DMD # 57935

Article's Title:

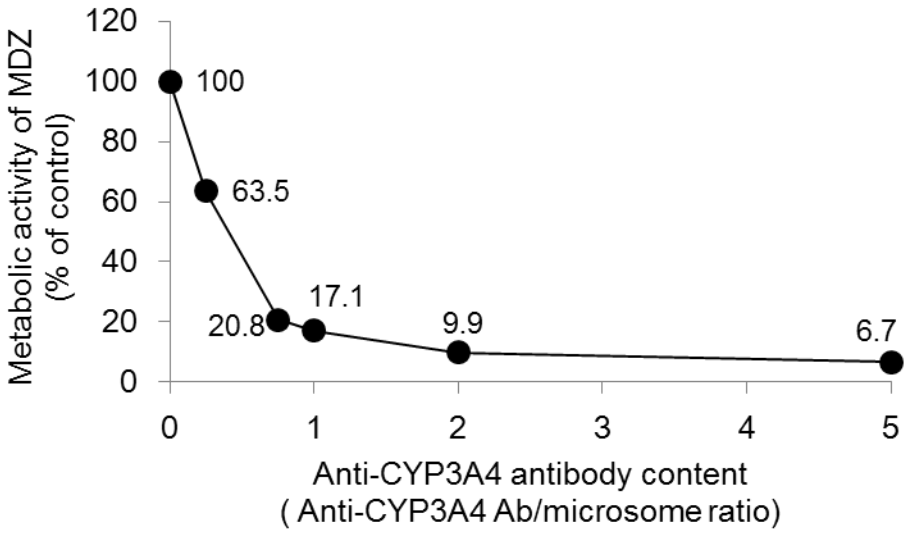
A Useful Model Capable of Predicting the Clearance of CYP3A4 Substrates in Humans: Validity of CYP3A4 Transgenic Mice Lacking Their Own Cyp3a Enzymes

Authors:

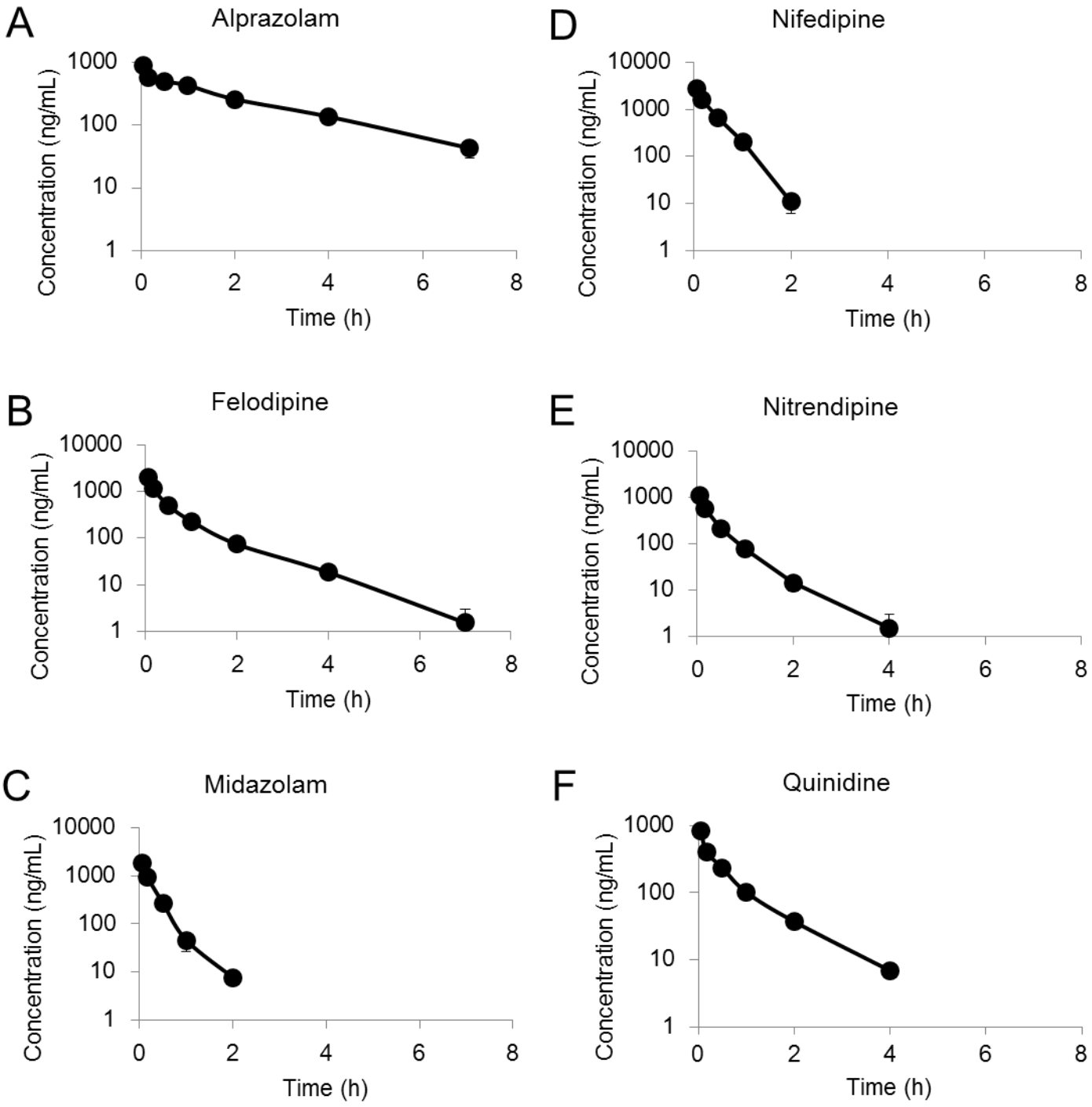
Tetsuya Mitsui, Takayuki Nemoto, Taiji Miyake, Shunsuke Nagao, Kotaro Ogawa, Motohiro Kato, Masaki Ishigai, and Hideyuki Yamada

Journal Title:

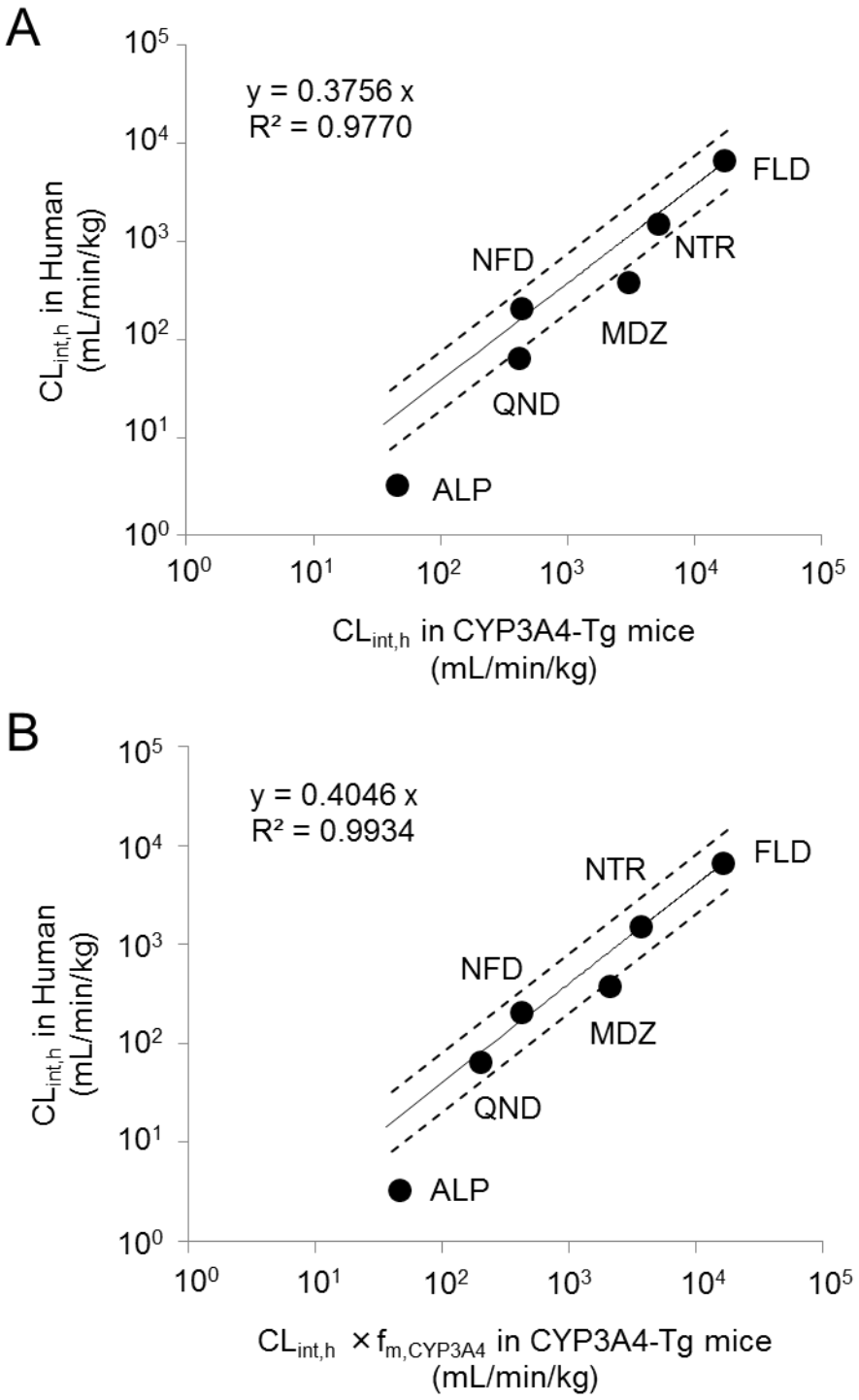
Drug Metabolism and Disposition



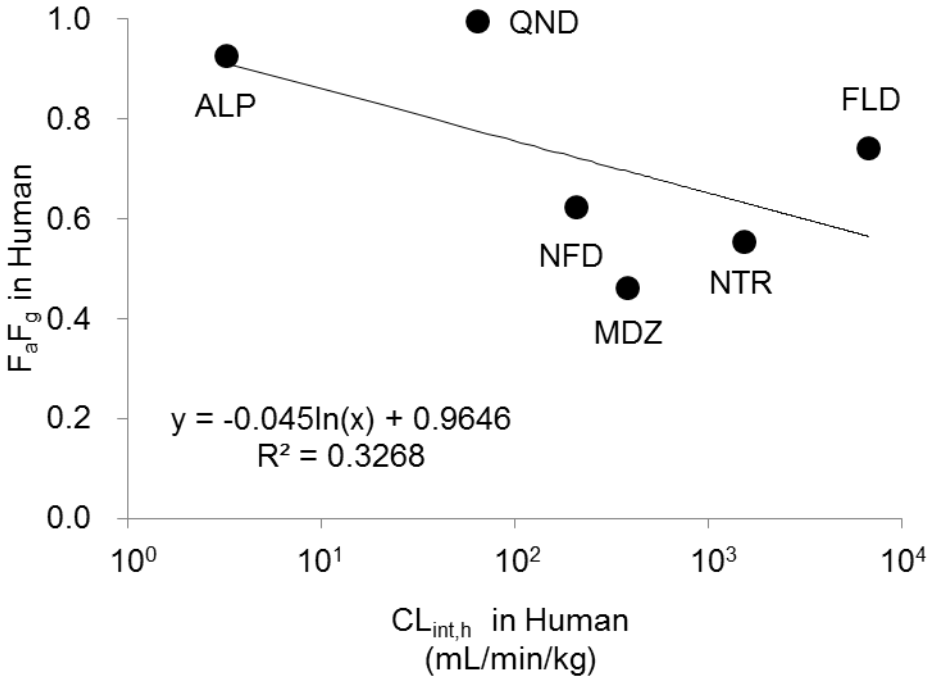
Supplemental Fig.1. Immunoinhibition effect of anti-CYP3A4 antibody on metabolic activity of midazolam by liver microsomes of human



Supplemental Fig.2. Plasma concentrations of CYP3A4 substrates of Alprazolam(A), Felodipine(B), Midazolam(C), Nifedipine(D), Nitrendipine(E) and Quinidine (F) following an intravenous administration to CYP3A4 Tg-mice. Each point represents the mean ±s.d. (n=3)



Supplemental Fig.3. Correlation estimated by linear regression analysis for the $CL_{int,h}$ of CYP3A4 substrates between CYP3A4-Tg mice and humans. The $CL_{int,h}$ in CYP3A4-Tg mice was calculated without (A) and with (B) multiplying by $f_{m,CYP3A4}$.
The solid line represents a regression line empirically fitted to the data for all substrates, and dotted lines represent the levels of the 2-fold or 1/2-fold of the regression value.



Supplemental Fig.4. Correlation for the $CL_{int,h}$ and F_aF_g of CYP3A4 substrates in humans. The solid line represents a regression line empirically fitted to the data for all substrates.

Supplemental TABLE 1-1

The gradient conditions of HPLC eluent for measurement of drug conditions excepting for the plasma unbound fraction analysis

Time	Mobile phase B % (v/v)					
(min)	ALP	FLD	MDZ	NFD	NTL	QND
0.0	15	15	5	15	15	5
3.0	—	—	25	—	—	25
5.0	90	90	90	90	90	90
8.5	90	90	90	90	90	90
8.5	15	15	5	15	15	5
11.5	15	15	5	15	15	5

Supplemental TABLE 1-2

The gradient conditions of HPLC eluent for measurement of drug conditions for the plasma unbound fraction analysis

Time	Mobile phase B % (v/v)					
(min)	ALP	FLD	MDZ	NFD	NTL	QND
0.0	5	5	5	5	5	5
5.0	90	90	90	90	90	90
8.0	90	—	90	—	—	90
8.0	5	—	5	—	—	5
9.0	—	90	—	90	90	—
9.0	—	5	—	5	5	—
11.0	5		5	—	—	5
12.0	—	5	—	5	5	—

Supplemental TABLE 2-1

Mass number of the monitor ions for each compound for measurement of drug concentrations excepting for the plasma unbound fraction analysis

Target ion /	Drug					
analytical mode	ALP	FLD	MDZ	NFD	NTL	QND
precursor (m/z)	309.2	384.1	325.9	345.1	361.1	325.0
product (m/z)	281.1	351.9	291.1	122.0	329.2	184.4
Polarity	Positive	Positive	Positive	Negative	Positive	Positive

Supplemental TABLE 2-2

Mass number of the monitor ions for each compound for measurement of drug concentrations for the plasma unbound fraction analysis

Target ion /	Drug					
analytical mode	ALP	FLD	MDZ	NFD	NTL	QND
precursor (m/z)	309.2	382.2	326.3	345.2	359.2	325.5
product (m/z)	281.1	144.9	291.3	121.8	122.0	172.2
Polarity	Positive	Negative	Positive	Negative	Negative	Positive

Supplemental TABLE 3

Accuracy of the predicted human CL_h of six CYP3A4 substrates based on the correlation of $CL_{int,h}$ between human and WT mice compared with observed values

	CL_h (mL/min/kg)		Accuracy
Substrate	Observed	Predicted	(%)
Alprazolam	1.03	4.65	452
Felodipine	16.4	16.3	99
Midazolam	7.26	NC	NC
Nifedipine	5.82	1.06	18
Nitrendipine	12.3	14.2	116
Quinidine	4.14	4.03	97

Supplemental TABLE 4

Pharmacokinetic parameters in human after oral administration

Substrate	F[a]	$F_a \times F_g$[b]
Alprazolam	0.88	0.93
Felodipine	0.16	0.74
Midazolam	0.30	0.46
Nifedipine	0.45	0.62
Nitrendipine	0.23	0.55
Quinidine	0.80	0.99

[a]Each value was quoted from the references

[b]Each value was calculated by using the following equation $F = F_a \times F_g \times F_h$