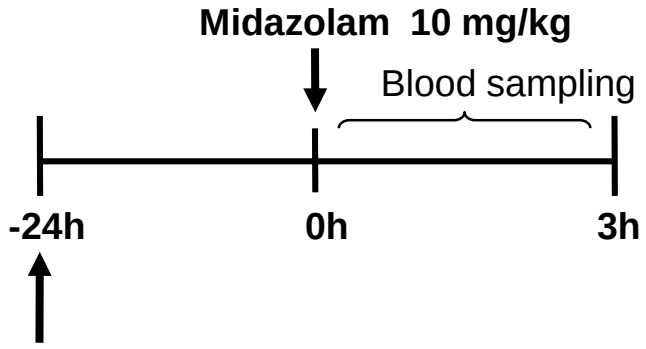
CYP3A4

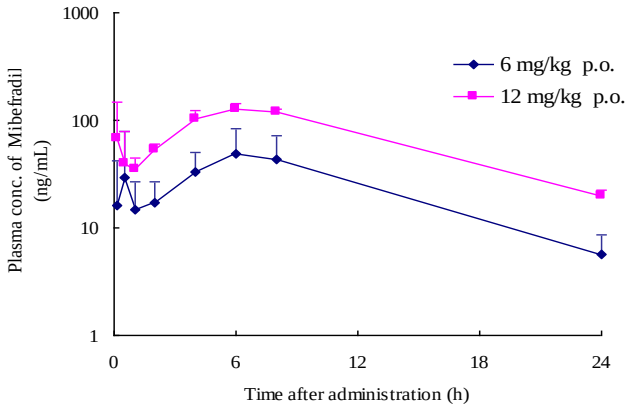


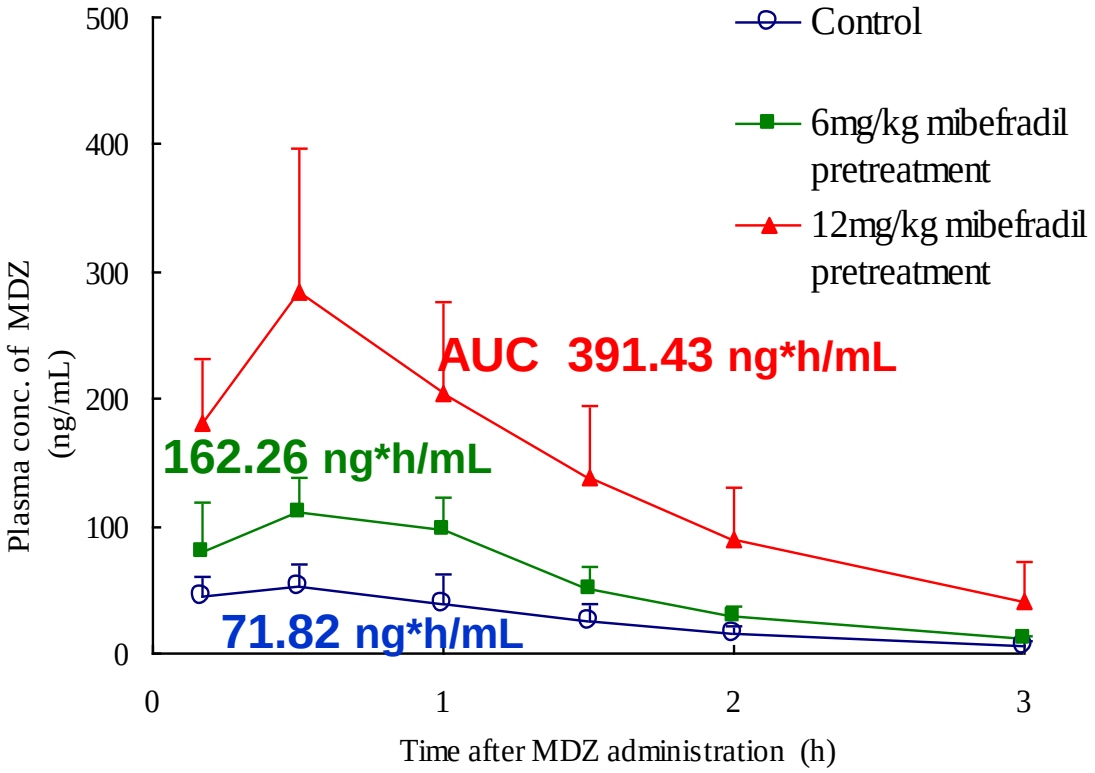
Best poster award 2004

Sekiguchi N etal., Drug Metab Pharmacokinet 24:500–510, 2009

Mechanism-based inhibition by Mibefradil in rats

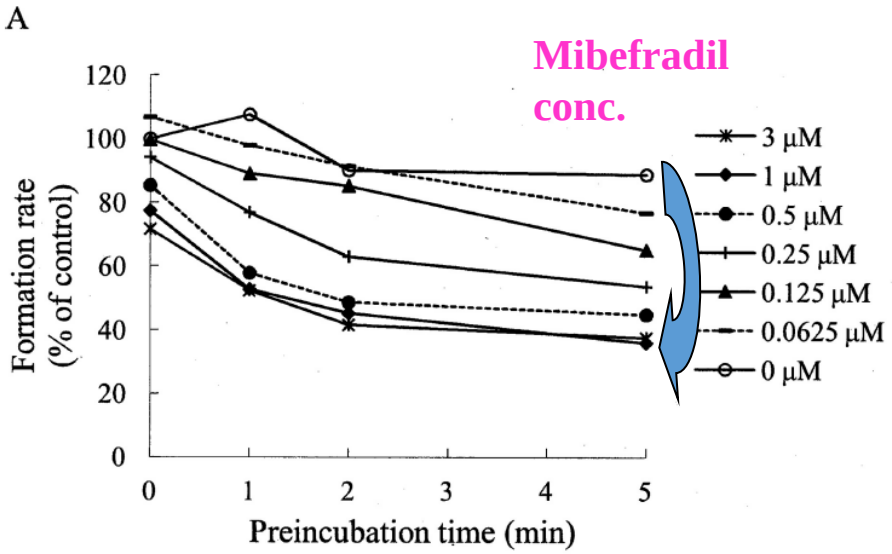






Sekiguchi et al.: Xenobiotica 38: 368-381, 2008

Estimation of MBI parameters



Inactivation parameters of mibefradil on midazolam metabolism in rrCYP3A2, rrCYP2C11, and rat liver microsomes

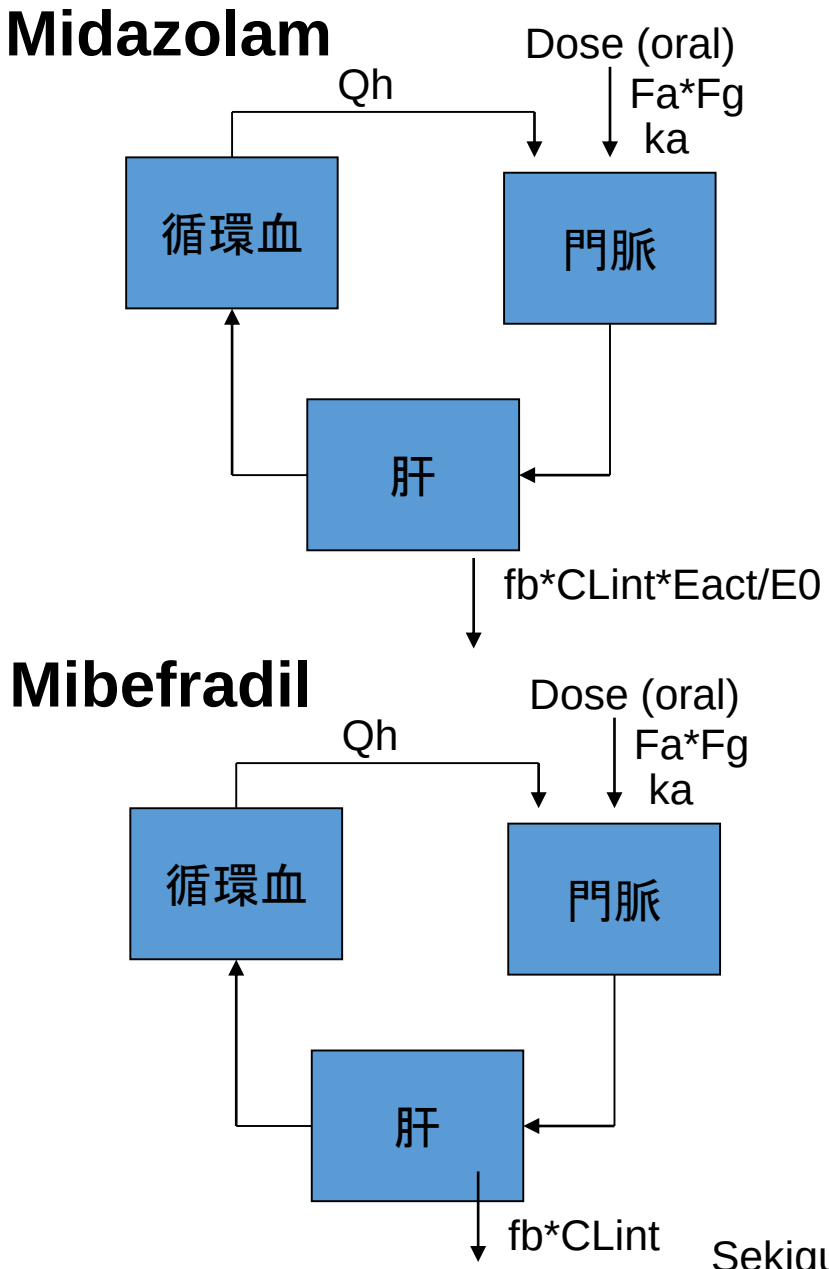
	k_{inact}	$K_{I, app}$
	min^{-1}	μM
CYP3A2		
4-Hydroxylation	0.386	0.263
1′-Hydroxylation	0.231	0.410
CYP2C11		
4-Hydroxylation	0.238	6.82
1′-Hydroxylation	0.565	11.4
Rat liver microsomes		
4-Hydroxylation	0.390	0.596
1′-Hydroxylation	0.203	0.737

fm=0.891

fm=0.109

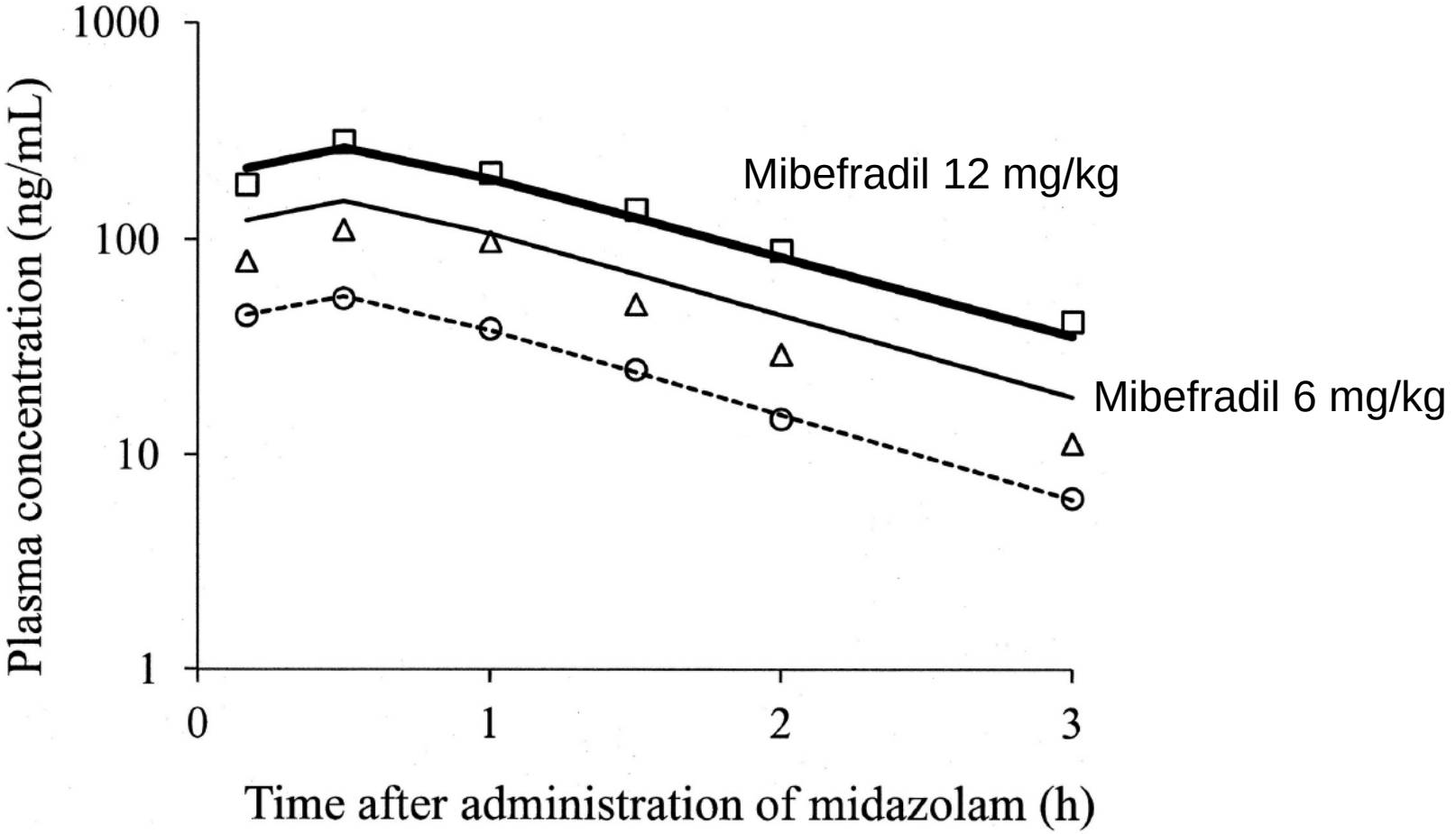
Sekiguchi etal. Drug Metab Dispos 39:1255–1262, 2011

Physiological model of the time profiles of midazolam and mibefradil concentrations



parameter		value	
physiological parameters of rat			
body weight		250	g
V_h		0.011	L
V_{pv}		0.000275	L
Q_h		0.882	L/h
E0		5	nmol/g live
k_{deg}		0.03	h^{-1}
Midazolam			
dose		2500	μ g
Fa*Fg		1	
$f_{u,S}$		0.04	
$K_{p,S}$		1	
$CL_{int,S}$		802.7	L/h
$k_{a,S}$		5.679	h^{-1}
$V_{sys,S}$		0.9448	L
Mibefradil			
dose		1500	μ g
		3000	μ g
Fa*Fg		1	
$f_{u,I}$		0.035	
$K_{p,I}$		1	
$CL_{int,I}$	6mg/kg dosed	75.64	L/h
	12mg/kg dosed	49.35	L/h
$k_{a,I}$	6mg/kg dosed	0.1740	h^{-1}
	12mg/kg dosed	0.1648	h^{-1}
$V_{sys,I}$	6mg/kg dosed	3.811	L
	12mg/kg dosed	3.546	L
k_{inact}		9.71	h^{-1}
$K_{I,app}$		130	μ g/L

Sekiguchi etal. Drug Metab Dispos 39:1255–1262, 2011

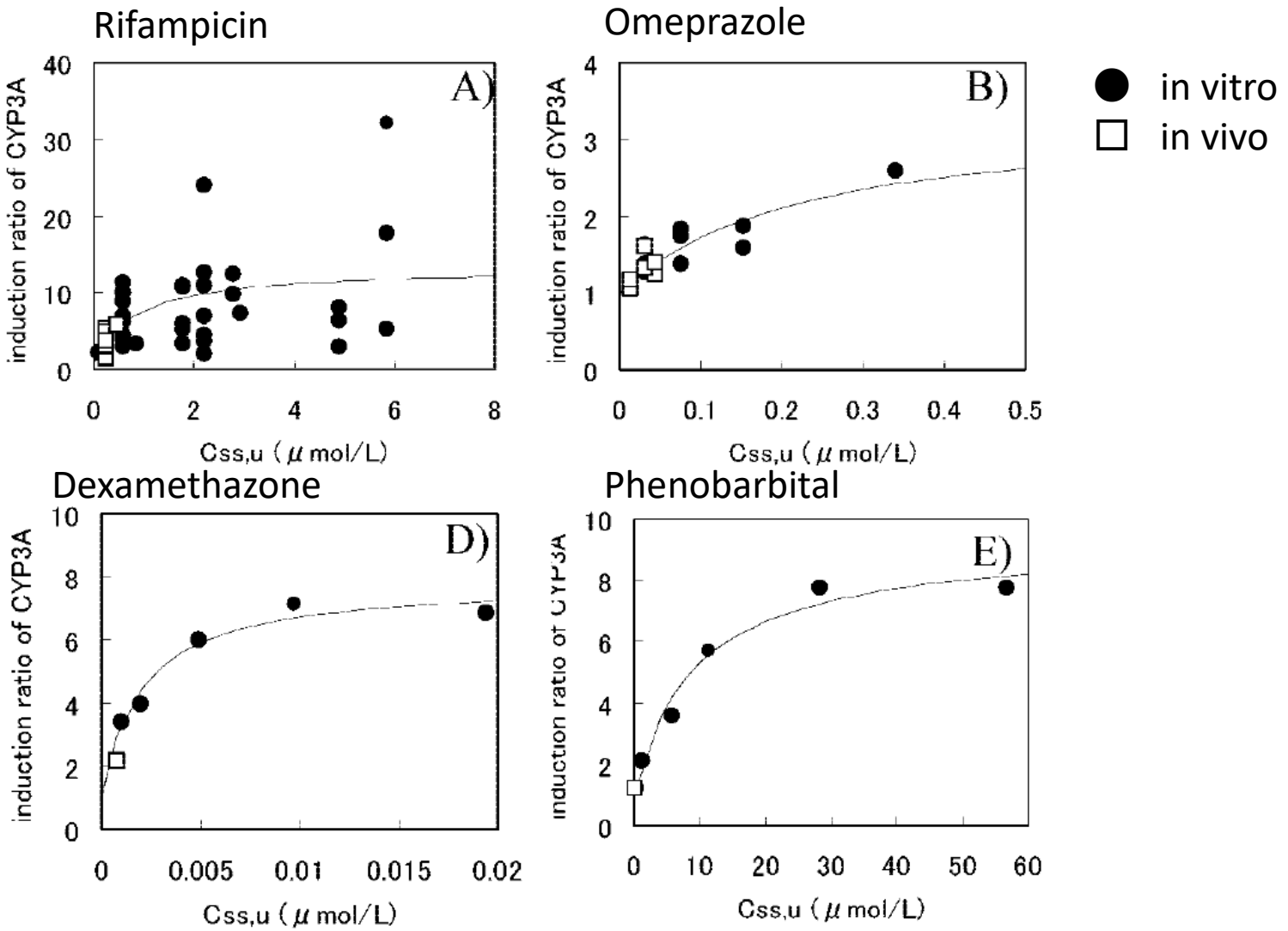


Predicted and observed concentrations of midazolam in rats

Sekiguchi etal. Drug Metab Dispos 39:1255–1262, 2011

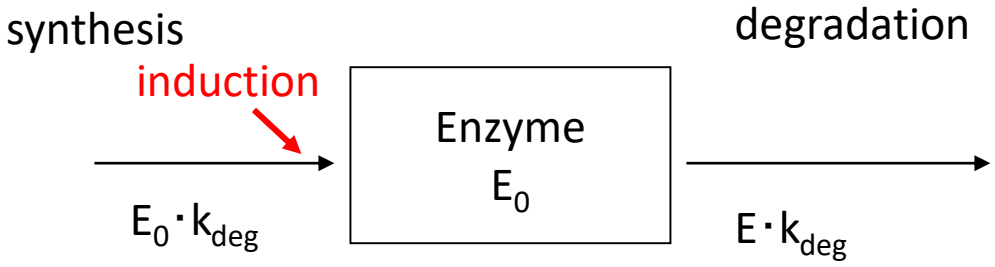
CYP induction

CYP induction



Kato M etal., Drug Metab Pharmacokinet 20:236–243, 2005

Model for CYP induction



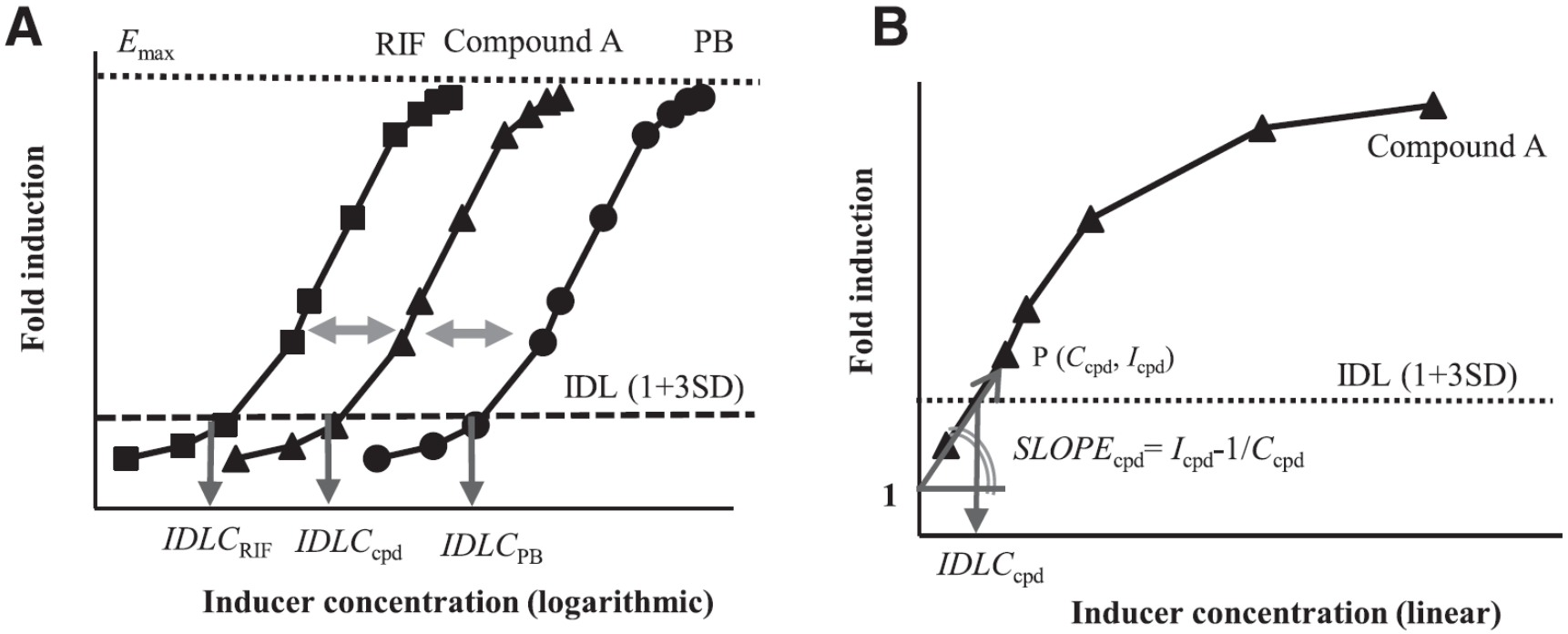
$$\frac{dE_{act}}{dt} = \frac{Emax \cdot Iu}{EC50 + Iu} + k_{deg} \cdot E_0 - k_{deg} \cdot E_{act}$$

At steady state

$$\frac{E_{act}}{E_0} = 1 + \frac{Emax \cdot Iss,u}{EC50 + Iss,u} = \frac{AUC(control)}{AUC(inducer)}$$

Relative factor approach

$$RF = \frac{EC50_{positive}}{EC50_{test}} = \frac{slope_{test}}{slope_{positive}}$$

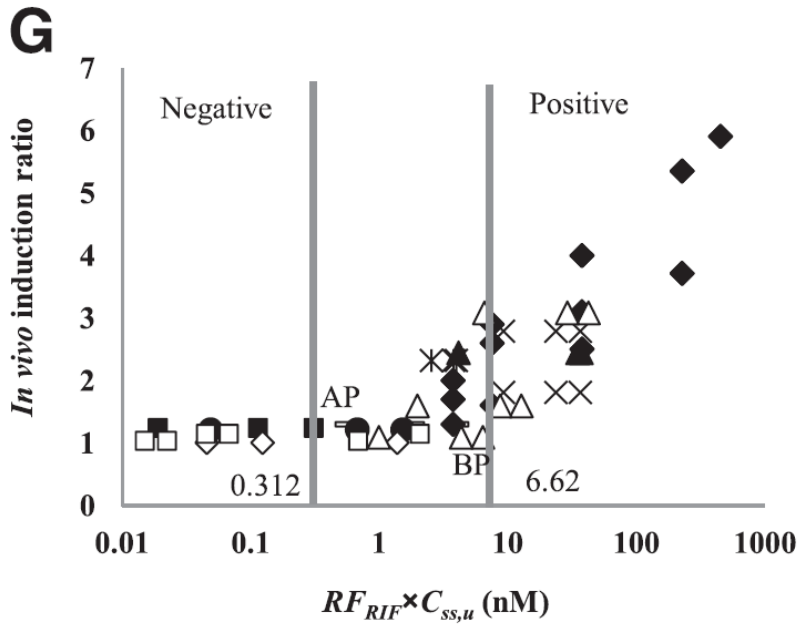


Kaneko A etal. Xenobiotica 39:803–810, 2009

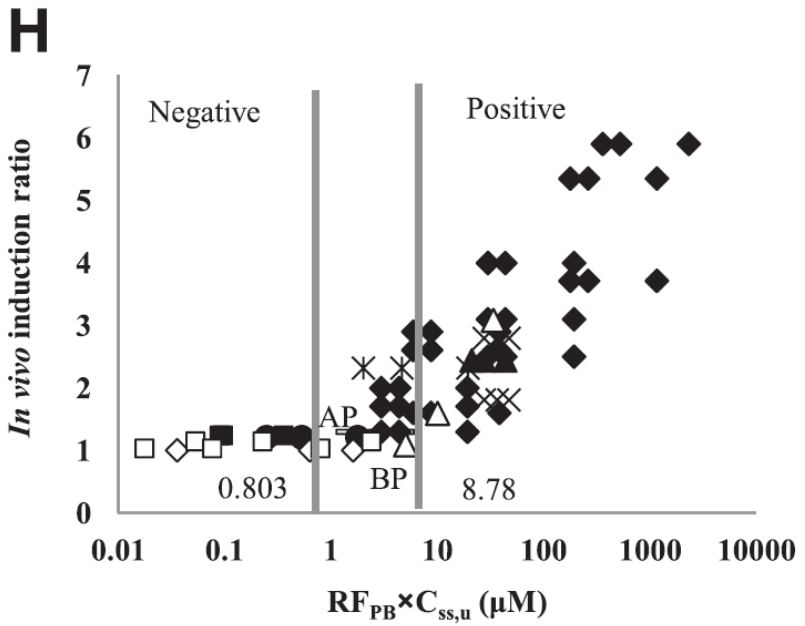
Kuramoto S etal. Drug Metab Dispos 45:1139–1145, 2017

Risk assessment

Low Risk High Risk



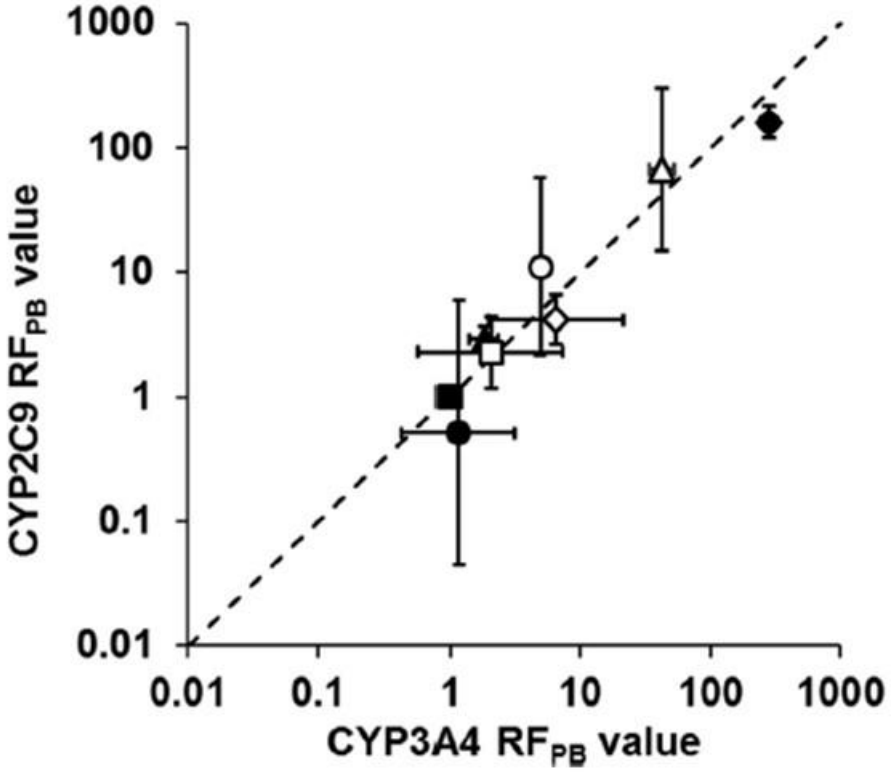
Rifampicin equivalent concentration



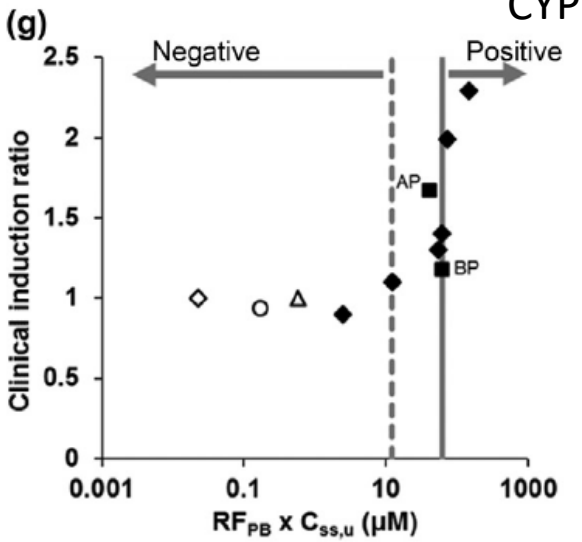
Phenobarbital equivalent concentration

Kuramoto S etal. Drug Metab Dispos 45:1139–1145, 2017

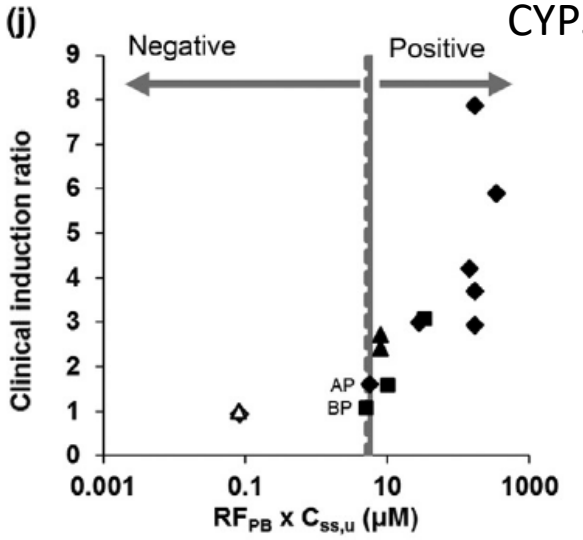
Risk assessment of CYP2C9



CYP2C9



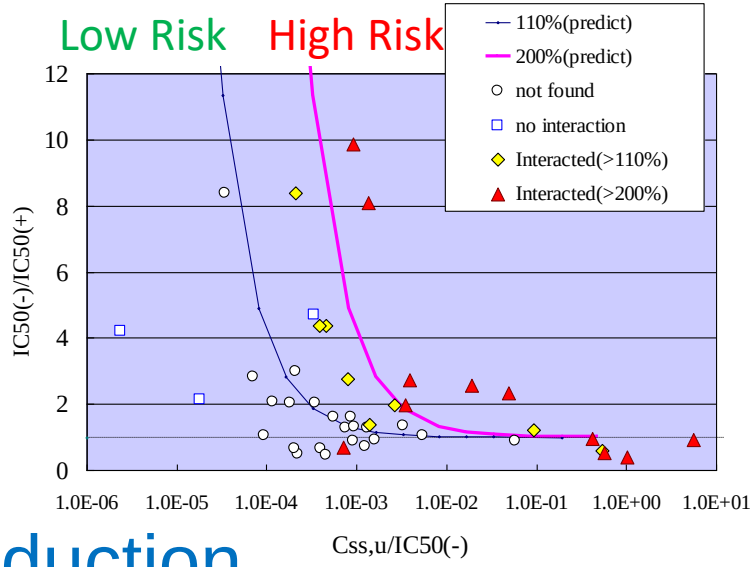
CYP3A



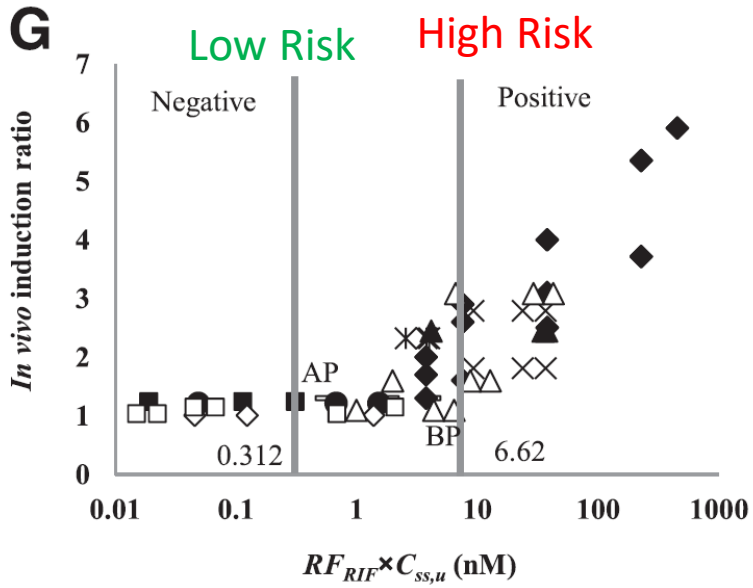
Endo-Tsukude C etal., Drug Metab Pharmacokinet 34:325–333, 2019

Static model

Inhibition

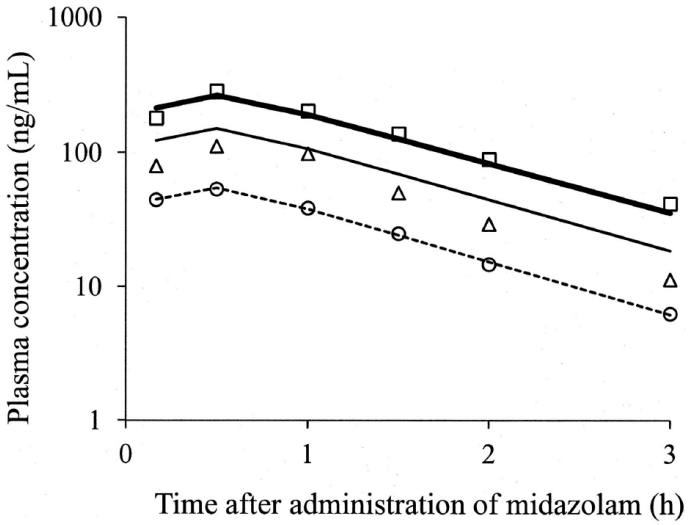


Induction



Dynamic model

Inhibition



Sekiguchi N etal., Drug Metab Pharmacokinet 24:500–510, 2009
Sekiguchi etal. Drug Metab Dispos 39:1255–1262, 2011
Kuramoto S etal. Drug Metab Dispos 45:1139–1145, 2017

Acknowledgements

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PKPD seminar members