Development of novel pharmacokinetic evaluation systems through collaboration research between pharmaceutical science and bioengineering

Hiroshi Arakawa, PhD

Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University

My Career

2013 Ph.D., Graduate School of Natural Science and Technology, Kanazawa University

- **Role of OATP1A2 in drug absorption and prostate cancer growth**

Dr. Ikumi Tamai

Dr. Takeo Nakanishi

Dr. Yoshiyuki Shirasaka

2013 Assist. Prof., Faculty of Pharmacy, Takasaki University of Health and Welfare

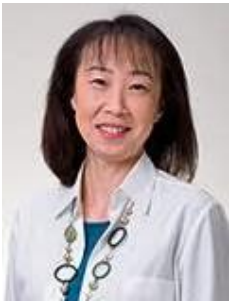
- **Utility of 3D culture of human hepatocytes for dug metabolism and hepatotoxicity**

Dr. Takuo Ogihara

2016 Assist. Prof., Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University
(Broadly belonged to 3 pharmaceutical laboratories)

- **Enterohepatic interaction in pharmacokinetics using an organs-on-a-chip**
- **Endoplasmic reticulum drug transporters**
- **Construction of novel renal pharmacokinetic/toxicokinetic systems**

Dr. Yukio Kato



Dr. Miki Nakajima

2019 Assoc. Prof., Kanazawa University

Challenges in *in vitro* assay for Pharmacokinetics

There are challenges in in vitro assay for pharmacokinetic and drug safety assay.

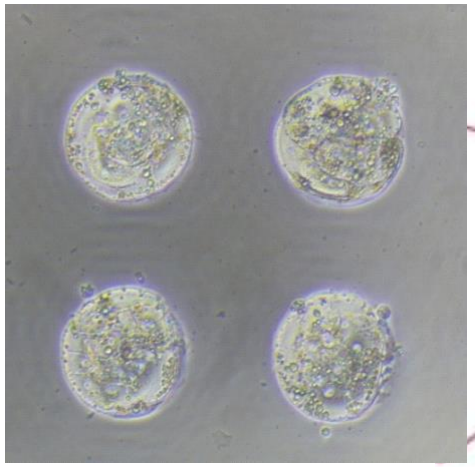
- **Reduction of drug metabolic activity**
- **Limitation of exposure periods**
- **Organs interactions**
- **Distribution process to organelle**
- **Species Difference**

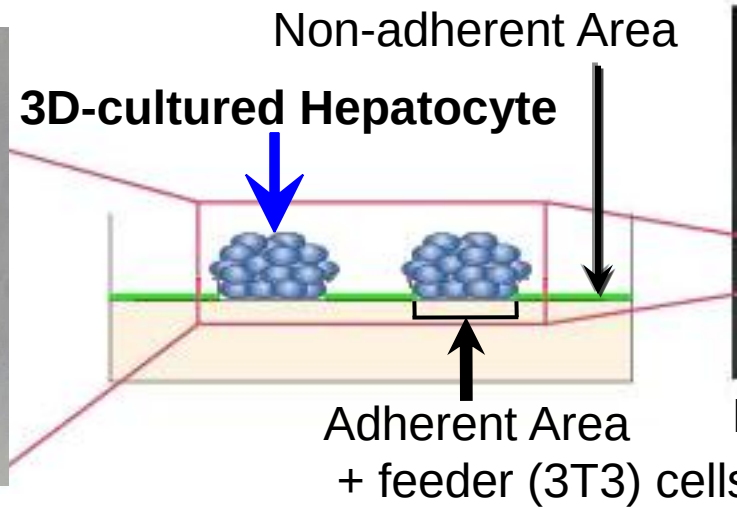
Microsomes

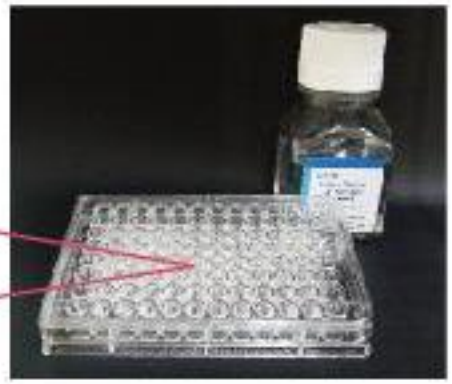
To overcome such concerns, I am constructing novel in vitro assays with bioengineering researchers.

Cryopreserved Hepatocytes

Three-dimensional (3D)-Cultured Human Hepatocytes







Provided from Toyo Gosei

- be able to cultivate hepatocytes over one month
- high metabolic activity

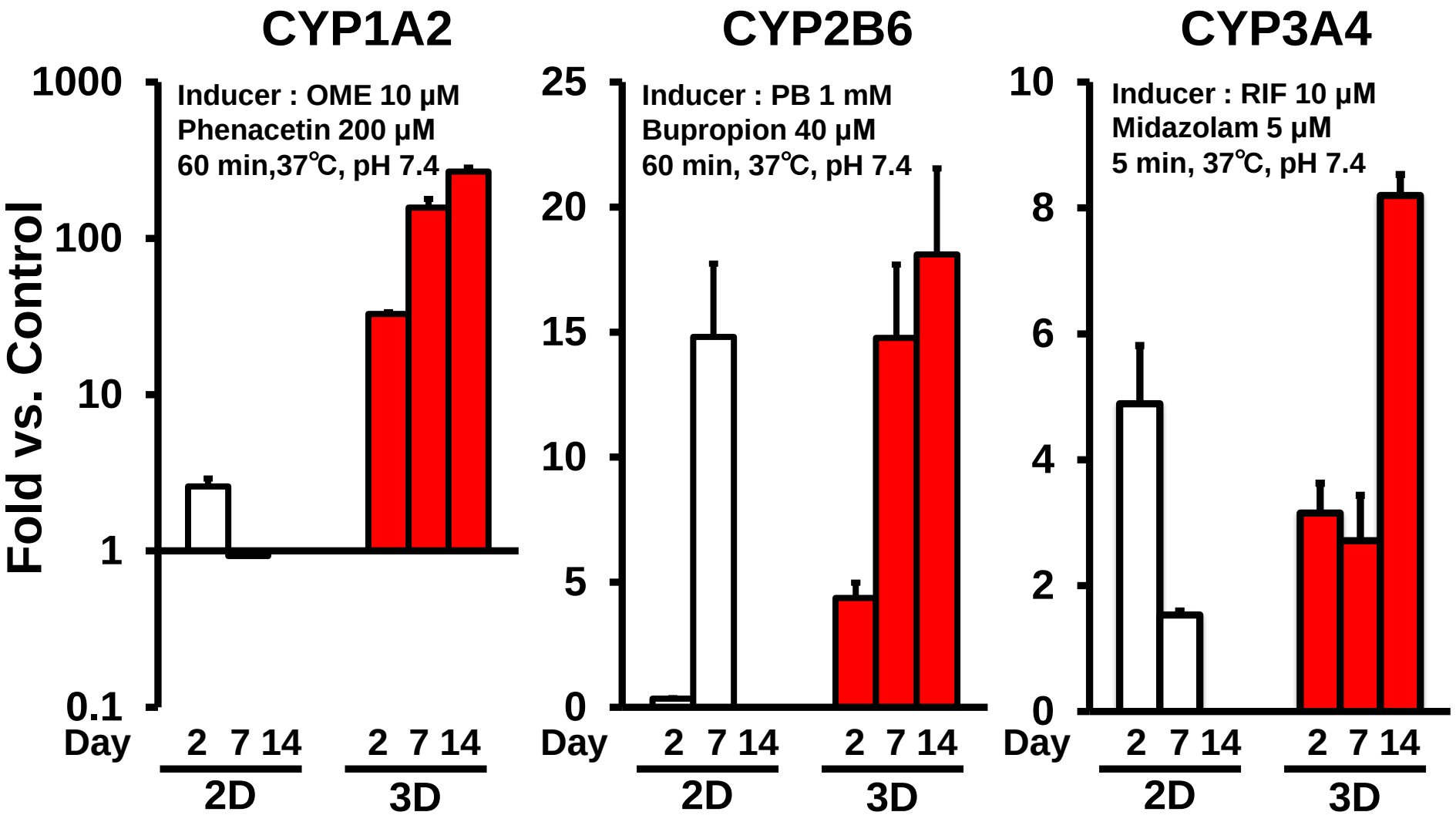
We evaluate of utility of three dimension (3D) culture of human hepatocytes in these concerns.

- Metabolic activity
- Drug-induced liver toxicity
- Enzyme induction

1) ***Drug Metab Pharmacokinet***, 2014,29:373-378.
2) ***Biol Pharm Bull***, 2017,40:967-974.
3) ***J Toxicol Sci***, 2017,42:499-507.

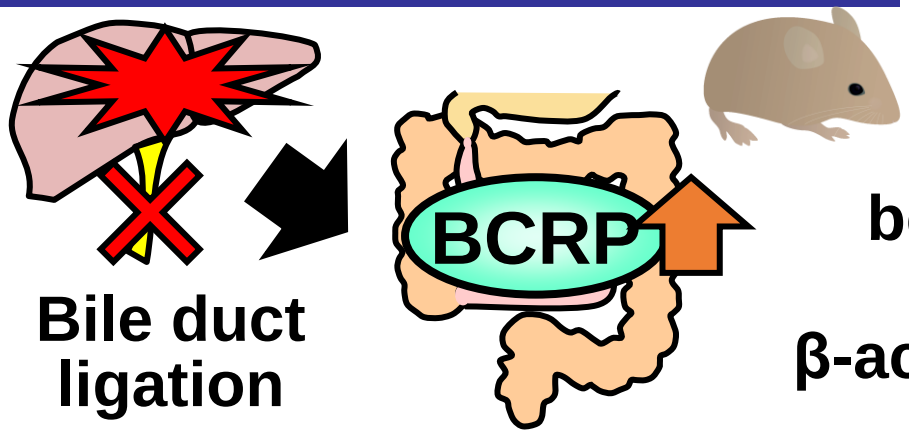
Enzyme Induction in 3D-cultured hepatocytes

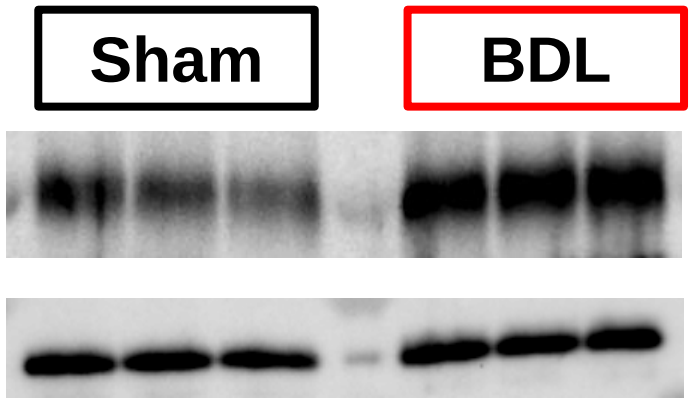
Mean ± S.E.M. (n = 3)



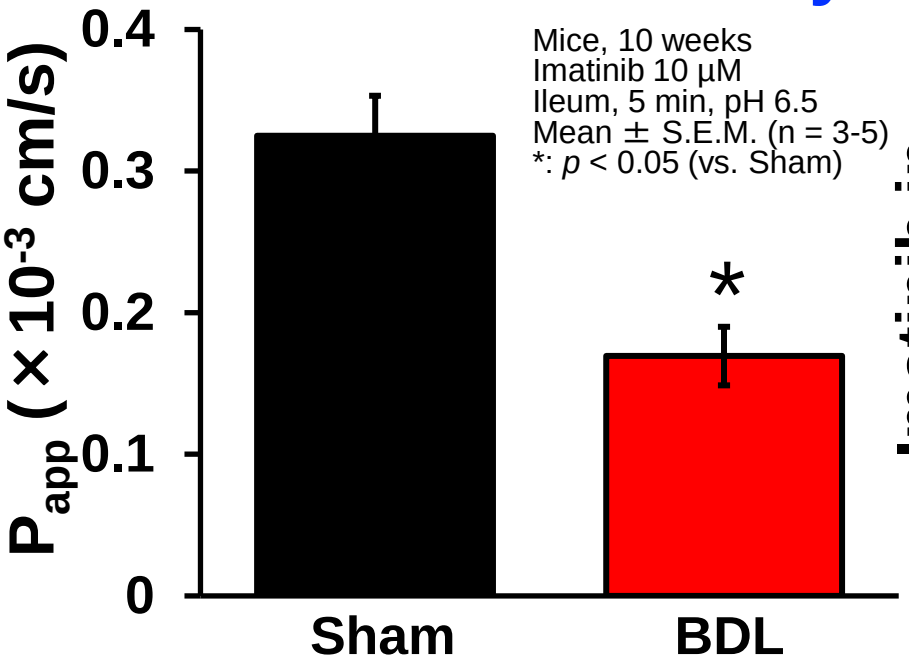
Biol Pharm Bull, 2017,40:967-974.

Reduction of Intestinal Imatinib Absorption in Cholestasis

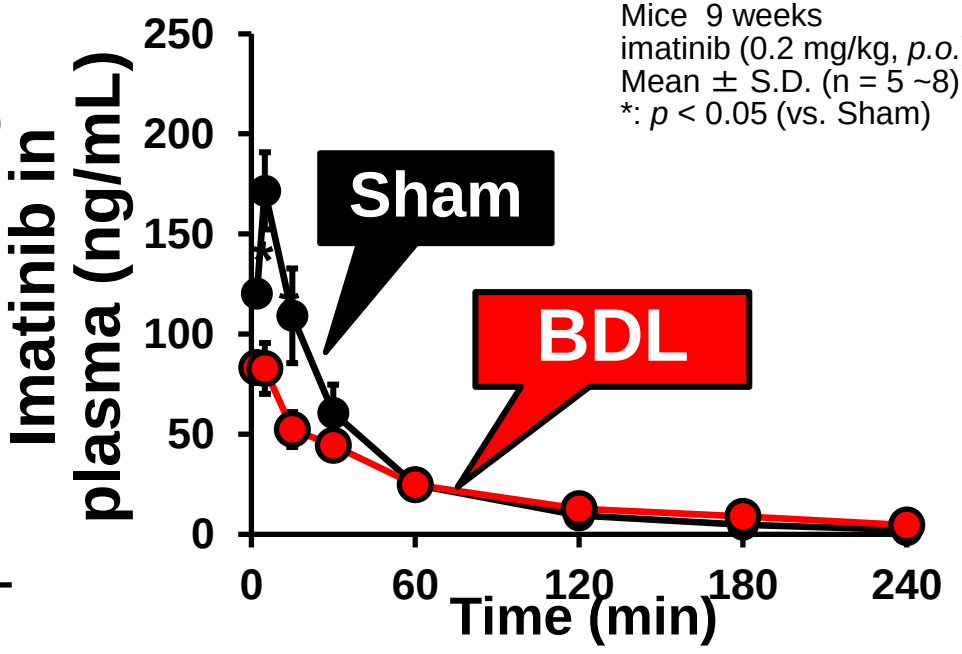




Intestinal Permeability

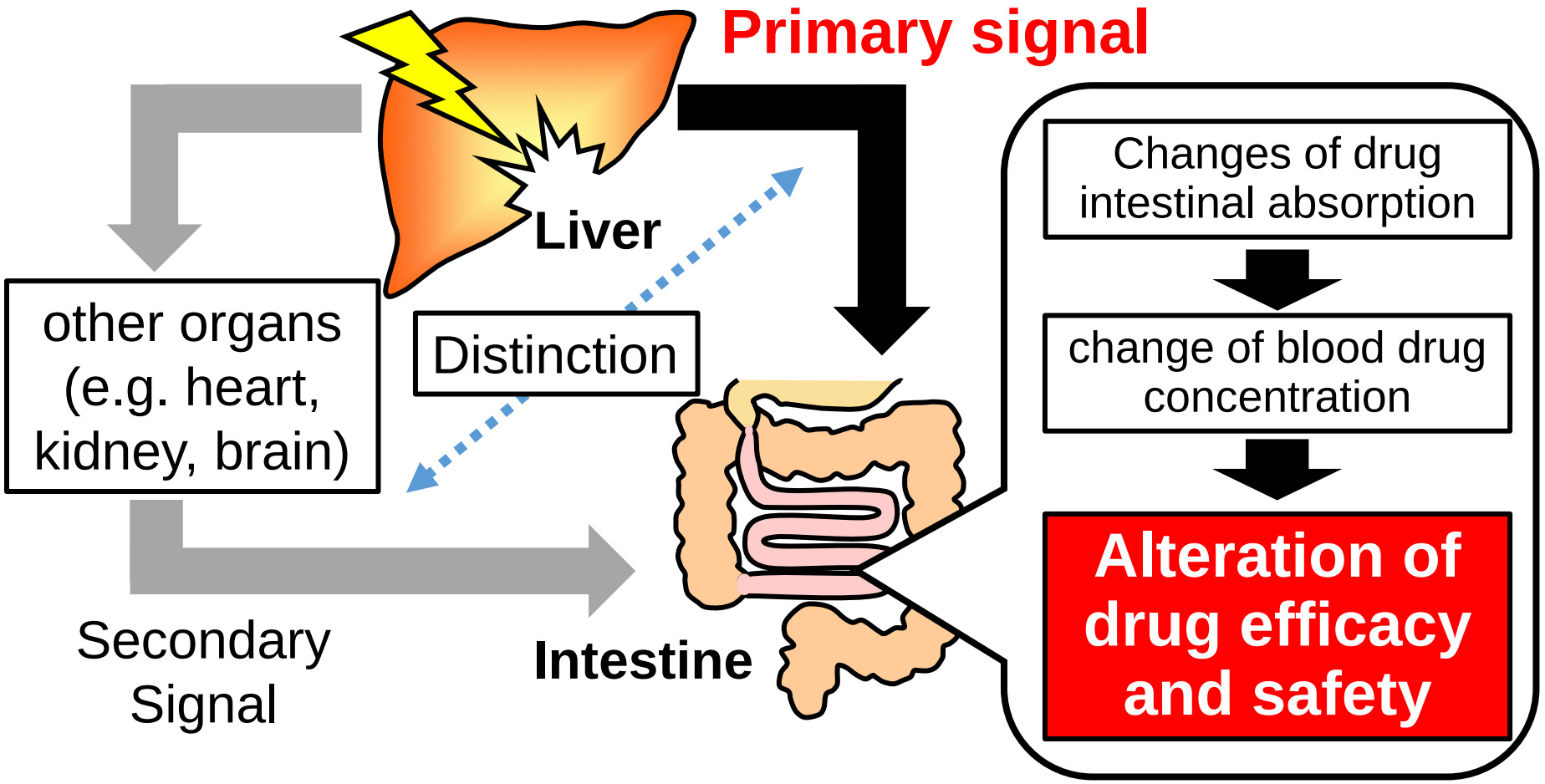


Plasma Concentration



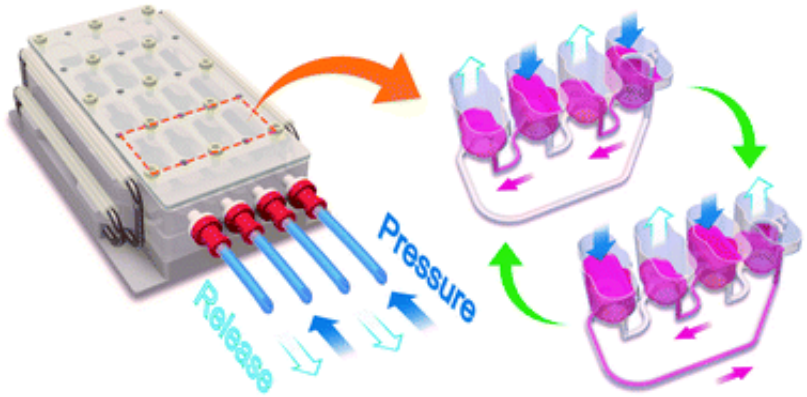
J Pharm Sci, 2019,108:3130-3137.

Limitations of animal study for organs Interaction

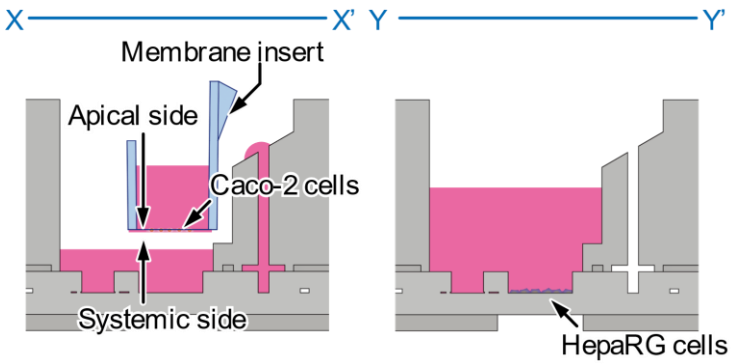


It needs to evaluate organs interaction by *in vitro* assay systems equipped with human cells.

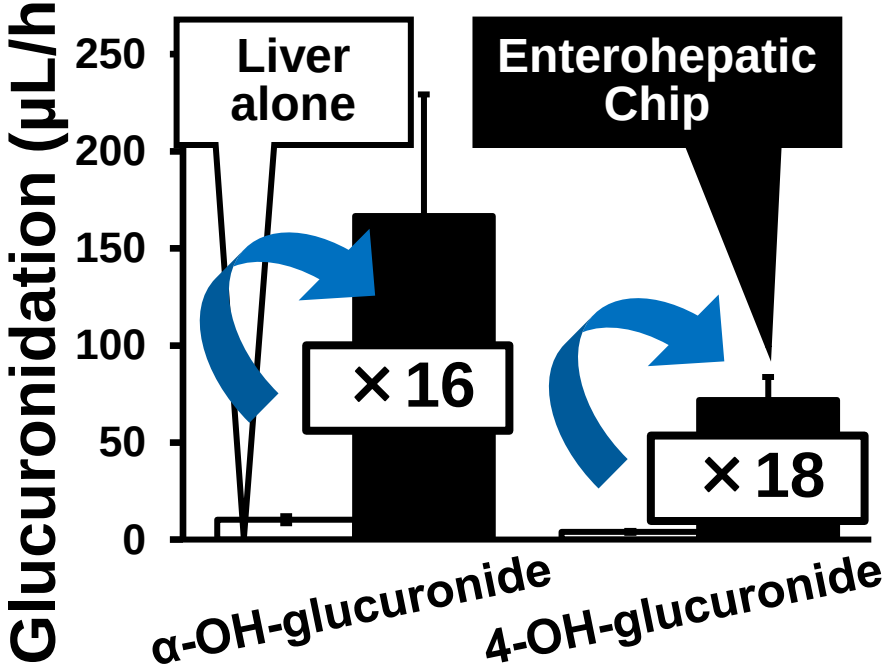
Evaluations of Organs interaction by MPS



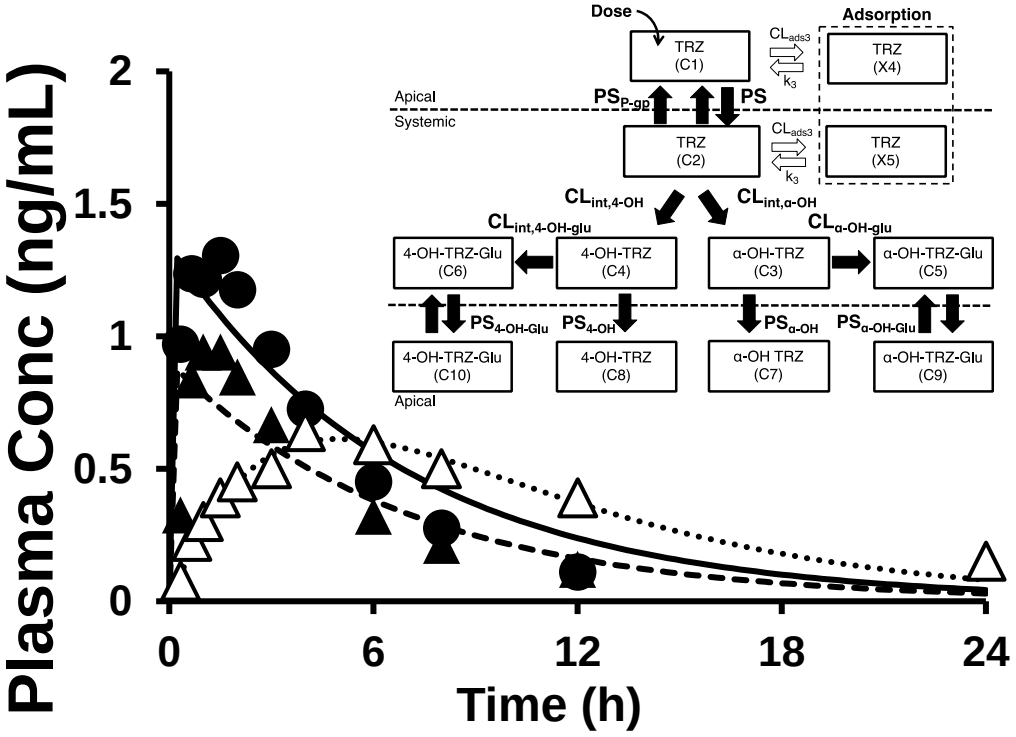
Lab Chip, 2020,20:537-547.



Clarification of tissue interactions



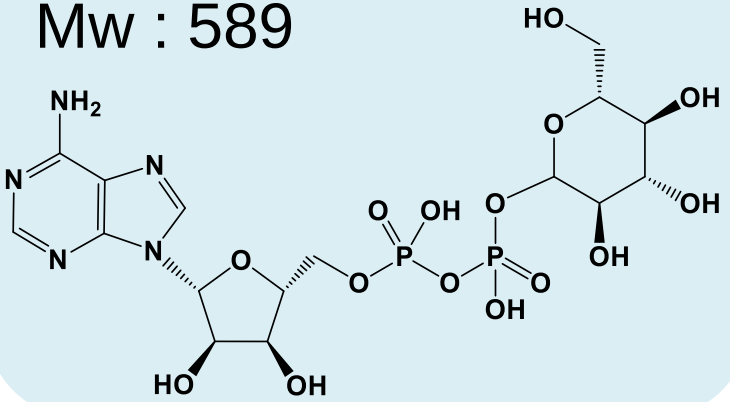
Prediction of human PK

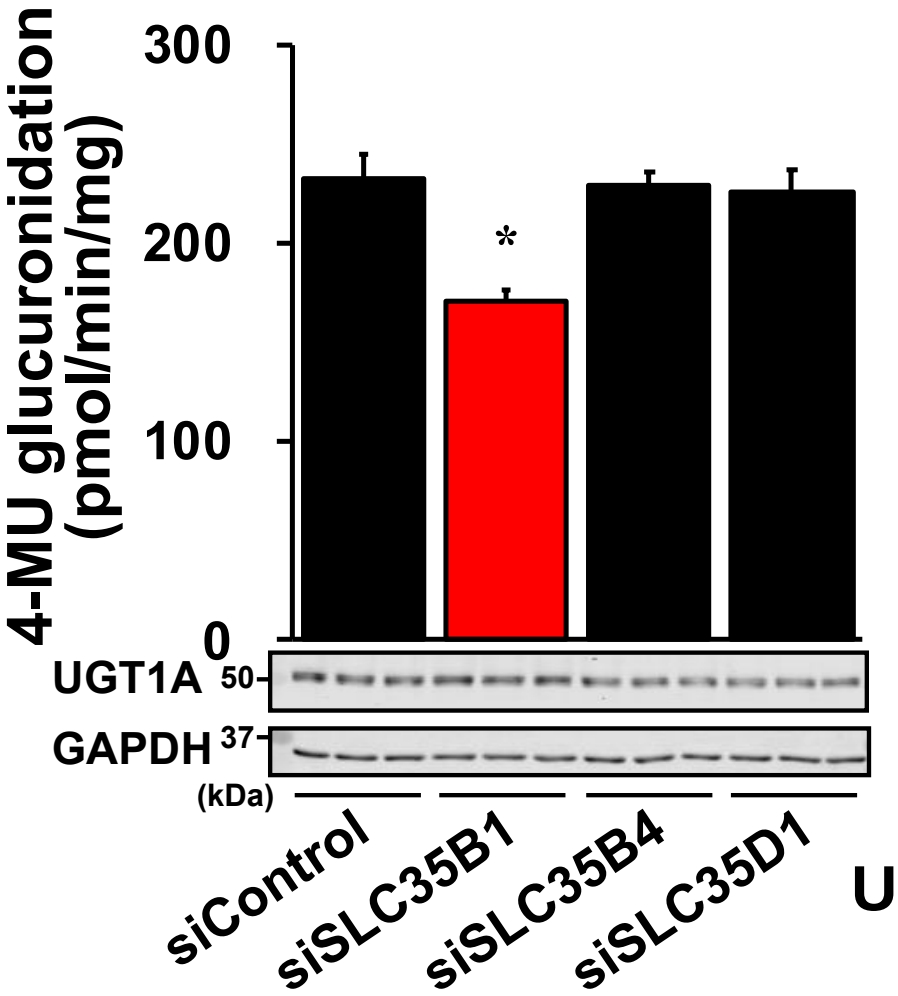


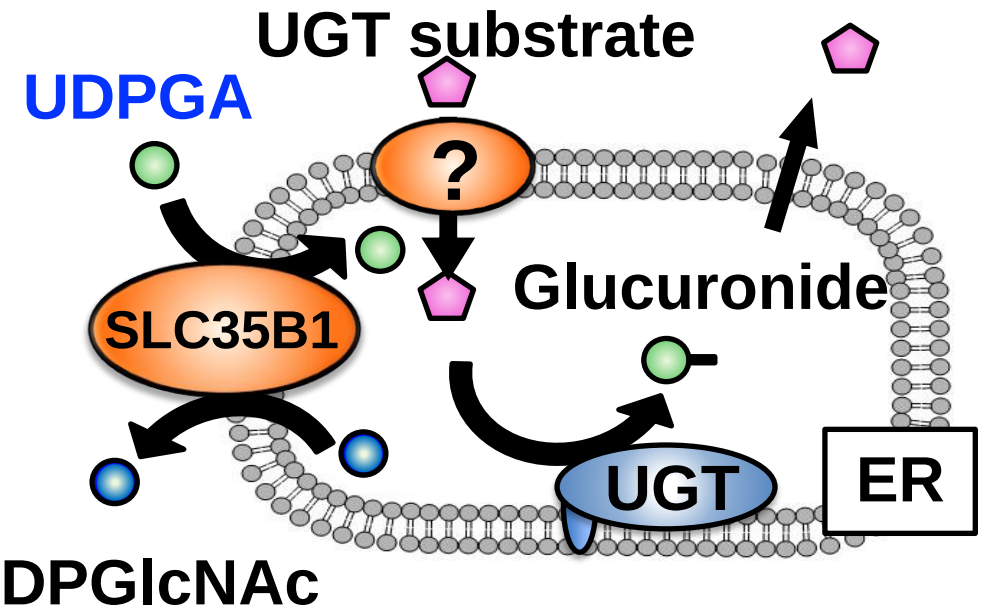
Role of endoplasmic reticulum transporters in drug glucuronidation

SLC35B1 is a responsible transporter for UDP-glucuronic acid in endoplasmic reticulum.

UDP-glucuronic acid
Mw : 589



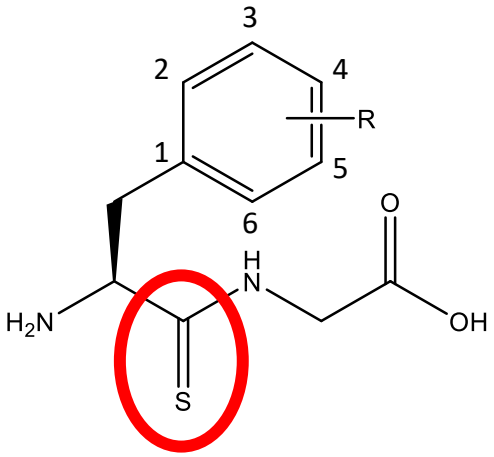




Biochem Pharmacol, 2020,175:113916.

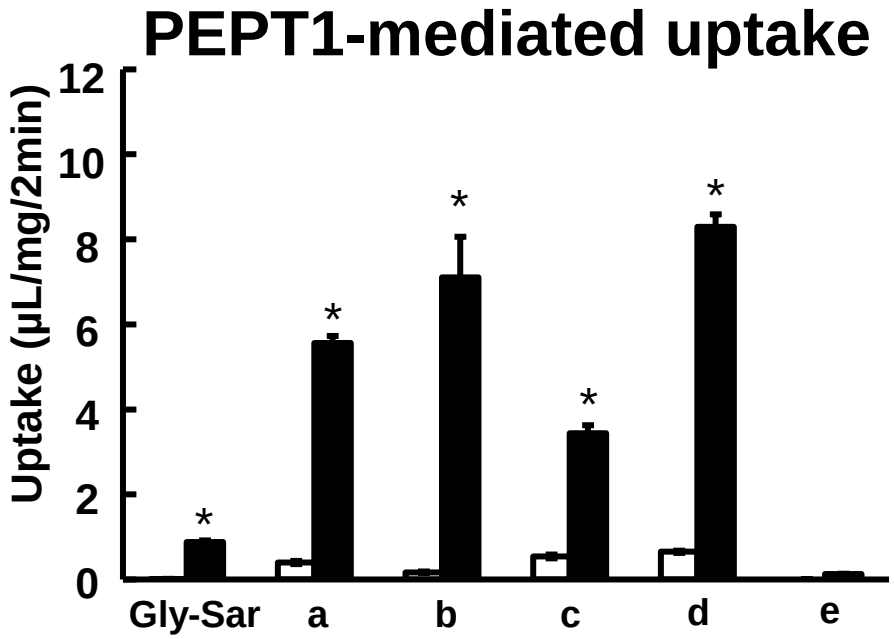
Development of pharmacokinetic probes

Int J Pharm, 2020,586:119575.

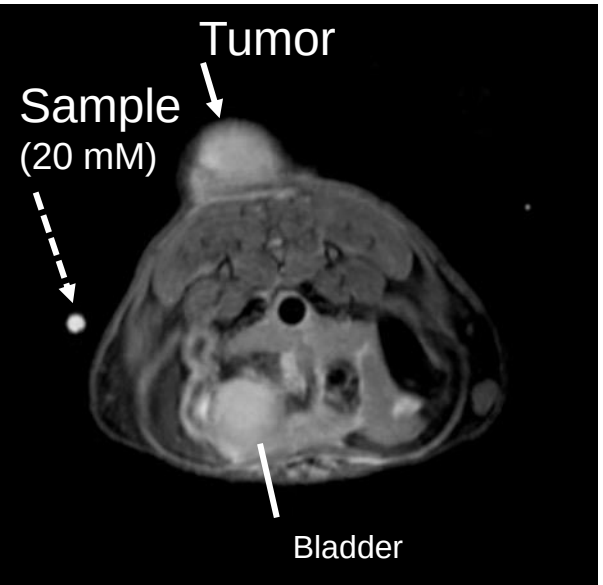


a, R = H
b, R = 4-F
c, R = (2,6)-F_2
d, R = (3,5)-F_2
e, R = 4-CF_3

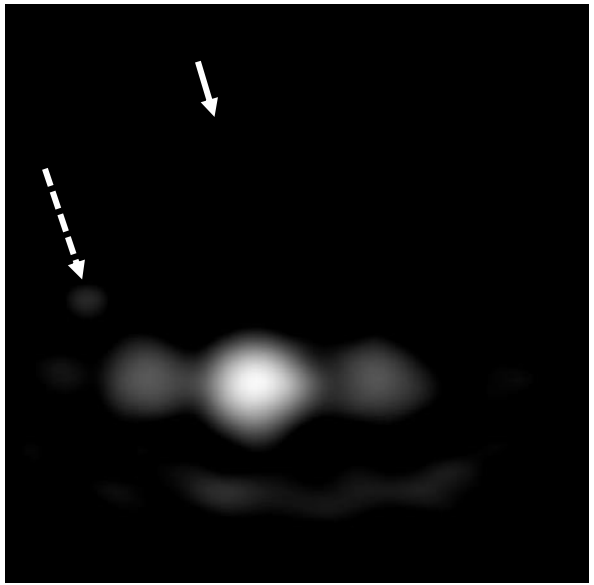
Resistance to peptidases



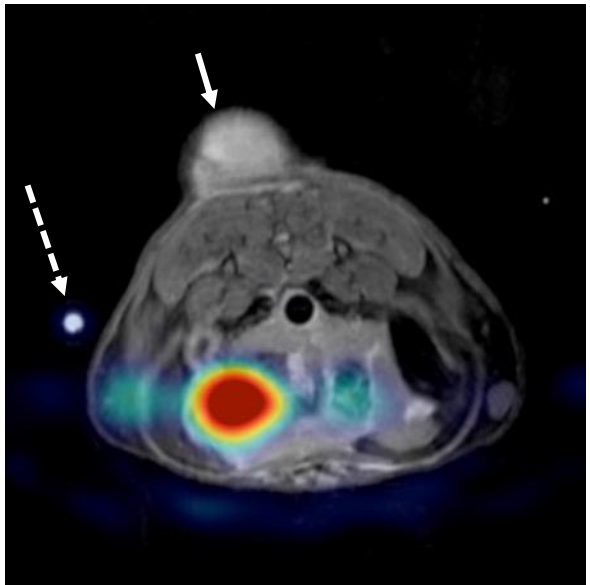
^{1}H MRI



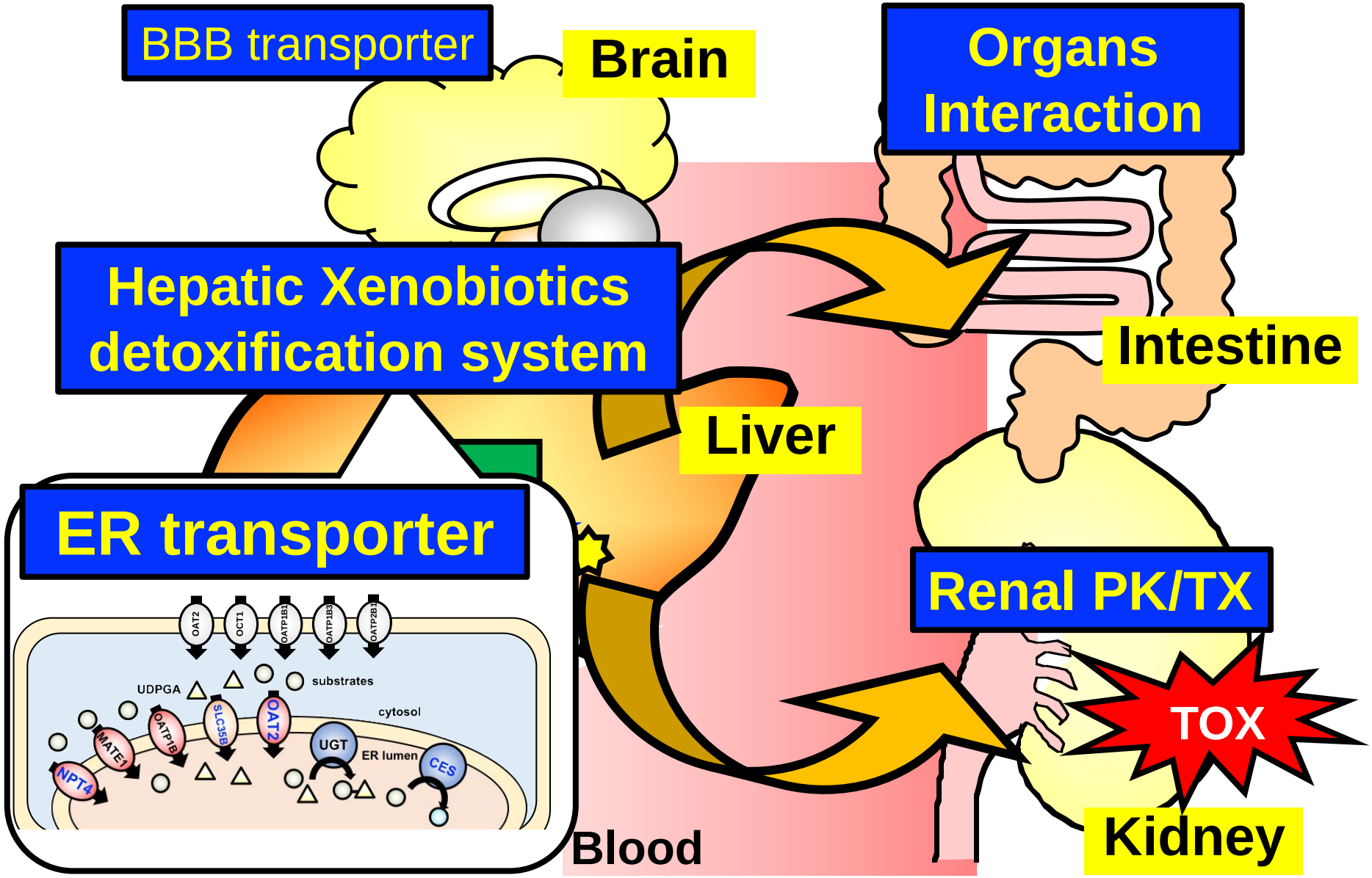
^{19}F MRI (3 h)



Fusion image



Future Aspects



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