Mitsubishi Tanabe Pharma

JSSX 2020 Kitagawa Memorial Award
for Dedication to Drug Discovery

Promotion of drug development based on drug interaction studies

Toshiyuki Kume, ph. D.

Sohyaku. Innovative Research Division

Mitsubishi Tanabe Pharma Corporation

Research Topics

Mitsubishi Tanabe Pharma

- Establishment of investigation methods to estimate the contribution of non-CYP enzymes involved in the drug metabolism
- Identification of transporters involved in the hepatic clearance of an investigational drug
- Evaluation of animal models for drug-drug interaction (DDI) studies
- Prediction of DDI using in silico and PBPK modelling

Research Topics

Mitsubishi Tanabe Pharma

- Establishment of investigation methods to estimate the contribution of non-CYP enzymes involved in the drug metabolism
  - ✓ *flavin-containing monooxygenase (FMO)*
  - ✓ *UDP glucuronosyl transferase (UGT)*
- Identification of transporters involved in the hepatic clearance of an investigational drug
- Evaluation of animal models for drug-drug interaction (DDI) studies
- Prediction of DDI using in silico and PBPK modelling

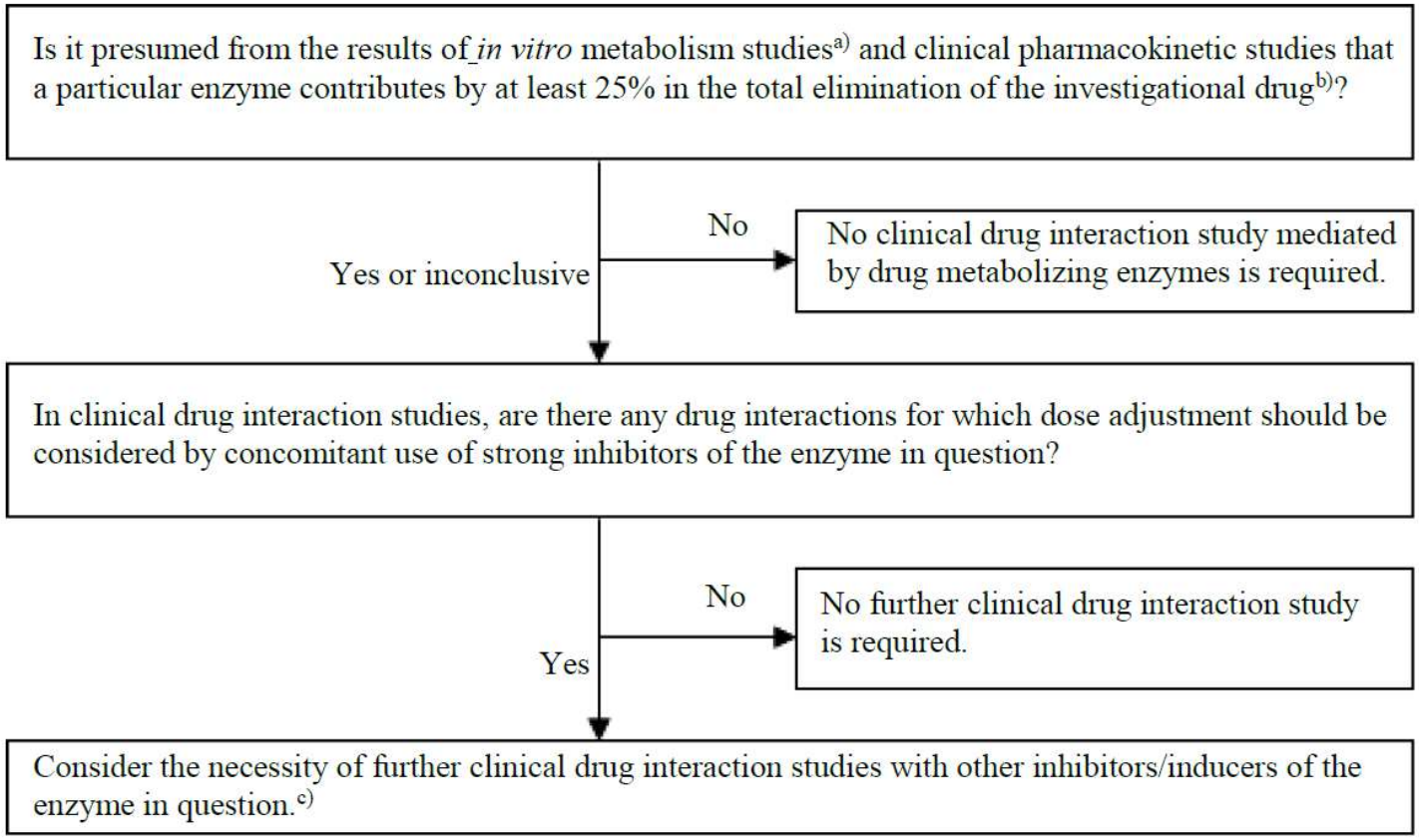
Flavin-containing monooxygenases (FMO) are the next major phase I enzyme after P450

Mitsubishi Tanabe Pharma

Decision trees as an affected drug

Notified by the Ministry of Health, Labour and Welfare (MHLW) in July 2018

Figure 1-1: Evaluation of the possibility of the investigational drug as an affected drug (Identification of the enzymes involved in the metabolism of the investigational drug)



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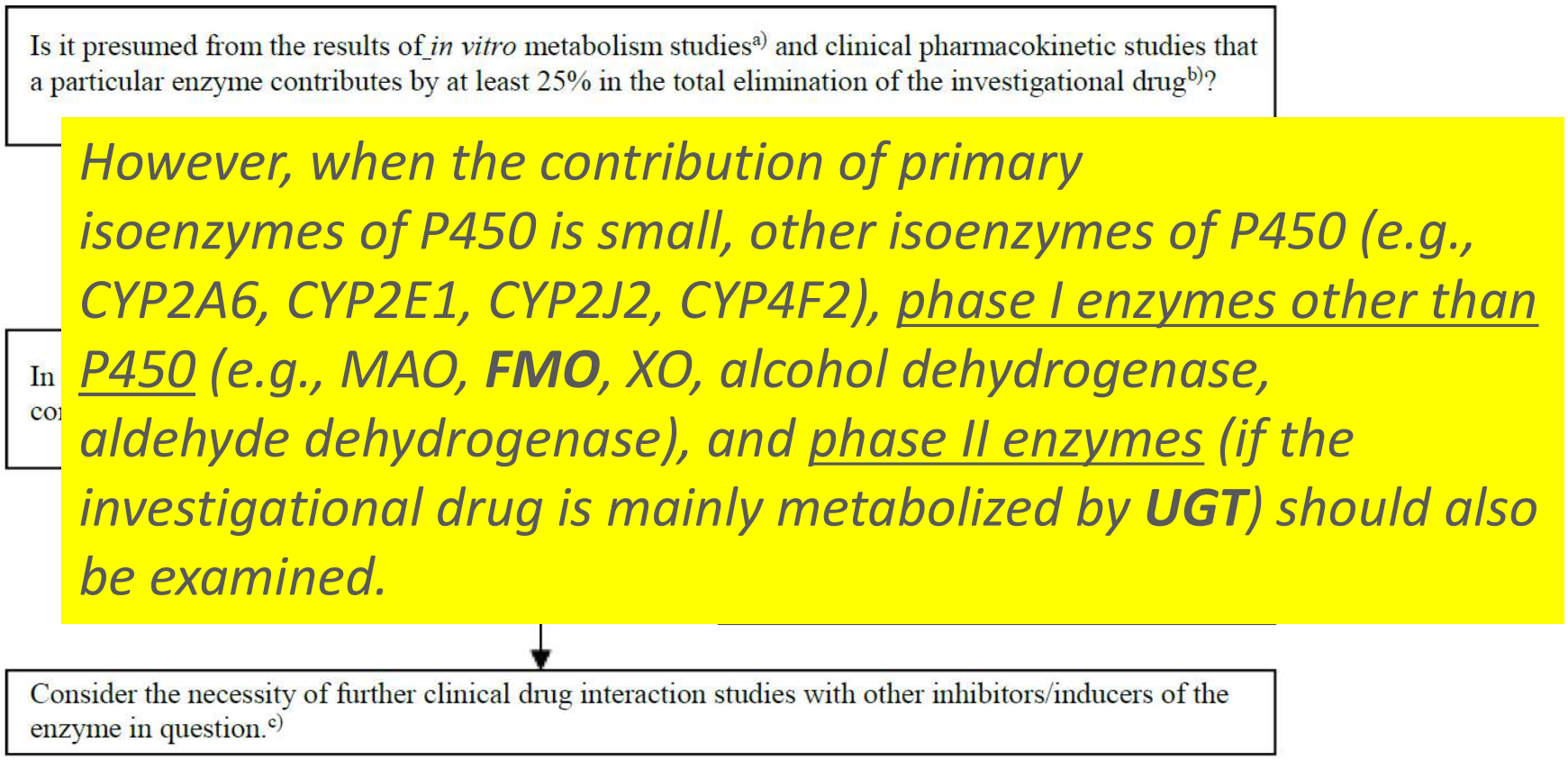
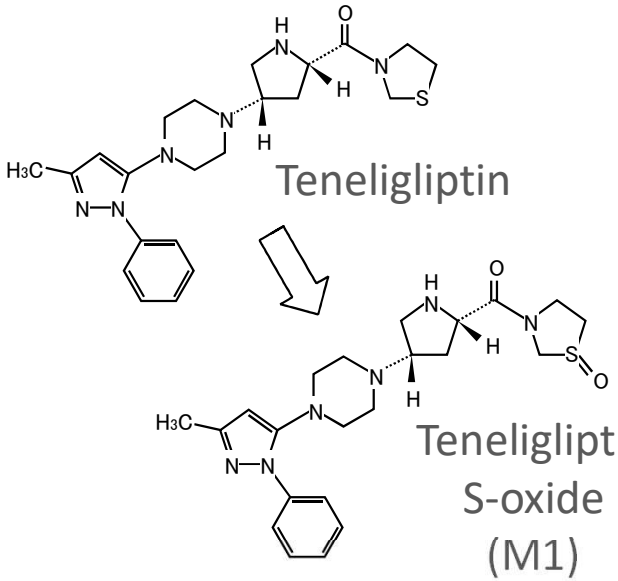


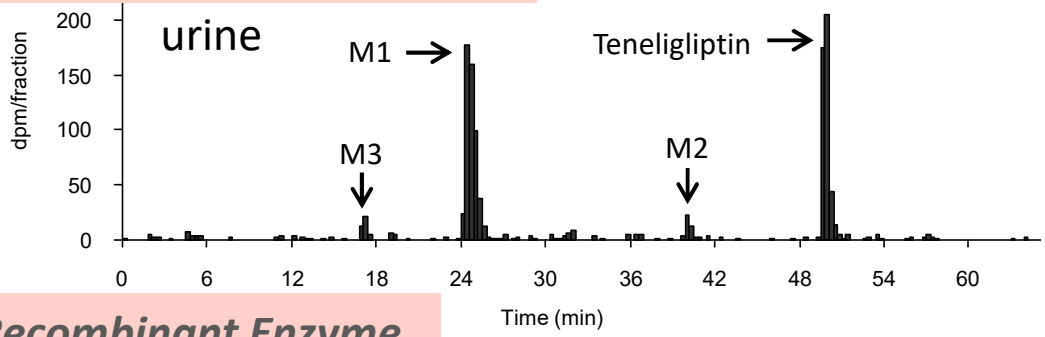
*However, when the contribution of primary isoenzymes of P450 is small, other isoenzymes of P450 (e.g., CYP2A6, CYP2E1, CYP2J2, CYP4F2), phase I enzymes other than P450 (e.g., MAO, **FMO**, XO, alcohol dehydrogenase, aldehyde dehydrogenase), and phase II enzymes (if the investigational drug is mainly metabolized by **UGT**) should also be examined.*

Teneligliptin is metabolized by both CYP3A4 and flavin-containing monooxygenase

Nakamaru Y. *et al.*, *Xenobiotica*, 44(3):242-53(2014).

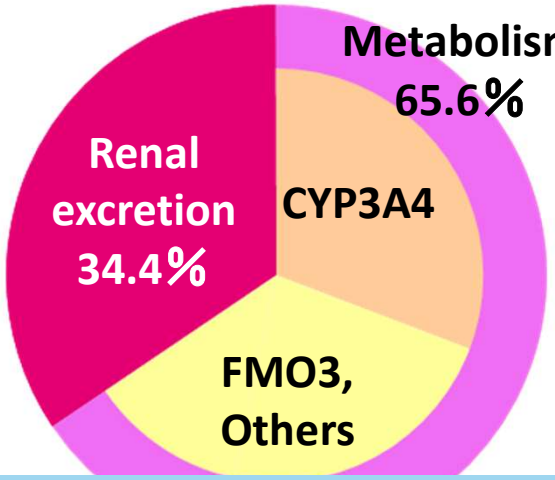


Human Mass Balance Studies



Recombinant Enzyme Studies

Isoform	(μM)	Vmax (pmol/pmol P450 or FMO/min)	Clearance (μL/pmol P450 or FMO/min)
CYP3A4	37.9	33.7	0.889
FMO1	221.5	57.6	0.260
FMO3	126.1	52.1	0.413



Multiple Clearance Pathways

Enzyme Inhibition Studies

	Metabolic activity (pmol/mg protein/min)	Relative metabolic activity (% of control)	Percent inhibition
Control	327.5	100.0	
Quinidine (1 μM)	336.0	102.6	−2.6
Ketoconazole (0.5 μM)	173.5	53.0	47.0
Methimazole (200 μM)	107.5	32.8	67.2

Benzydamine N-oxygenation as an index for flavin-containing monooxygenase activity

Taniguchi-Takizawa T. *et al.*,
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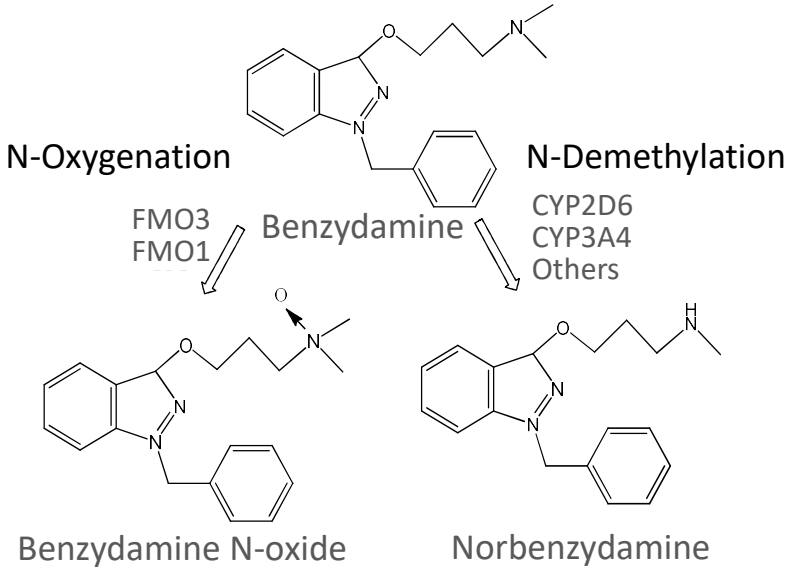

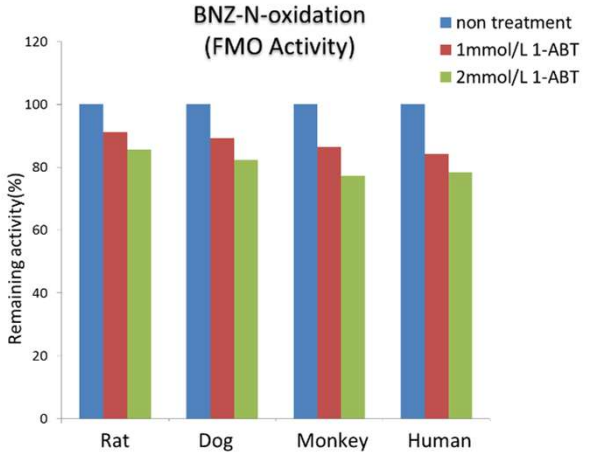

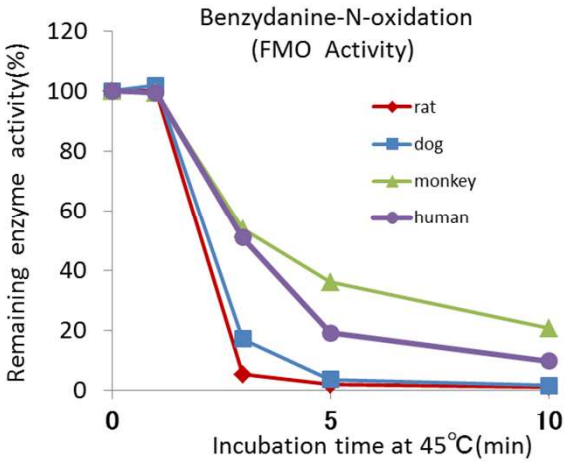

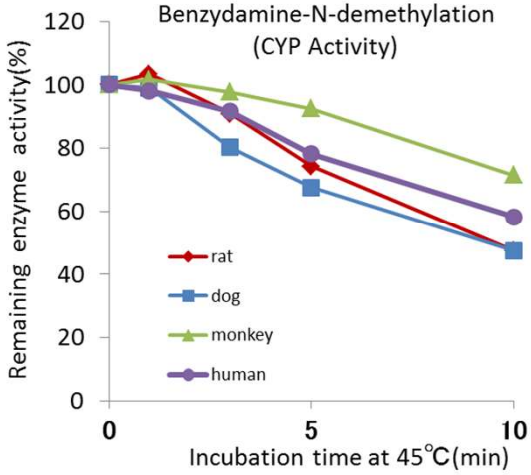

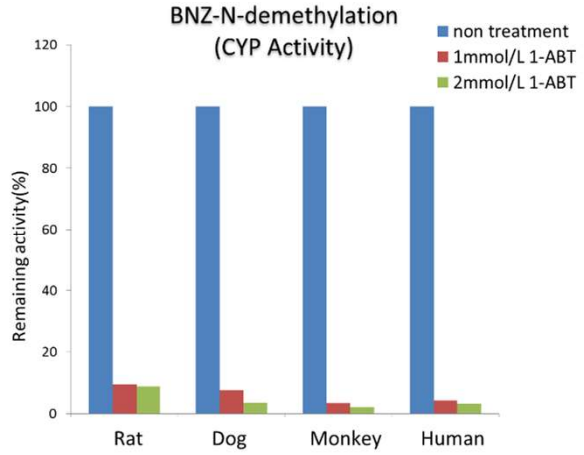

Preheating

ABT treatment

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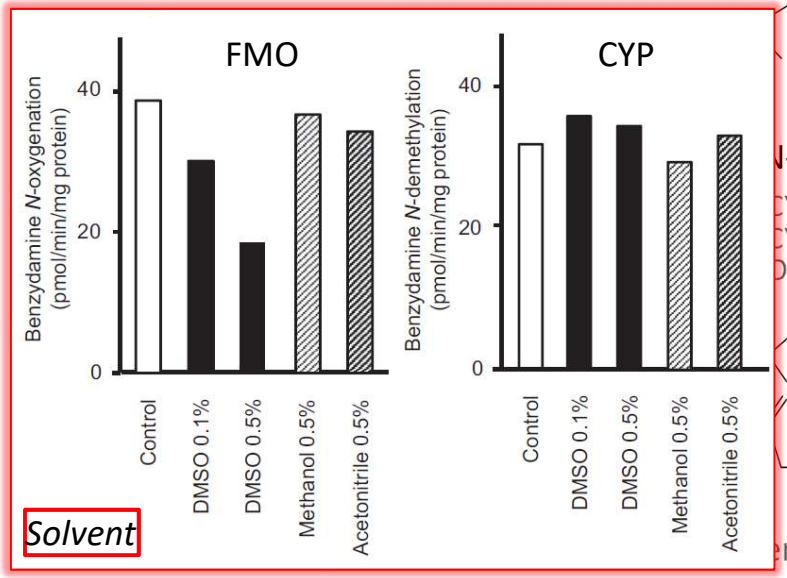
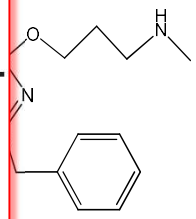
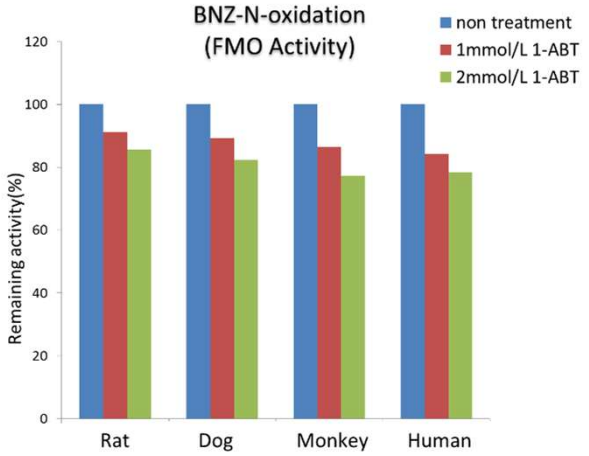
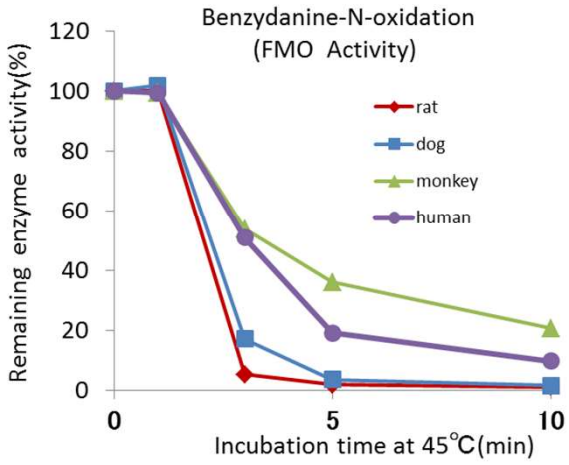


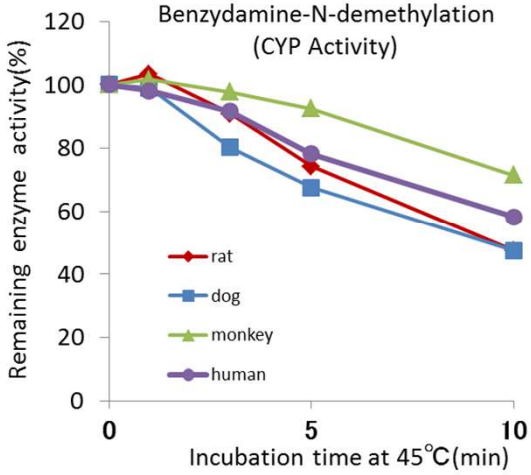
-Demethylation
YP2D6
YP3A4
thers

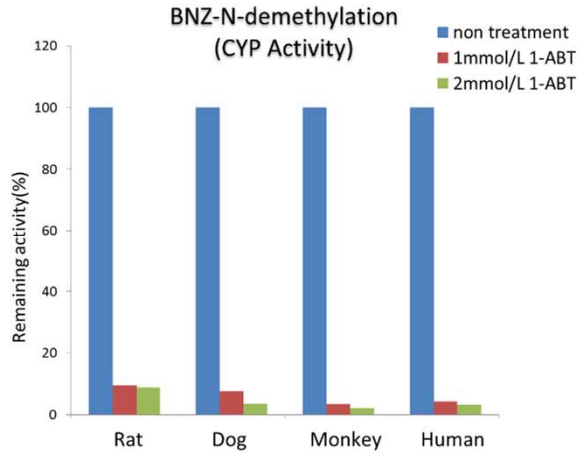


nzydamine









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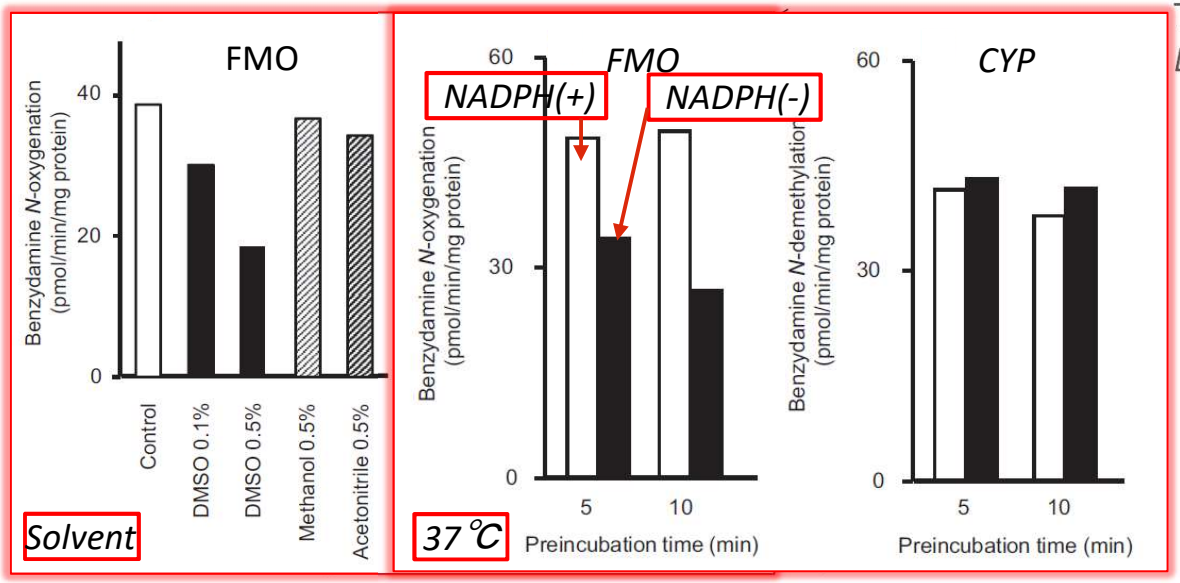
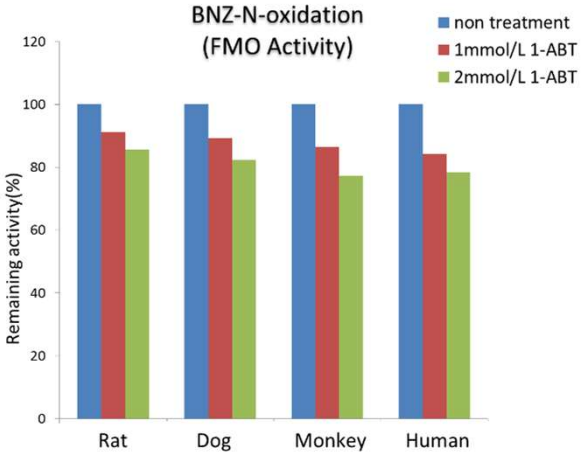
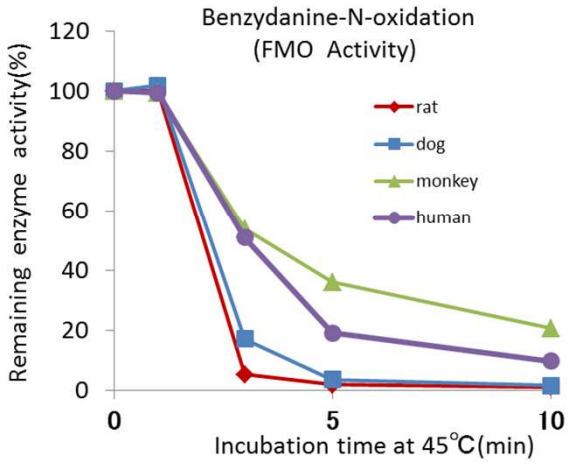
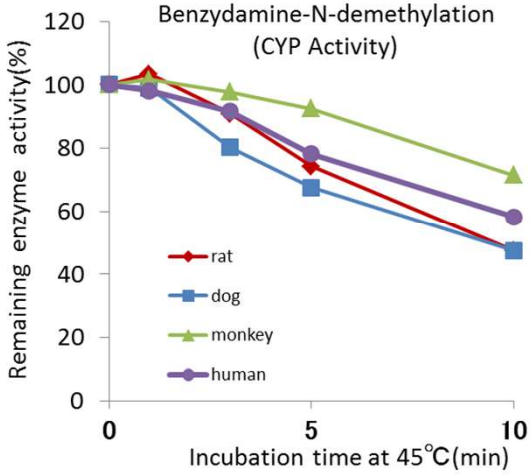
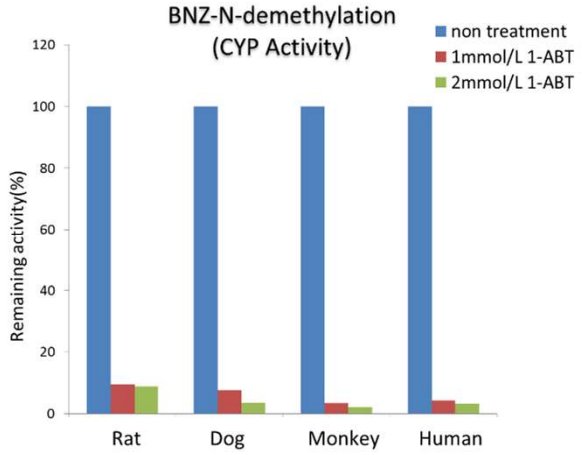








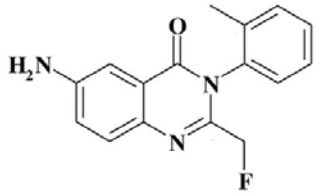


Preheating

ABT treatment

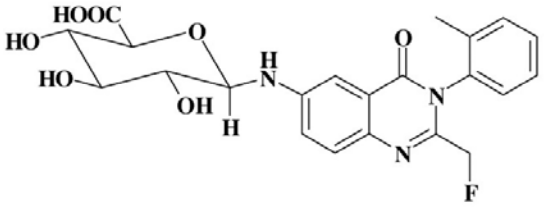
Afloqualone is metabolized to its N-glucuronide mainly by UGT1A4 in human liver

Kaji H. and Kume T.,
Drug Metab Dispos. 33(1):60-7(2005)



Afloqualone (AFQ)

N-acetylation



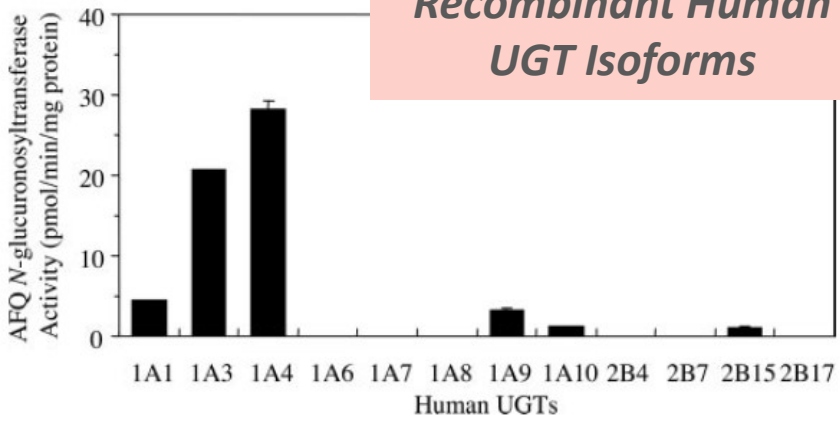
AFQ *N*-glucuronide (Main metabolite in human urine)

Enzyme Kinetic Studies (liver microsomes)

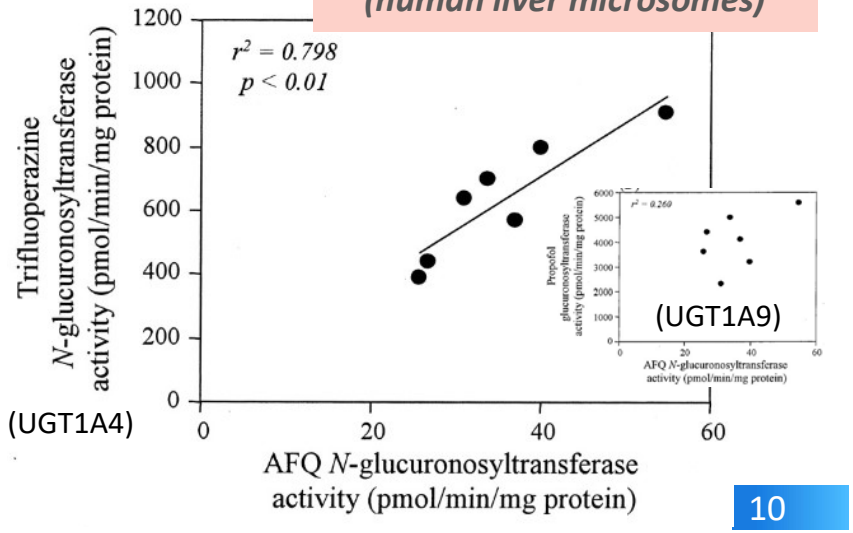
Species	K_m or S_{50}	V_{max}	CL_{int} [a] or CL_{max} [b]
	μM	*pmol/min/mg protein*	*μl/min/mg protein*
Human[c]	2019 ± 85.9	871.2 ± 17.9	0.432
Rat[c]	611.0 ± 26.3	89.2 ± 1.3	0.146
Dog[d]	582.1 ± 13.2	236.9 ± 2.4	0.219
Monkey[c]	732.5 ± 47.2	90.1 ± 2.1	0.123
Rabbit[c]	24.8 ± 0.7	9375 ± 68.9	378.2

[a] CL_{int} calculated as V_{max}/K_m for Michaelis-Menten kinetics.
[b] CL_{max} calculated as described under *Materials and Methods*.
[c] Michaelis-Menten.
[d] Hill equation (n = 1.45 ± 0.033).

Recombinant Human UGT Isoforms



Correlation Analysis (human liver microsomes)



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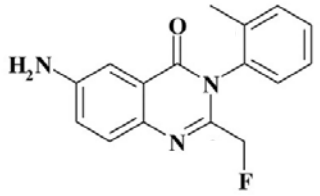

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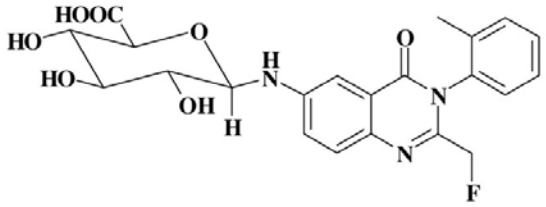

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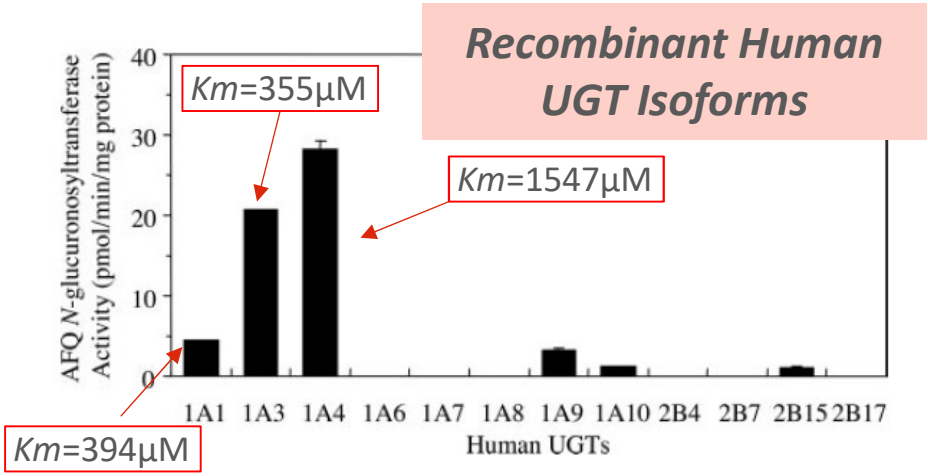
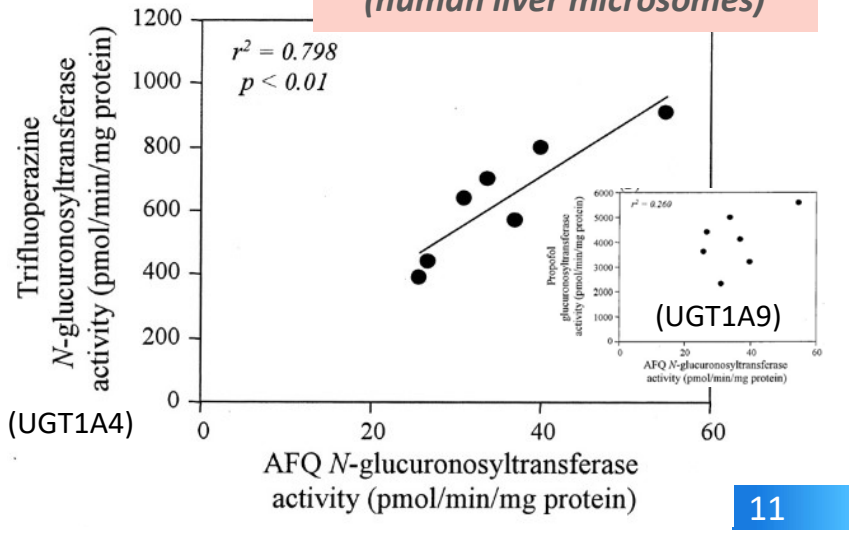
Recombinant Human UGT Isoforms



Correlation Analysis (human liver microsomes)

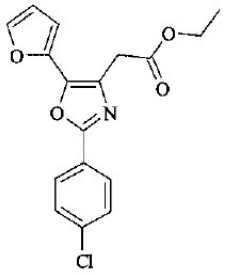


Marked Species Differences of UDP-Glucuronosyltransferase in the liver and intestine

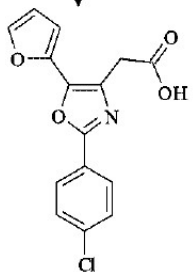
Mitsubishi Tanabe Pharma

TA-1801

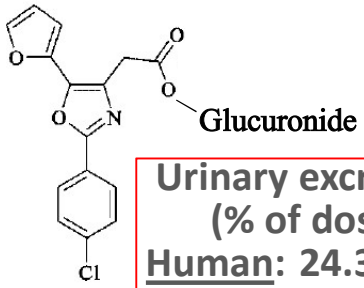
(hypolipidemic agent)



TA-1801



M1 (TA-1801A)



Urinary excretion (% of dose)

Human:	**24.3**
Rat:	**9.6**
Rabbit:	**7.5**
Dog:	**0.04**

[Liver]

Rabbit>Human=Rat=Dog

(UGT1A1, 1A9, 2B7)

[Intestine]

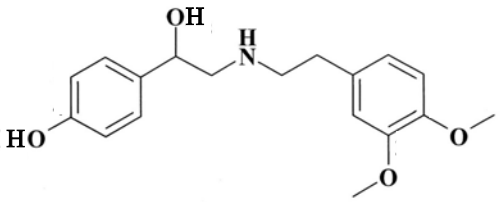
Human>>Rabbit>Rat=Dog

(UGT1A1, 1A3, 2B7)

Kaji H. and Kume T.,
Drug Metab. Pharmacokinet. 20(3):206-11(2005)
Drug Metab. Pharmacokinet. 20(3):212-8(2005)

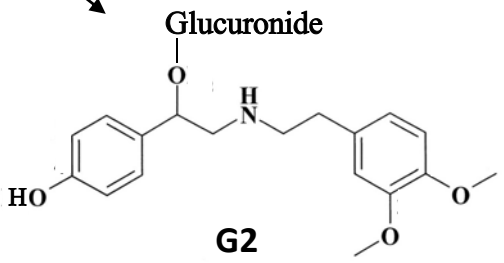
Denopamine

(β1-adrenoceptor
selective partial agonist)

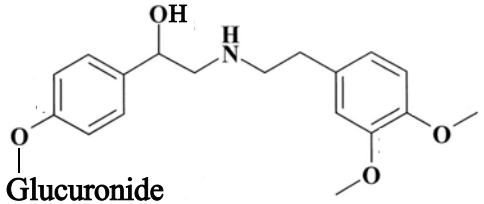


Human liver and intestine (UGT2B7) Dog, Monkey

Rat Rabbit Dog Monkey



G2



G1

Kaji H. and Kume T.,
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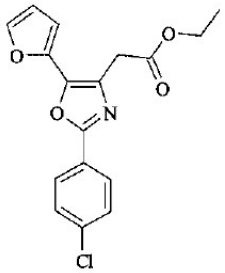
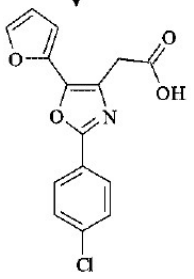
TA-1801

(hypolipidemic agent)

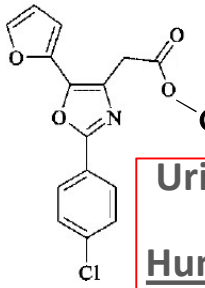


TA-1801



M1 (TA-1801A)

Species	CLint (ul/min/mg protein)	
	Liver	Jejunum
Human	23.6	47.9
Rat	26.7	1.11
Rabbit	110	5.46
Dog	29.5	0.87



Glucuronide

Urinary excretion (% of dose)

Human: 24.3
Rat: 9.6
Rabbit: 7.5
Dog: 0.04

[Liver]

Rabbit>Human=Rat=Dog
(UGT1A1, 1A9, 2B7)

[Intestine]

Human>>Rabbit>Rat=Dog
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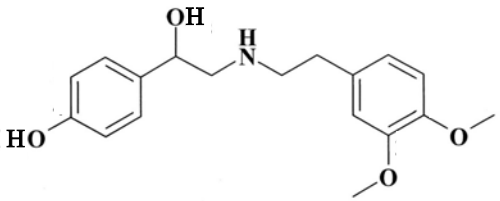
(β1-adrenoceptor selective partial agonist)



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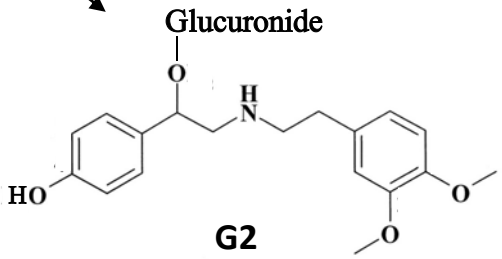
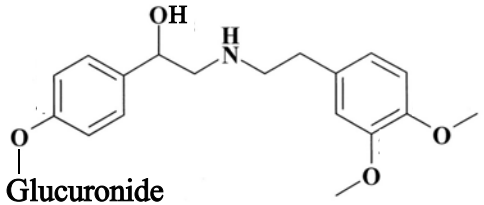


Glucuronide

G2



Glucuronide

G1

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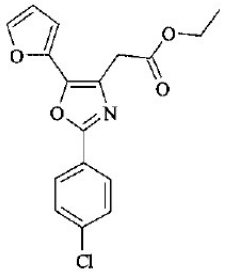
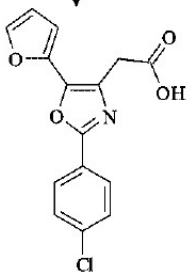
TA-1801
(hypolipidemic agent)

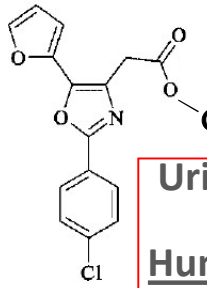


TA-1801



M1 (TA-1801A)

Species	CLint (ul/min/mg protein)	
	Liver	Jejunum
Human	23.6	47.9
Rat	26.7	1.11
Rabbit	110	5.46
Dog	29.5	0.87



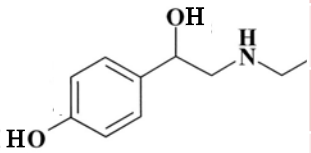
Glucuronide

Urinary excretion (% of dose)
Human: 24.3
Rat: 9.6
Rabbit: 7.5
Dog: 0.04

[Liver]
Rabbit>Human=Rat=Dog
(UGT1A1, 1A9, 2B7)
[Intestine]
Human>>Rabbit>Rat=Dog
(UGT1A1, 1A3, 2B7)

Kaji H. and Kume T.,
Drug Metab. Pharmacokinet. 20(3):206-11(2005)
Drug Metab. Pharmacokinet. 20(3):212-8(2005)

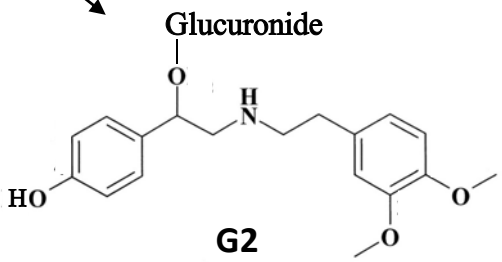
Denopamine
(β1-adrenoceptor selective partial agonist)



Source of UGT	CLint (ul/min/mg protein)	
	G1	G2
Rat liver	1220	-
Rabbit liver	152	-
Dog liver	2.14	1.62
Monkey liver	1.96	3.40
Human liver	-	2.54
Human jejunum	-	0.39
UGT2B7	-	2.43

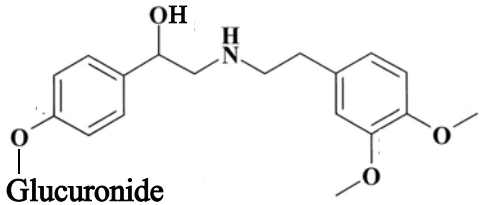
Human liver and intestine
(UGT2B7)
Dog, Monkey

Rat
Rabbit
Dog
Monkey



Glucuronide

G2



Glucuronide

G1

Kaji H. and Kume T.,
Drug Metab Dispos. 33(3):403-12(2005).

Research Topics

Mitsubishi Tanabe Pharma

- Establishment of investigation methods to estimate the contribution of non-CYP enzymes involved in the drug metabolism
  - ✓ *flavin-containing monooxygenase (FMO)*
  - ✓ *UDP glucuronosyl transferase (UGT)*
- Identification of transporters involved in the hepatic clearance of an investigational drug
- Evaluation of animal models for drug-drug interaction (DDI) studies
  - ✓ *drug metabolism (CYP3A)*
  - ✓ *drug transport (OATP)*
- Prediction of DDI using in silico and PBPK modelling

Cynomolgus Monkey as an animal model for study of Drug-drug Interaction (Drug Metabolism)

In vitro similarities (Inhibition kinetics)

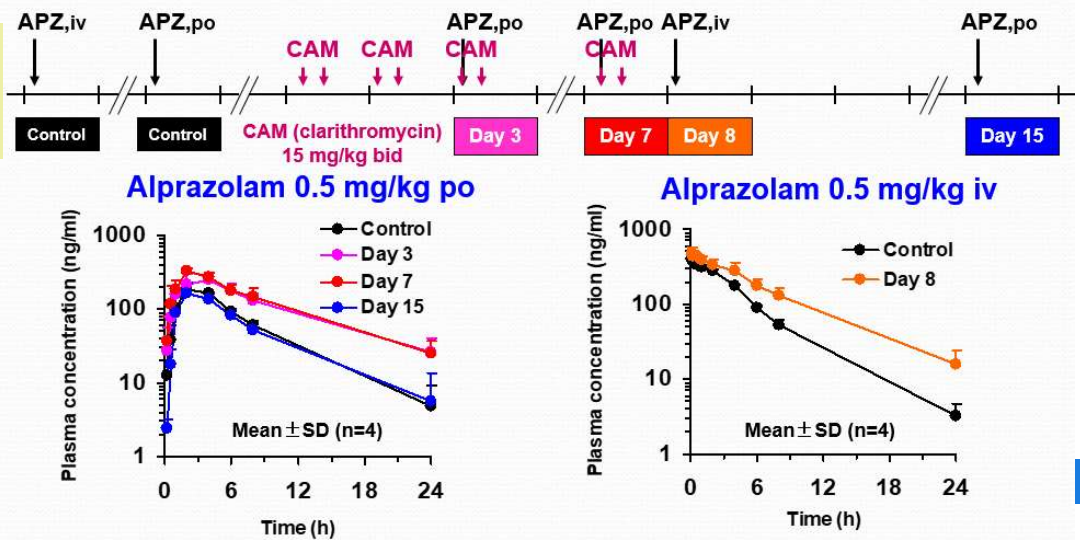
Azole Antifungal	Monkey K_i (μM)	Human K_i (μM)
Ketoconazole	0.025	0.032
Itraconazole	0.096	0.130
Fluconazole	14	21

Macrolide Antibiotics	Monkey K_I (μM)	Monkey K_{inact} (min^{-1})	Human K_I (μM)	Human K_{inact} (min^{-1})
Erythromycin	6.4	0.0352	15.6	0.0325
Clarithromycin	13.5	0.0325	12.3	0.0425
Azithromycin	455	0.0037	449	0.0072

In vivo similarities (Inhibitor or Inducer)

Substrate / Inhibitor or Inducer	Monkey	Monkey AUC_i/AUC	Human	Human AUC_i/AUC
Midazolam /				
Ketoconazole	20 mg/kg, single	21.7	400 mg, qd, 4 days	15.9
Erythromycin	15 mg/kg, bid, 3 days	9.1	500 mg, tid, 7 days	4.4
Clarithromycin	15 mg/kg, bid, 3 days	6.0	500 mg, bid, 7 days	8.4
Azithromycin	15 mg/kg, bid, 3 days	1.6	500 mg, qd, 3 days	1.3
Simvastatin /				
Ketoconazole	20 mg/kg, single	6.3	400 mg, qd, 10 days	12.6
Alprazolam /				
Erythromycin	–	–	400 mg, tid, 10 days	2.5
Clarithromycin	15 mg/kg, bid, 7 days	2.2	–	–
Rifampicin	20 mg/kg, qd, 5 days	0.10	450 mg, qd, 4 days	0.12

Alprazolam / Clarithromycin (Time-dependent inhibition)

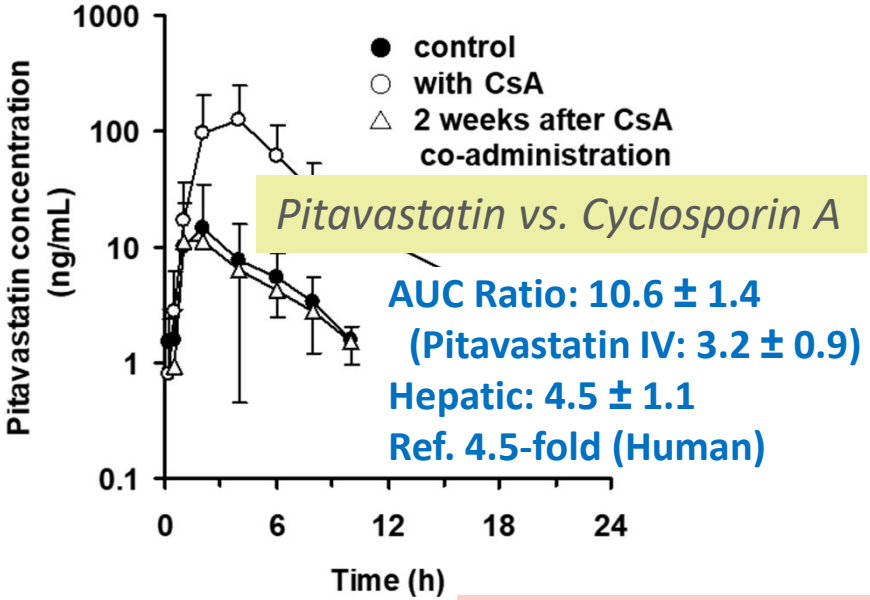


Ogasawara et al.,
Drug Metab Dispos. 35(3):410-8(2007)
Drug Metab Dispos. 37(1):122-8(2009)
Drug Metab Dispos. 37(11):2127-36(2009)
Ohtsuka et al.,
Drug Metab Dispos. 38(10):1806-13(2010)
4th APISSX, poster presentation

Cynomolgus Monkey as an animal model for study of Drug-drug Interaction (Drug Transporter)

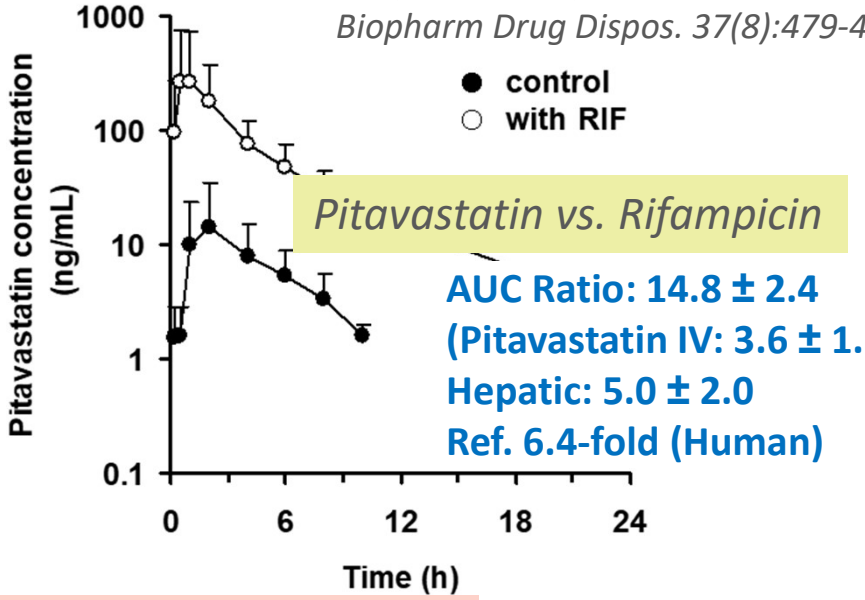
Takahashi et al.,
Drug Metab Dispos. 41(10):1875-82(2013)
Biopharm Drug Dispos. 37(8):479-490(2016)

***In vivo similarities** (Monkey studies)*



Pitavastatin vs. Cyclosporin A

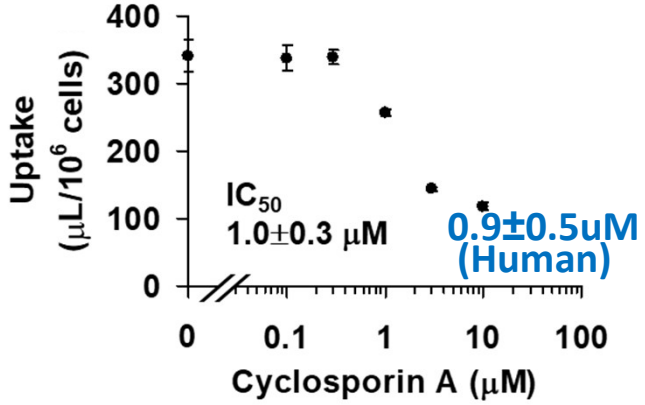
AUC Ratio: 10.6 ± 1.4
(Pitavastatin IV: 3.2 ± 0.9)
Hepatic: 4.5 ± 1.1
Ref. 4.5-fold (Human)

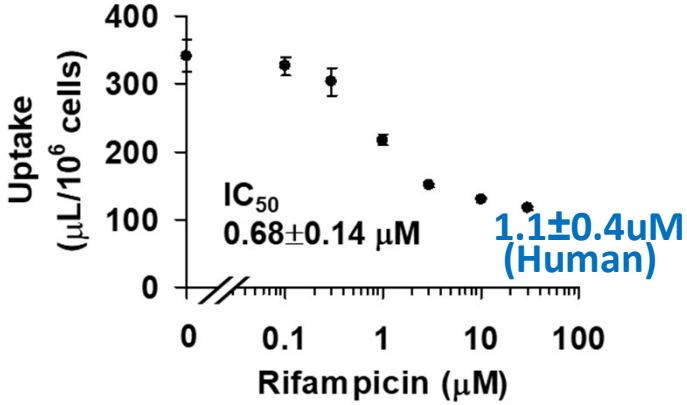


Pitavastatin vs. Rifampicin

AUC Ratio: 14.8 ± 2.4
(Pitavastatin IV: 3.6 ± 1.6)
Hepatic: 5.0 ± 2.0
Ref. 6.4-fold (Human)

In vitro similarities
(Monkey hepatocytes / Pitavastatin uptake inhibition)





Research Topics

Mitsubishi Tanabe Pharma

- Establishment of investigation methods to estimate the contribution of non-CYP enzymes involved in the drug metabolism
- Identification of transporters involved in the hepatic clearance of an investigational drug
- Evaluation of animal models for drug-drug interaction (DDI) studies

Minoru Tsuda-Tsukimoto

- Prediction of DDI using in silico and PBPK modelling
  - ✓ *enzyme induction (CYP2B6/CAR)*
  - ✓ *creatinine transport (MATEs)*

Harutoshi Kato

Tomohisa Nakada

Early assessment of DDI potential will contribute to more efficient drug development

Mitsubishi Tanabe Pharma

Notified by the Ministry of Health, Labour and Welfare (MHLW) in July 2018

Objectives

If **the possibility of drug interactions** that may become major clinical problems **is judged in the early development phase** based on these guidelines, **more efficient development of drugs is expected to become possible.** In addition, **adequate provision of information** obtained during the drug development process to clinical practice may avoid the occurrence of adverse reactions based on drug interactions and/or decrease in the efficacy of drug therapy. These actions may be expected **to lead to an optimized risk-benefit balance of drugs, eventually promoting the proper use of drugs**.

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Thank you for your attention !

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