Quantitative Prediction of Intestinal First-pass Metabolism in Human

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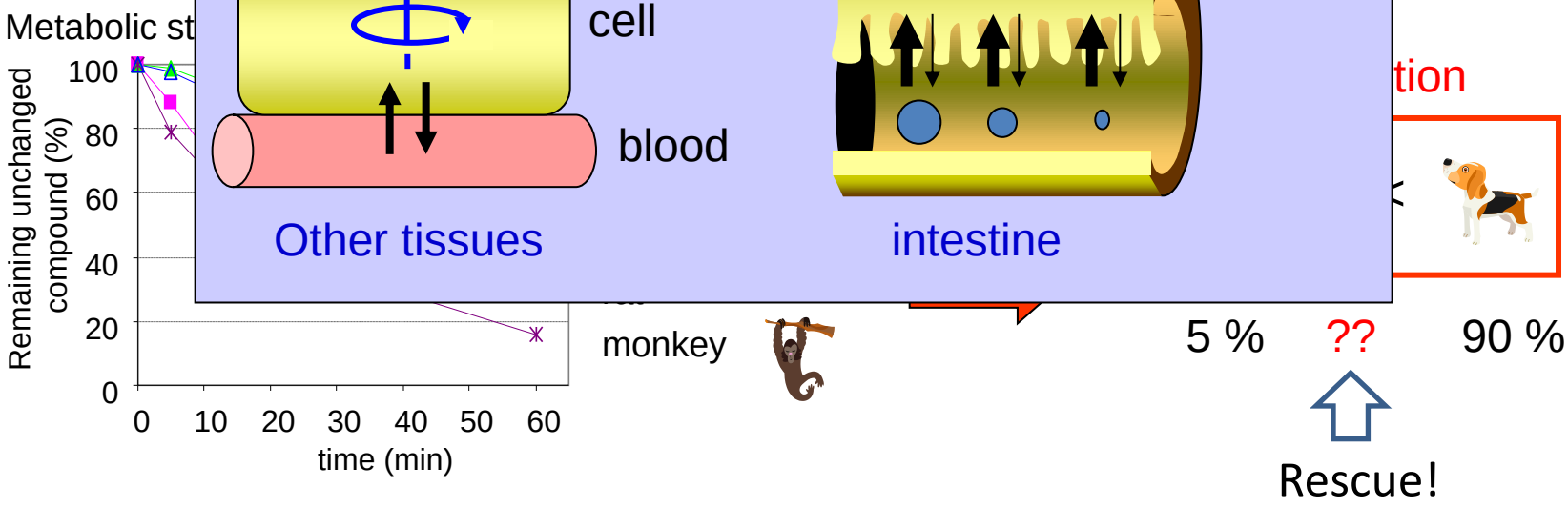
Human Fg Prediction－Past

- ✓ Many researchers reported quantitative prediction methods, however, their prediction accuracy was not high.
- ✓ Our previous method was limited to a semi-quantitative assessment based on comparison with animals.

I faced a drug candidate which showed low Fg in preclinical species in my s



We needed quantitative prediction method and information on species differences !

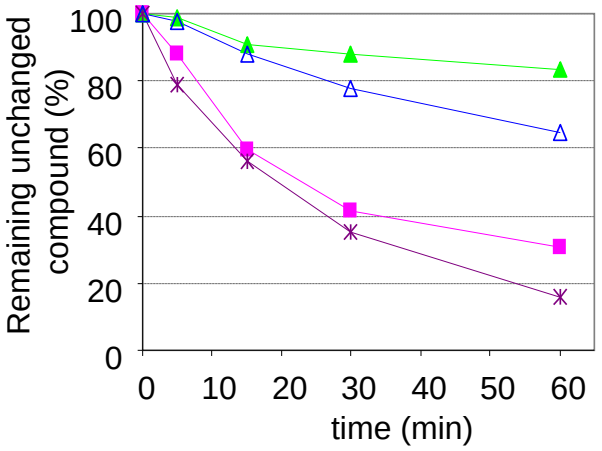
Human Fg Prediction－Past

- ✓ Many researchers reported quantitative prediction methods, however, their prediction accuracy was not high.
- ✓ Our previous method was limited to a semi-quantitative assessment based on comparison with animals.

I faced a drug candidate which showed low Fg in preclinical species in my second year (2006).

In vitro

Metabolic stability in intestinal microsomes



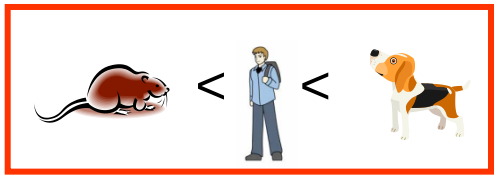
dog

human

rat

monkey

In vivo Fg prediction



5 %　??　90 %

Rescue!

We needed quantitative prediction method and information on species differences !

Prediction of Human Fg

1. Nishimuta H., et al. **Prediction of the intestinal first-pass metabolism of CYP3A substrates in humans using cynomolgus monkeys**
   Drug Metab Dispos 38(11):1967-75 (2010)

2. Nishimuta H., et al. **Prediction of the intestinal first-pass metabolism of CYP3A and UGT substrates in humans from in vitro data**
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3. Nishimuta H., et al. **Significance of reductive metabolism in human intestine and quantitative prediction of intestinal first-pass metabolism by cytosolic reductive enzymes**
   Drug Metab Dispos 41(5):1104-11 (2013)

Species differences in intestinal metabolic activities

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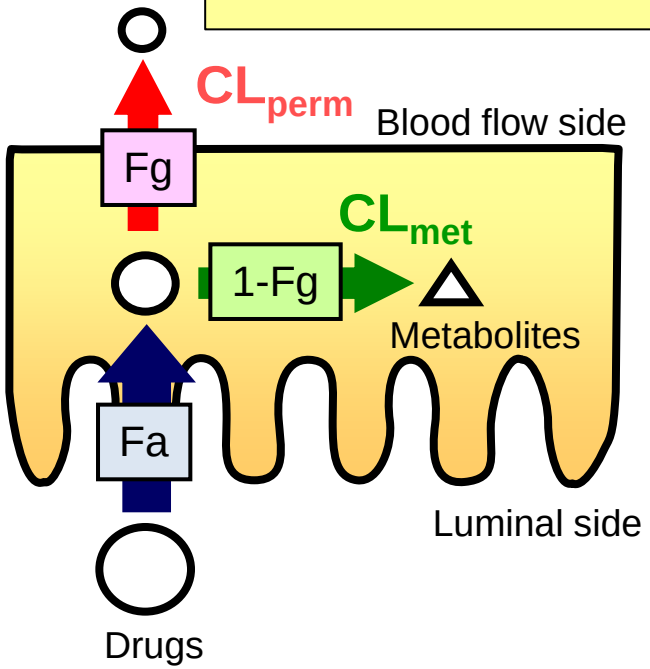
Concept: Prediction of human Fg for CYP3A and UGT substrates from in vitro data

$$Fg = \frac{fu_{intestine} \cdot CL_{perm}}{fu_{intestine} \cdot CL_{perm} + fu_{intestine} \cdot CL_{met}}$$

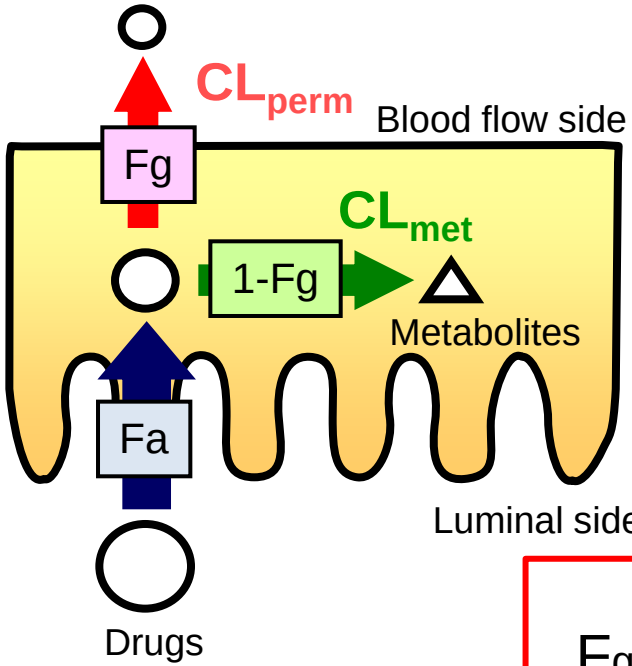


CL_{perm}: permeability clearance
CL_{met}: metabolic clearance

Nishimuta H et al., 2011

Concept: Prediction of human Fg for CYP3A and UGT substrates from in vitro data

This study aimed to establish an accurate and simplified method of predicting Fg of CYP3A and UGT substrates using only in vitro data.



CL_{perm}: permeability clearance
CL_{met}: metabolic clearance

$$Fg = \frac{CL_{perm}}{CL_{perm} + CL_{met}}$$

$PAMPA_{pH7.4}$ → CL_{perm} (numerator and denominator)

$HIM\ or\ HLM$ → CL_{met}

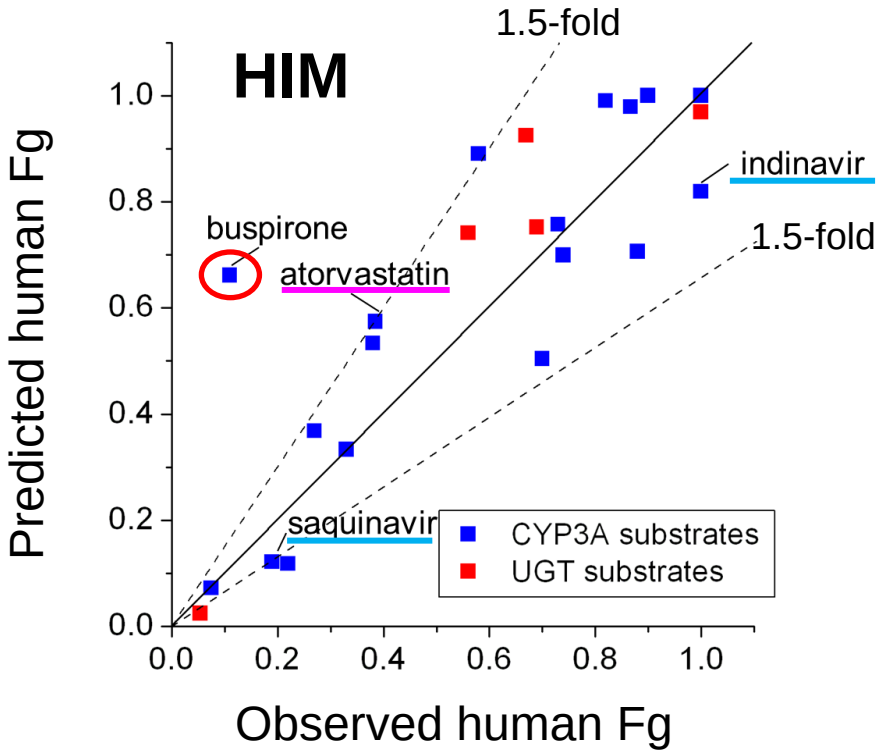
HIM: human intestinal microsomes
MIM: monkey intestinal microsomes

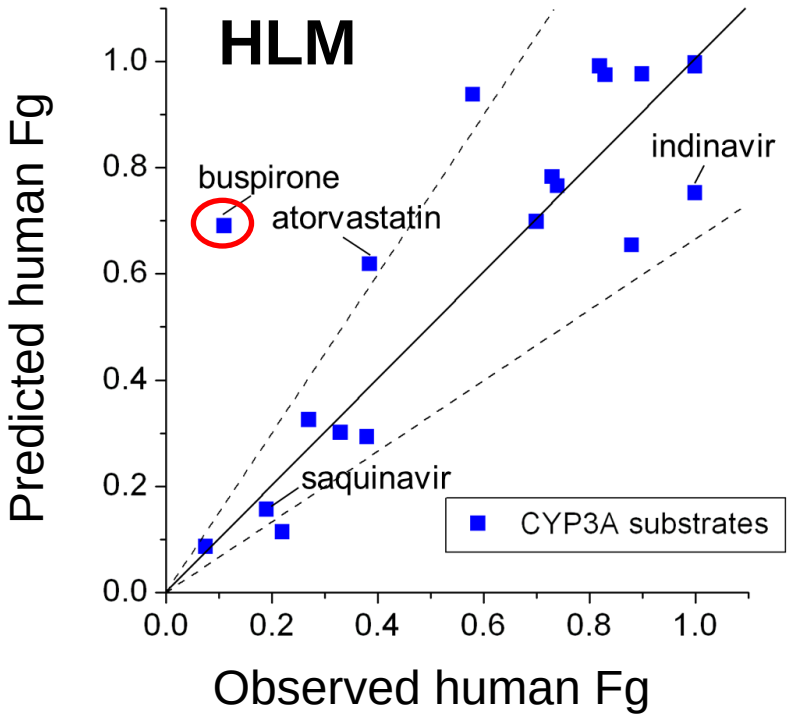
$$Fg,\mathrm{predicted} = \frac{0.011 \bullet P_{app,\,PAMPA(pH7.4)}}{0.011 \bullet P_{app,\,PAMPA(pH7.4)} + CL_{int,\,HIM}}$$

$$CL_{int,\,HIM} = CL_{int,\,HLM}/2.2$$

Nishimuta H et al., 2011

Prediction of human Fg from HIM and HLM





- ✓ Fg values were predicted well for compounds except for buspirone.
- ✓ The predictability of Fg was improved for lower permeability compounds (atorvastatin) by taking permeability into account.
- ✓ Fg would be largely underestimated in the case of using Caco-2 permeability instead of PAMPA for indinavir and saquinavir (P-gp substrates).

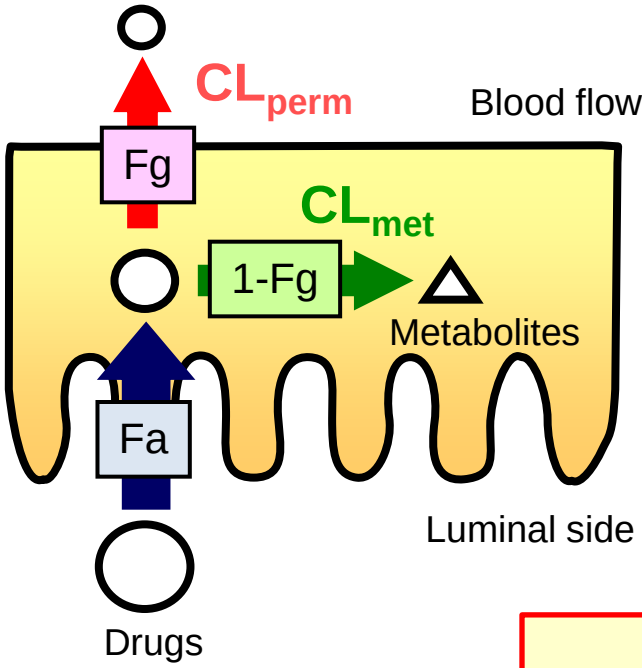
Our idea of using PAMPA at pH 7.4 was more appropriate for prediction of Fg than the method using only metabolic activity or that using cell lines.

Nishimuta H et al., 2011

Concept: Prediction of human Fg for CYP3A substrates using cynomolgus monkeys

There was an outlier (buspirone) in in vitro method. There is a possibility that this is due to physiological complexities unique to the intestine.

→ **Assumed "monkey = human"**



$$Fg = \frac{CL_{perm}}{CL_{perm} + CL_{met}}$$

Fg

Fg

1-Fg

$$Fg_{,human\ (predicted)} = \frac{CL_{perm,monkey}}{CL_{perm,monkey} + CL_{met,monkey} \cdot \frac{CL_{int,HIM}}{CL_{int,MIM}}}$$

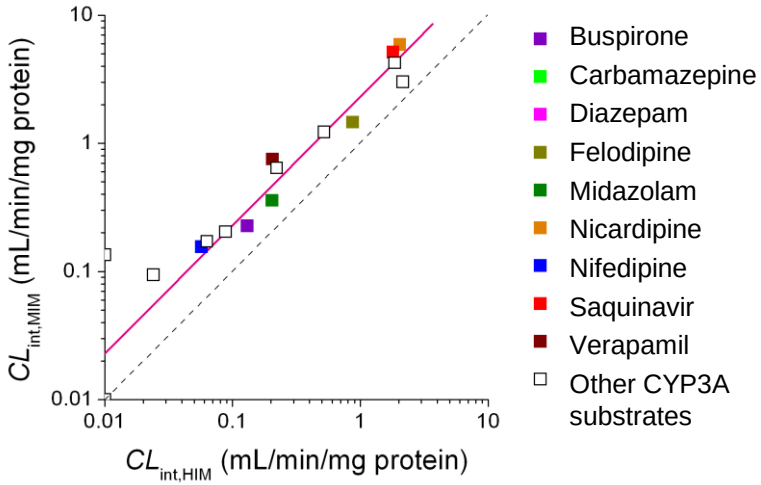
$$Fg_{,human\ (predicted)} = \frac{Fg_{,monkey}}{Fg_{,monkey} + (1 - Fg_{,monkey}) \bullet \frac{CL_{int,HIM}}{CL_{int,MIM}}}$$

CL_{perm}: permeability clearance
CL_{met}: metabolic clearance

HIM: human intestinal microsomes
MIM: monkey intestinal microsomes

Nishimuta H et al., 2010

IN VITRO METABOLIC ACTIVITY

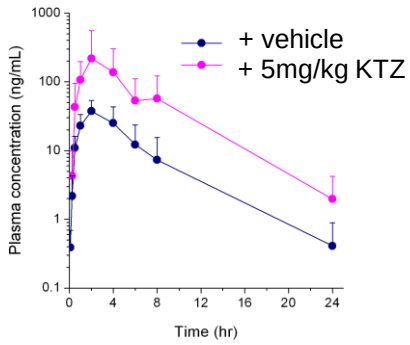


$$F_{g,human(predicted)} = \frac{F_{g,monkey}}{F_{g,monkey} + (1 - F_{g,monkey}) \cdot \frac{CL_{int,HIM}}{CL_{int,MIM}}}$$

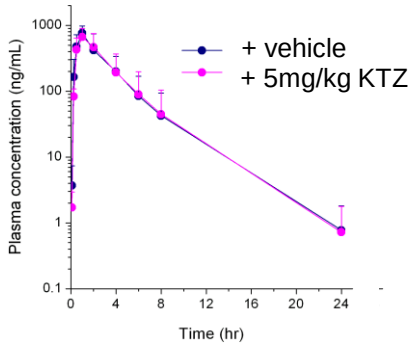
HOW TO ESTIMATE $F_{g,\,monkey}$ *IN VIVO*

$$Fg_{,monkey(observed)} = \frac{AUC_{(+vehicle)}}{AUC_{(+ketoconazole)}}$$

Midazolam

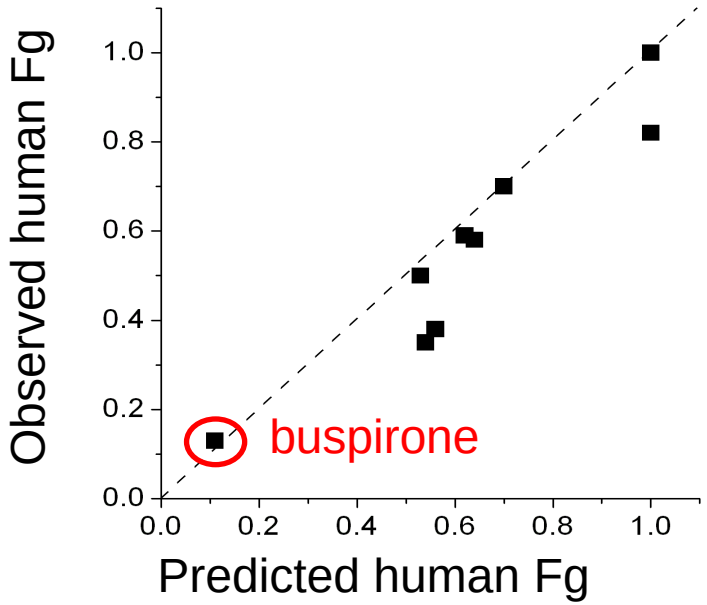


Carbamazepine



The dose of KTZ was set under the condition that KTZ inhibited only intestinal CYP3A metabolic activity by in vitro and in vivo studies.

PREDICTION OF $F_{g,human}$



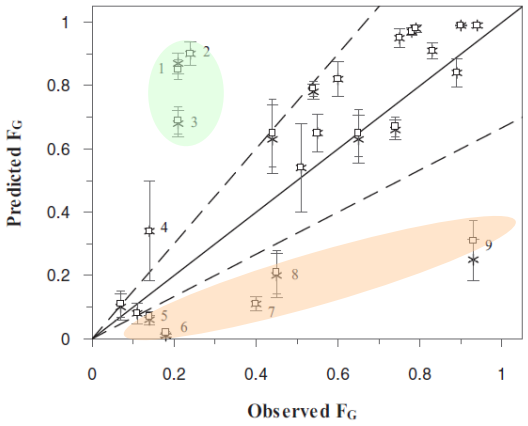
We established a new methodology using cynomolgus monkeys to predict $Fg_{,human}$ of CYP3A substrates precisely.

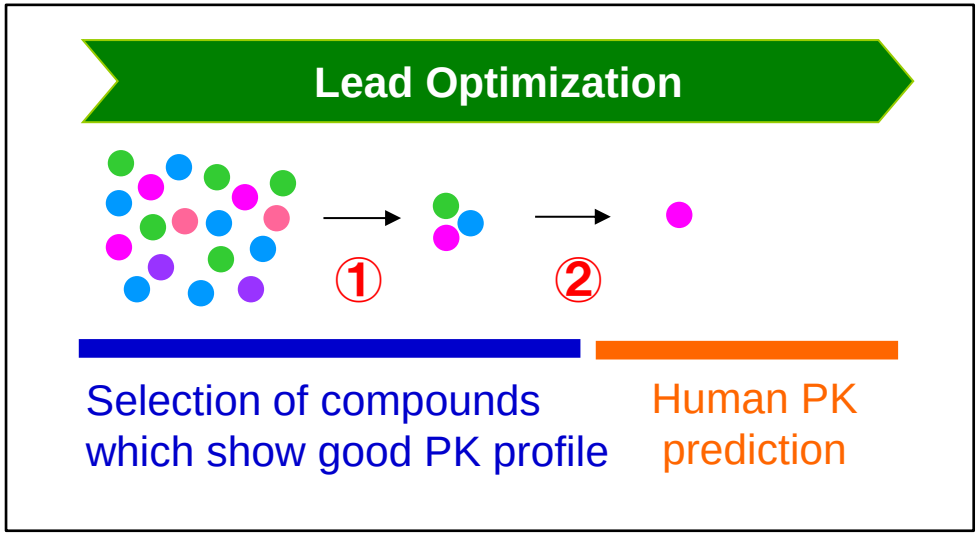
Nishimuta H et al., 2010

Human Fg Prediction ― Prediction accuracy of our method

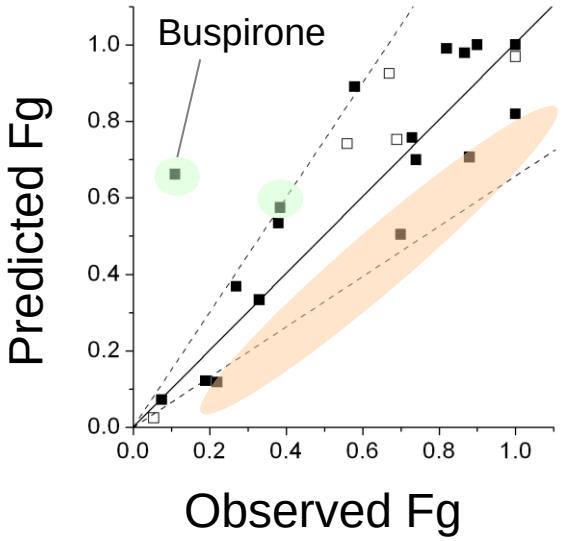
Reported method using Caco-2

DMD 38(7):1147-58 (2010)

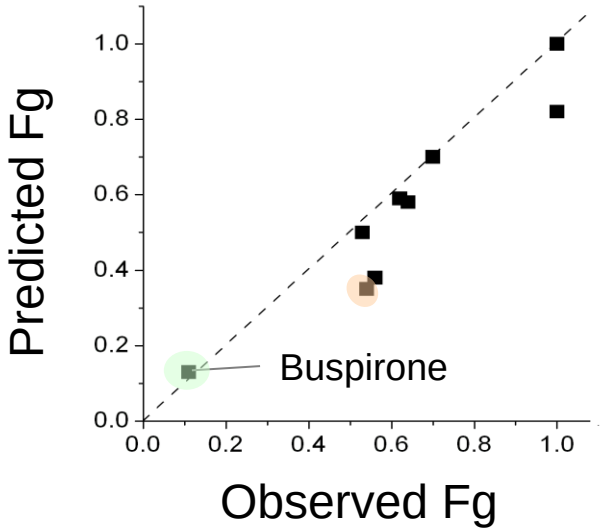




① In vitro method



② Monkey method



Summary

- ✓ We established new methods to predict human Fg which are useful from early to late in drug discovery.

- ✓ We provided useful information on species differences in intestinal metabolism.

Future View

- ✓ Human PK prediction
  - using new tool
  - in special population

- ✓ Translational research
  - PK/PD

Looking back

2005.3.	M.S. Kyushu University (Prof. Sawada)
2005.4.-	Sumitomo Dainippon Pharma., Co, Ltd.
2012.3.	Ph.D. Kyushu University (Prof. Ohdo)
2013.4.-2014.4.	The University of Manchester
2015.4.-2016.4.	Maternity Leave

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2013.4.-2014.4. **The Univer ester**

2015.4.-2016.4. **Maternity Leave**

Prof. Sawada:
"You should get PhD after joining company"

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I was assigned a DMPK representative of a project which had many DMPK problems in 2006

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I proposed to my boss
“I would like to
research about
intestinal metabolism”.

Looking back

2005.3. **awada)**

200 **d.**

Human PK prediction for prodrugs

6. Nishimuta H., Houston JB., and Galetin A.
Hepatic, intestinal, renal, and plasma hydrolysis of prodrugs in human, cynomolgus monkey, dog, and rat: implications for in vitro-in vivo extrapolation of clearance of prodrugs.
Drug Metab Dispos 42(9):1522-31 (2014)

7. Nishimuta H, Tsamandouras N, Aarons L, and Galetin A.
Reduced physiologically-based pharmacokinetic model for the prodrug candesartan cilexetil and its active metabolite candesartan acid.
19th North American Regional ISSX Meeting and 29th JSSX Annual Meeting, San Francisco, 2014.

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I have enjoyed fruitful work and life !

Acknowledgment

Sumitomo Dainippon Pharma Co., Ltd.
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Tetsuya Nakagawa, PhD

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Prof. Leon Aarons