JSSX Award for Young Scientists
(The Japanese Society for the Study of Xenobiotics Award for Young Scientists)

Studies on human pharmacokinetic predictions to accelerate drug development and understand inter-patient variabilities in clinical settings

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36th JSSX Annual Meeting COI disclosure information

Chie Emoto is an employee of Chugai Pharmaceutical Co. Ltd., but is working outside the subject area of the presentation.

Acknowledgments: introduction of outstanding mentors

Dr. Fukuda

Clinical Pharmacology in Pediatrics

Prof. Yamazaki

Cytochrome P450 enzymes, especially CYP3A family

Dr. Iwasaki (today's chair)

DMPK research on Drug Discovery and Pre-Clinical stages

肖像権保護のため、写真は削除いたしました

Acknowledgments

The following list of mentors and collaborators with their affiliations at that time

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All students in Yamazaki's lab

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Miki Nakajima
All students in Yokoi's lab

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Pharmacology
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Drug Safety
Yasushi Sato
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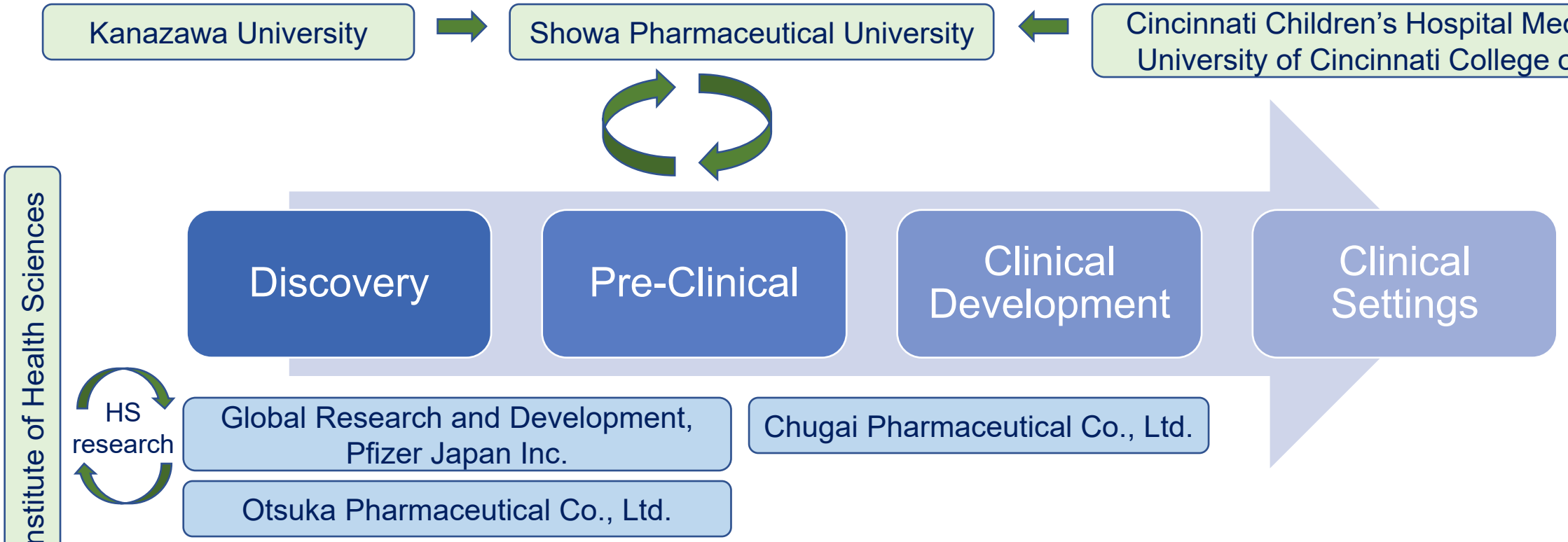
ありがとうございました

Research Areas Covered in Both Academia and Pharma



Role of cytochrome P450 enzymes:

- Characterization of non-specific P450 inhibitors
- Prediction of hepatic clearance at early drug discovery stage
- Reaction phenotyping based on RAF approach
- Evaluation system for induction of CYP3A4 using chimeric mice with a humanized liver
- Functional characterization of CYP3A4.16
- Novel drug reaction mediated by CYP3A4 and CYP3A5
- Species differences in P450s between cynomolgus monkeys and humans
- Evaluation of intestinal metabolism and absorption using the Ussing chamber system, etc.

Pediatric population:

- PK characterization of multiple drugs in pediatric patients
- Pediatric PBPK modeling and simulations of multiple drugs for pediatric populations
- Ontogeny study of OCT1 transporter
- Pharmacogenomic study of OCT1 and MRP3, etc.

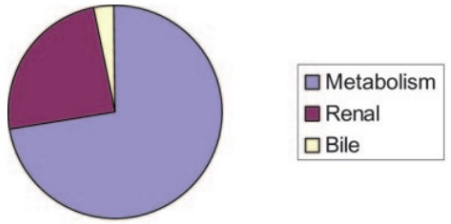
Today's topics highlighted in blue

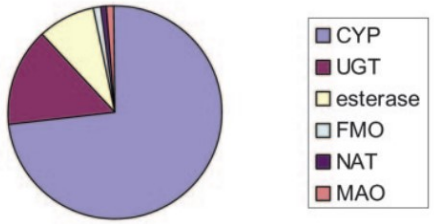
Early Drug Discovery Stage:
Establishing standard methodologies on quick decision

Methodologies for Investigating Drug Metabolism at the Early Drug Discovery Stage: Prediction of Hepatic Drug Clearance and P450 Contribution

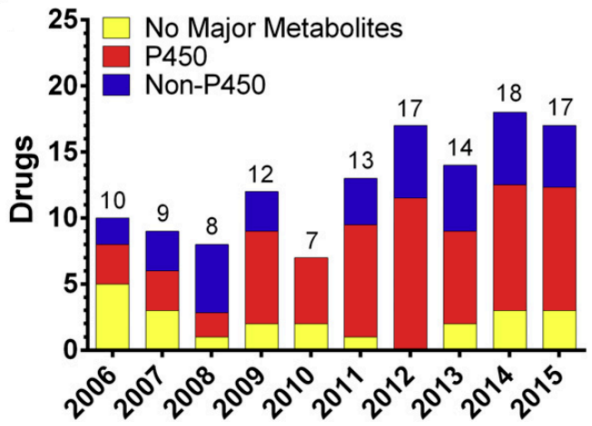
Current Drug Metabolism, 2010

Chie Emoto[1], Norie Murayama[1], Amin Rostami-Hodjegan[2] and Hiroshi Yamazaki[1,3,*]

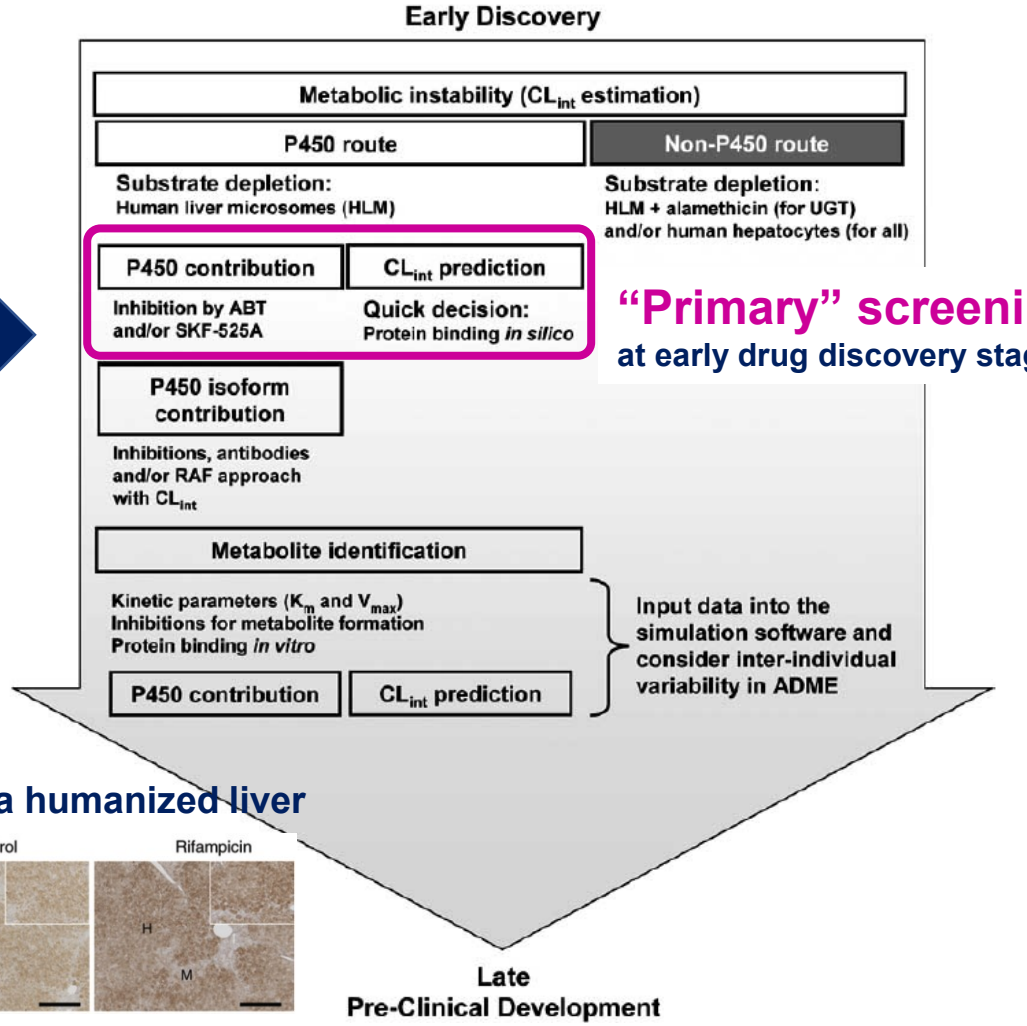




Williams et al., *Drug Metab Dispos*, 2004

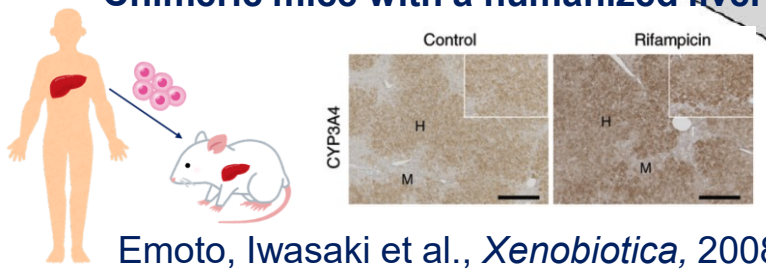


Cerny, *Drug Metab Dispos*, 2016



"Primary" screening
at early drug discovery stage

Chimeric mice with a humanized liver

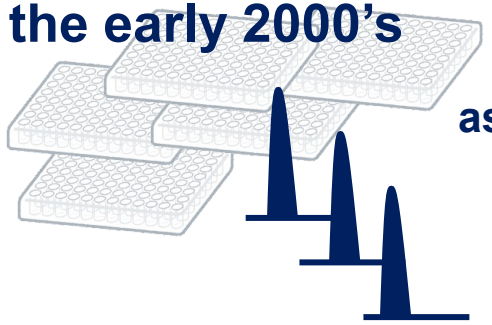


Emoto, Iwasaki et al., *Xenobiotica*, 2008

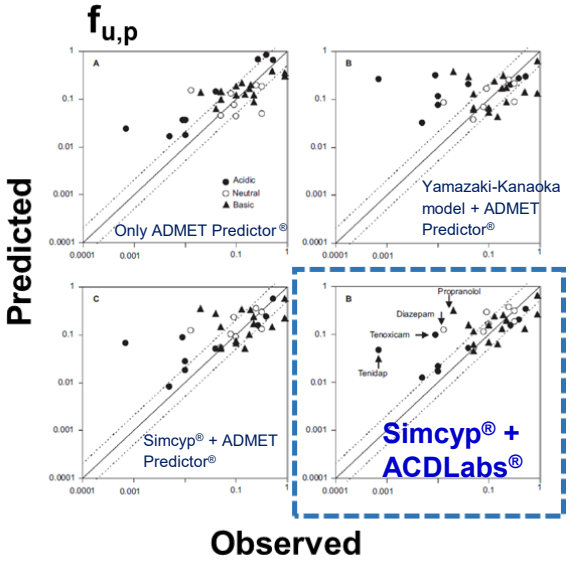
Emoto et al., *Current Drug Metabolism*, 2010

Discovery | Pre-Clinical | Clinical Development | Clinical Settings

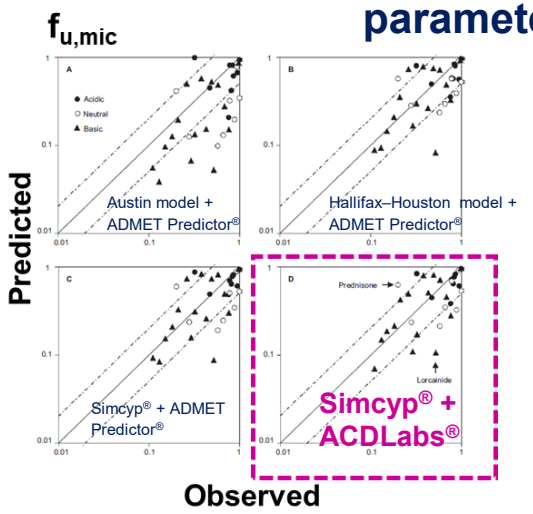
In the early 2000's



Automation of screening assays with high-throughput LC-MS/MS method

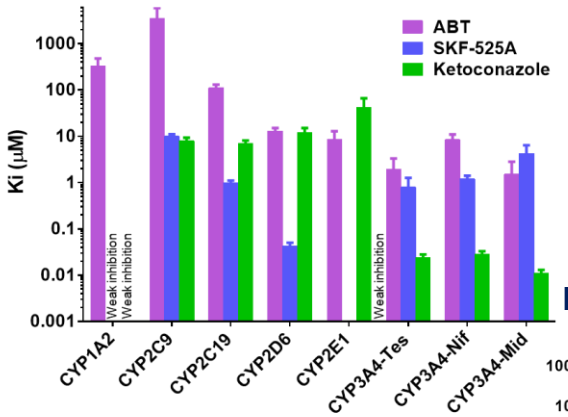


Binding prediction method using physicochemical parameters

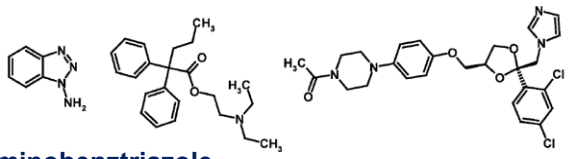


P450s' contribution

Recombinant CYP enzymes



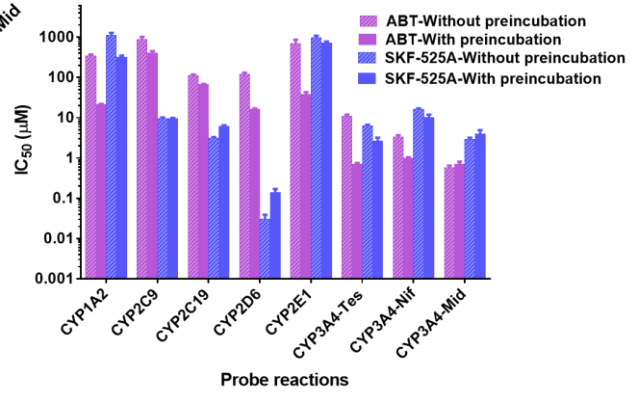
SKF-525A



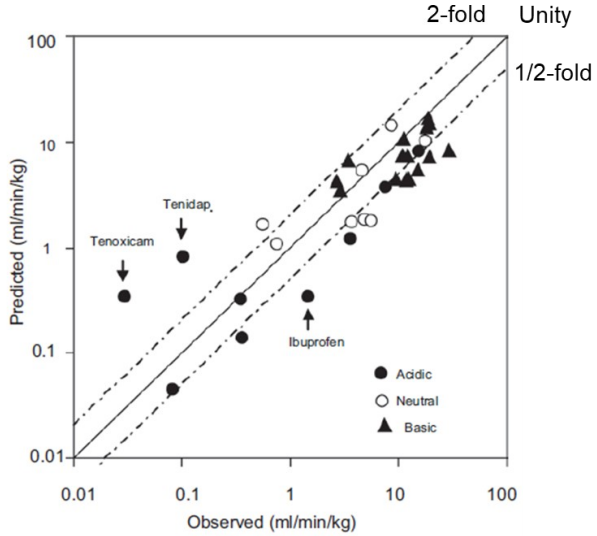
1-aminobenztriazole (ABT)

Ketoconazole (CYP3A inhibitor)

Human liver microsomes



$CL_{hep,met}$ prediction



Candidate selection

Emoto, Iwasaki et al., *Drug Metab. Pharmacokinet.*, 2003
Emoto, Iwasaki et al., *Drug Metab. Pharmacokinet.*, 2005
Emoto, Yamazaki et al., Xenobiotica, 2009

Pre-Clinical Stage:

Characterizing hepatic and intestinal P450s in monkeys

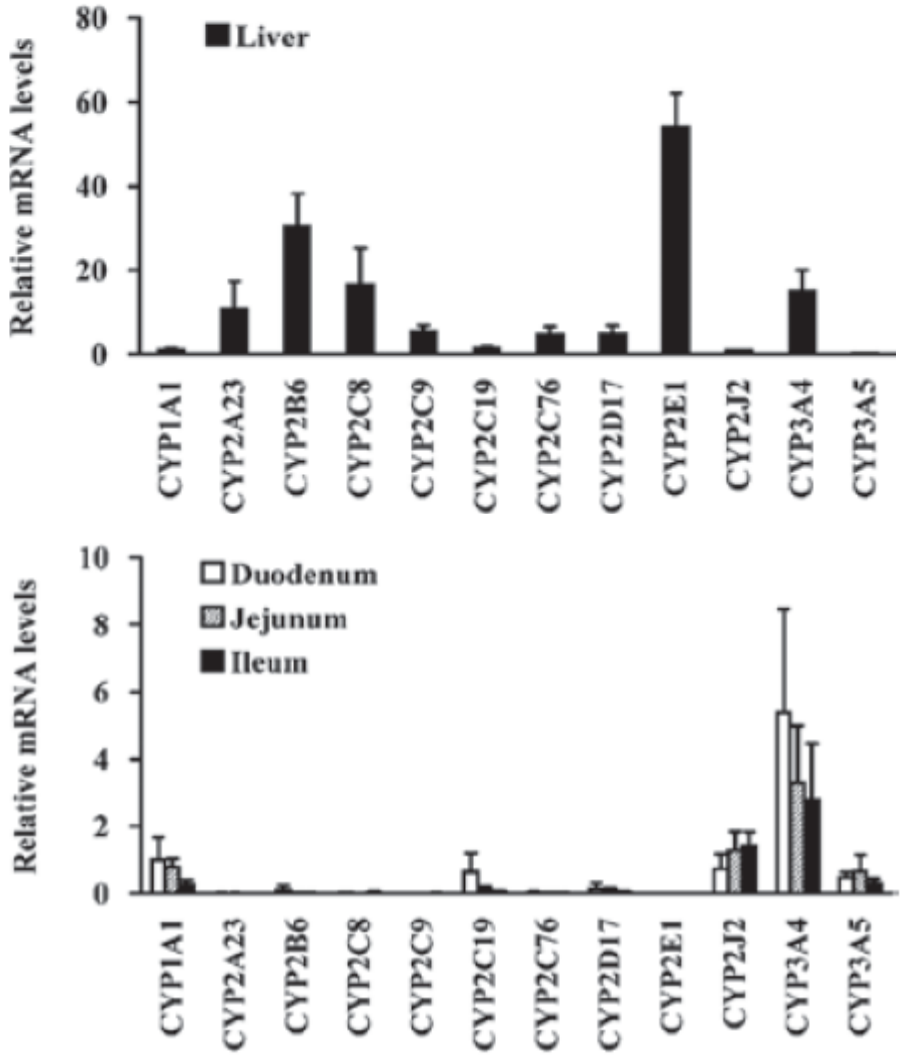
Homology of P450 enzymes between cynomolgus monkeys and humans

Cynomolgus	Human	cDNA identity (%)	AA identity (%)	Cynomolgus	Human	cDNA identity (%)	AA identity (%)
CYP1A1	CYP1A1	95	94	CYP2C18	CYP2C18	96	96
CYP1A2	CYP1A	95	93	CYP2C19	CYP2C9	95	93
CYP2A23	CYP2A6	95	92		CYP2C19	94	92
	CYP2A7	93	89	CYP2C76	CYP2C8	74	70
	CYP2A13	95	94		CYP2C9	77	71
CYP2A24	CYP2A6	96	95		CYP2C18	78	72
	CYP2A7	95	94		CYP2C19	76	72
	CYP2A13	95	94	CYP2D17	CYP2D6	94	93
CYP2A26	CYP2A6	94	93	CYP2D44	CYP2D6	93	91
	CYP2A7	94	91	CYP2E1	CYP2E1	95	94
	CYP2A13	94	93	CYP2J2	CYP2J2	95	95
CYP2B6	CYP2B6	94	91	CYP3A4	CYP3A4	95	94
CYP2C8	CYP2C8	95	92	CYP3A5	CYP3A5	94	91
CYP2C9	CYP2C9	94	93	CYP3A43	CYP3A43	97	97
	CYP2C19	93	91				

Emoto, Yoda, Uno, Iwasaki, Kashiyama, Yamazaki et al., *Current Drug Metabolism*, 2013

Pre-Clinical Stage:
Characterizing hepatic and intestinal P450s in monkeys

CYP isoform Expression (mRNA)



Diclofenac hydroxylation as an example

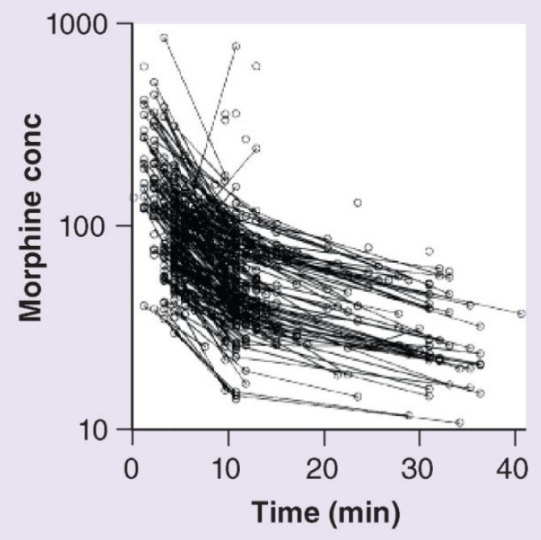
Microsomes	Parameter	Cynomolgus	Human
Liver	K_m (μM)	77.3 ± 7.0	6.3-7.1
	V_{max} (pmol/min/mg)	111 ± 7	83.0-137
	CL_{int} (μL/min/mg)	1.43	13.2-19.4
With Sulfaphenazole	IC_{50} (μM)	>50	0.25 - 1.5
Intestine	K_m (μM)	77.8 ± 2.9	1.7-8.2
	V_{max} (pmol/min/mg)	349 ± 4	1160-3500
	CL_{int} (μL/min/mg)	4.49	215-1200
With Sulfaphenazole	IC_{50} (μM)	22.5 ± 4.4	-

Yoda, Emoto, Kashiyama et al., *Xenobiotica*, 2012
Emoto, Yoda, Iwasaki, Kashiyama, Yamazaki et al., *Current Drug Metabolism*, 2013

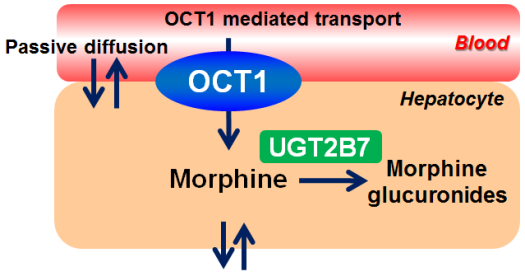
Clinical Setting: Target to Neonates

Implementing ontogeny & PGx into a PBPK model

Large inter-patient PK variability



Fukuda et al., *Pharmacogenomics*, 2013



Research strategy: Develop a quantitative PBPK model of morphine in neonates

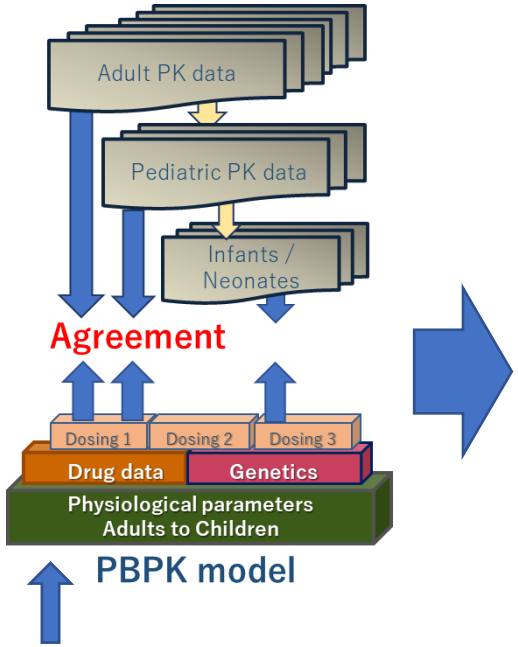
Step 1	Step 2	Step 3	Step 4	Step 5
Source data: Reported PK data	**OCT1-genotyped** children (N= 146)	**Reported PK data**: • Descriptive PK • PopPK/Bayesian	**OCT1-genotyped** NICU patients	**OCT1-genotyped** NICU patients
Healthy volunteers	**Older children (6-16 years)**	**Neonates and infants (full-term)**	**Neonates (full-term, genotyped)**	**Individual Neonate (full-term)**
+	+	+	+	+
Morphine	**Morphine**	**Morphine**	**Morphine**	**Morphine**
Construction of a foundational model	Pediatric physiology and **PGx of OCT1**	**Ontogeny** of OCT1 and UGT2B7	**Ontogeny** of OCT1 and its **genotypes**	**Ontogeny** of OCT1 and its **genotypes**

Model development + PGx | **+ Ontogeny** | ***Proof of Concept*** | ***Individual patient inf.***

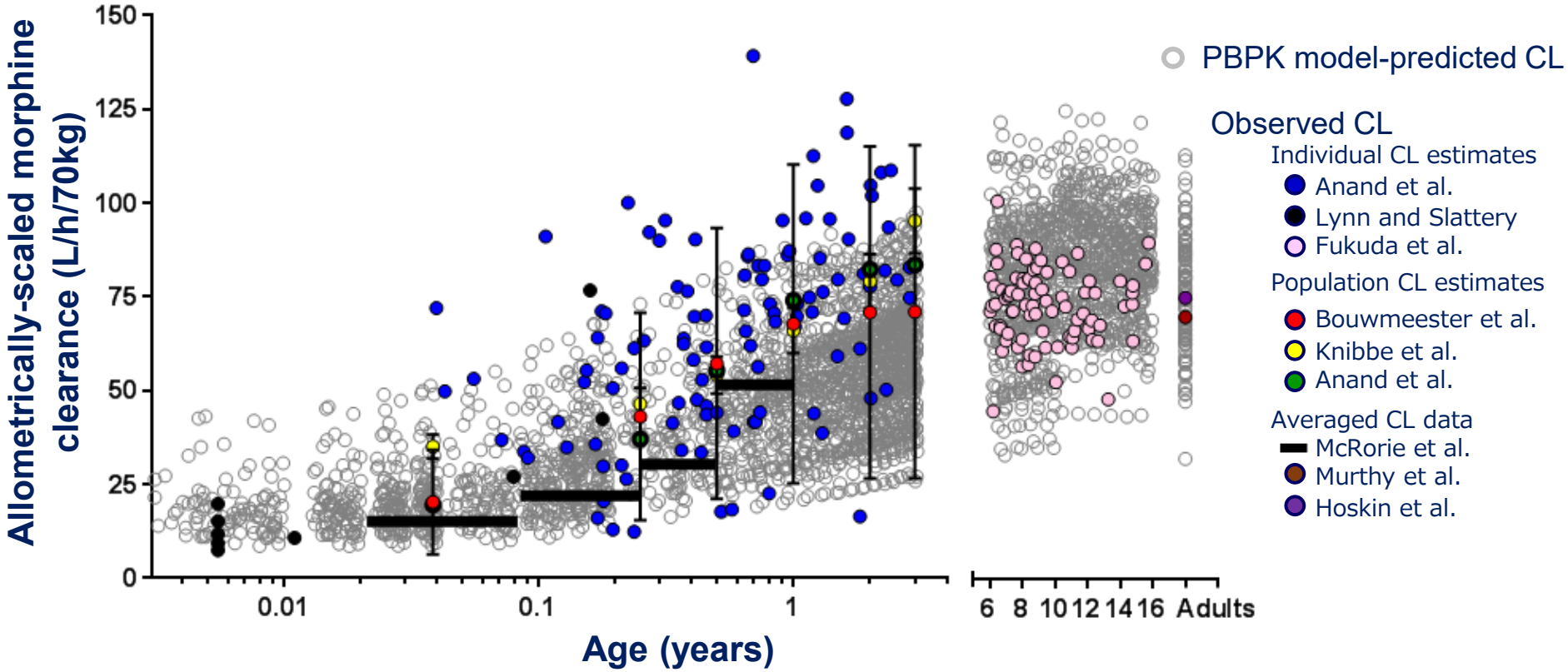
Emoto, Fukuda et al., *CPT: Pharmacometrics & Systems Pharmacology*, 2017
Emoto, Fukuda et al., *CPT: Pharmacometrics & Systems Pharmacology*, 2018
Hahn, Emoto, Fukuda et al., *Clinical Pharmacology & Therapeutics*, 2019
Emoto, Fukuda et al., *Clinical Pharmacology & Therapeutics*, 2020
Emoto, Fukuda et al, *Japanese Journal of Clinical Pharmacology and Therapeutics*, 2020

Clinical Setting: Target to Neonates

Implementing ontogeny & PGx into a PBPK model

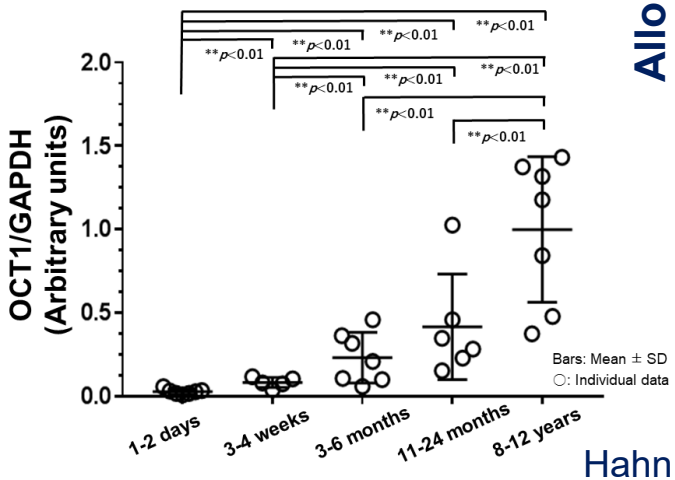


Step 3 **Developmental changes in morphine clearance predicted by PBPK modeling implementing ontogeny of OCT1 and UGT2B7**



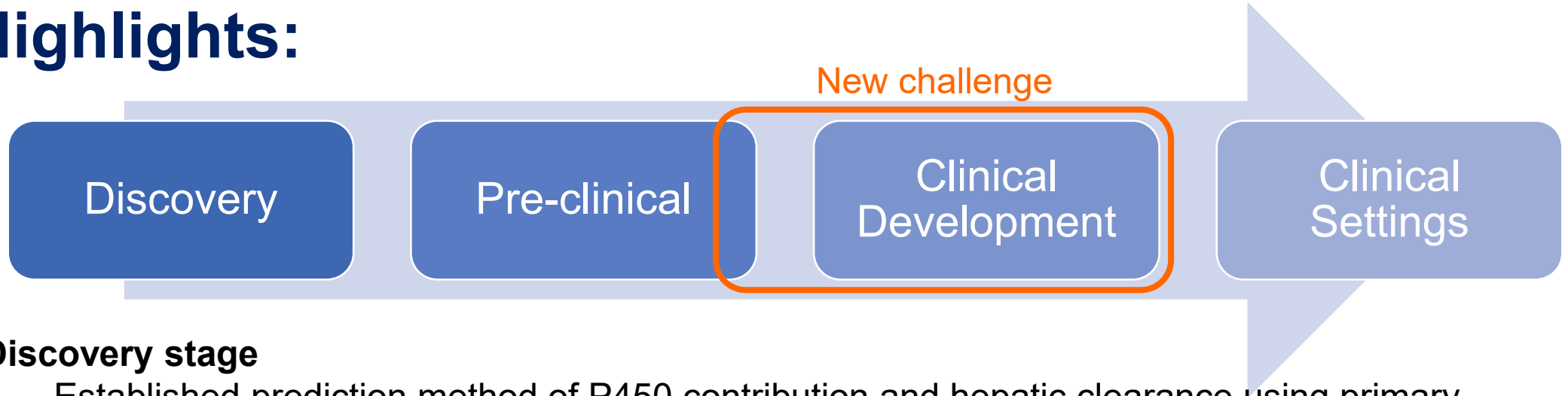
Emoto, Fukuda et al., *CPT Pharmacometrics Syst Pharmacol.*, 2018

OCT1 ontogeny



Hahn, Emoto, Fukuda et al., *Drug Metab Dispos*, 2017

Highlights:



Discovery stage

Established prediction method of P450 contribution and hepatic clearance using primary screening data and in-silico physicochemical parameters.

Pre-clinical stage

Identified species differences in hepatic and intestinal P450 enzymes between cynomolgus monkeys and humans

Clinical Development

New challenges connecting dots not only for smooth transition of DD process but also for informing clinic of optimal treatment options after approval

Clinical settings

Utilized pediatric PBPK model of morphine implementing ontogeny profiles of UGT2B7 and OCT1 to understand mechanistic insights to large variability in neonates and small infants