Title of Research: 22-3-01

Prediction of internal concentrations of chemicals orally administered using data-driven pharmacokinetic modeling

Principal Investigator: Prof. Hiroshi Yamazaki, PhD (Showa Pharmaceutical University, Laboratory of Drug Metabolism and Pharmacokinetics), 3-2-1, Higashi-tamagawa Gakuen, Machida, Tokyo 194-8543, Japan. (phone) +81-42-721-1406; (e-mail) hyamazak@ac.shoyaku.ac.jp.

Collaborator: Makiko Shimizu, ibid, (e-mail) shimizu@ac.shoyaku.ac.jp

Summary of Research: Physiologically based pharmacokinetic (PBPK) modelling can be used to evaluate internal exposure in humans without any reference to experimental data. The input parameters for PBPK models (i.e., fraction absorbed × intestinal availability, absorption rate constants, volumes of systemic circulation, and hepatic intrinsic clearances) were estimated for a panel of approximately 350 chemicals. These parameters of the human and rat PBPK models for a diverse range of compounds were successfully estimated using a light gradient boosting machine learning algorithm (LightGBM) based on < 30 *silico*-calculated chemical descriptors. This approach to pharmacokinetic modeling has the potential for application in computational toxicology and in clinical settings to assess the potential risk of drugs and general chemicals. Based on estimating interspecies toxicokinetics or internal exposures of lipophilic food components after oral doses in humans, this approach, which applies simple PBPK modeling with no reference to experimental pharmacokinetic data, has the potential to play a significant role in the extrapolation of reported liver toxicity levels in rats to humans.

Timeline: From March 1, 2024 to February 28, 2025

Publications:

1) Adachi K, Shimizu M, Shono F, Funatsu K, Yamazaki H. Octanol/water partition coefficients estimated using retention times in reverse-phase liquid chromatography and calculated *in silico* as one of the determinant factors for pharmacokinetic parameter estimations of general chemical substances. *J Toxicol Sci*, **49**, 127-137 (2024).

2) Adachi K, Sasaki T, Arai A, Shimizu M, Yamazaki H. Impact of variability of *in silico* and *in vitro* octanol/water partition coefficients of compounds on the input parameters and results of simplified human physiologically based pharmacokinetic models after virtual oral administrations. *J Toxicol Sci*, **49**, 459-466 (2024).

3) Adachi K, Ohyama K, Tanaka Y, Saito Y, Shimizu M, Yamazaki H. Modeled Hepatic/Plasma Exposures of Fluvastatin Prescribed Alone in Subjects with Impaired Cytochrome P450 2C9*3 as One of Possible Determinant Factors Likely Associated with Hepatic Toxicity Reported in a Japanese Adverse Event Database. *Biol Pharm Bull*, **47**, 635-640 (2024).

4) Adachi K, Ohyama K, Tanaka Y, Murayama N, Shimizu M, Saito Y, Yamazaki H. Modeled Hepatic/Plasma Exposures of Omeprazole Prescribed Alone in Cytochrome P450 2C19 Poor Metabolizers Are Likely Associated with Hepatic Toxicity Reported in a Japanese Adverse Event Database. *Biol Pharm Bull*, **47**, 1028-1032 (2024).

5) Adachi K, Hosoi M, Shimura Y, Shimizu M, Yamazaki H. Reported liver toxicity of food chemicals in rats extrapolated to humans using virtual human-to-rat hepatic concentration ratios generated by pharmacokinetic modeling with machine learning-derived parameters. *J Toxcol Sci*, in press.