

Title of Research:

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Human physiologically-based pharmacokinetic modeling of industrial chemicals with chimeric mice with humanized liver

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Summary of Research: A simplified physiologically based pharmacokinetic (PBPK) model was defined in humans using humanized-liver mice, in which the liver has been repopulated with human hepatocytes is one of the challenge for evaluation of species differences. In order to overcome limitation of available human hepatocytes, the human hepatic cell line HepaRG were evaluated as promising donor cells for liver reconstitution in the TK-NOG mouse model. Taken together, the utility of this simplified PBPK model with humanized mice could be also expanded to the industry researchers and regulatory authorities to investigate a variety of chemicals.

Timeline: From March 1, 2014 to February 28, 2016

Topics: The principal Investigator was the leading organizer for 19th International Conference on Cytochrome P450 (Tokyo, 2015).

Publications:

1. Adachi, K., Suemizu, H., Murayama, N., Shimizu, M., and Yamazaki, H. (2015) Human biofluid concentrations of mono(2-ethylhexyl)phthalate extrapolated from pharmacokinetics in chimeric mice with humanized liver administered with di(2-ethylhexyl)phthalate and physiologically based pharmacokinetic modeling. *Environ.Toxicol.Pharmacol.*, **39**, 1067-1073.
2. Miyaguchi, T., Suemizu, H., Shimizu, M., Shida, S., Nishiyama, S., Takano, R., Murayama, N., and Yamazaki, H. (2015) Human urine and plasma concentrations of bisphenol A extrapolated from pharmacokinetics established in *in vivo* experiments with chimeric mice with humanized liver and semi-physiological pharmacokinetic modeling. *Regul.Toxicol.Pharmacol.*, **72**, 71-76.
3. Nishiyama, S., Suemizu, H., Shibata, N., Guengerich, F. P., and Yamazaki, H. (2015) Simulation of human plasma concentrations of thalidomide and primary 5-hydroxylated metabolites explored with pharmacokinetic data in humanized TK-NOG mice. *Chem. Res.Toxicol.*, **28**, 2088-2090.
4. Yamazaki, H., Kunikane, E., Nishiyama, S., Murayama, N., Shimizu, M., Sugiyama, Y., Chiba, K., and Ikeda, T. (2015) Human plasma concentrations of tolbutamide and acetaminophen extrapolated from *in vivo* animal pharmacokinetics using *in vitro* human hepatic clearances and simple physiologically based pharmacokinetic modeling for radio-labeled microdose clinical studies. *Radioisotopes*, **64**, 509-519
5. Murayama, N., Usui, T., Slawny, N., Chesne, C., and Yamazaki, H. (2015) Human HepaRG cells can be cultured in hanging-drop plates for cytochrome P450 induction and function assays. *Drug Metab.Lett.*, **9**, 3-7.
6. Higuchi, Y., Kawai, K., Kanai, T., Yamazaki, H., Chesne, C., Guguen-Guillouzo, C., and Suemizu, H. Functional polymer-dependent 3D culture accelerates the differentiation of HepaRG cells into mature hepatocytes. *Hepatol.Res.*, in press
7. Shida, S. and Yamazaki, H. Human plasma concentrations of five cytochrome P450 probes extrapolated from pharmacokinetics in dogs and minipigs using physiologically based pharmacokinetic modeling. *Xenobiotica*, in press.
8. Utoh, M., Suemizu, H., Mitsui, M., Kawao, M., Toda, A., Uehara, S., Uno, Y., Shimizu, M., Sasaki, E., and Yamazaki, H. Human plasma concentrations of cytochrome P450 probe cocktails extrapolated from pharmacokinetics in mice transplanted with human hepatocytes and from pharmacokinetics in common marmosets using physiologically based pharmacokinetic modeling. *Xenobiotica*, in press.