Title of Project: Development of quantitative prediction methods for alteration in pharmacokinetics caused by interindividual variability in transporter function and transporter-mediated drug-drug interaction

Yuichi Sugiyama (RIKEN, Innovation Center, Head of Sugiyama Laboratory)

Research Area: Pharmacokinetics and drug metabolism
Keyword: Transporter, Drug-drug interaction, Polymorphism, PBPK modeling

Purpose and Background of the Research
Transporters are expressed in liver, kidney, intestine and blood-brain barrier and known to mediate transports of various drugs and endogenous molecules. It has been reported that transporter functions are altered by polymorphisms, hepatic/renal disorders and drug-drug-interactions (DDI) in human, which may affect pharmacokinetics (PK) and main/adverse effects of clinically-used drugs. The purpose of this study is to establish methods for the quantitative prediction of PK variation and alteration based on mechanisms.

Research Methods
In order to accomplish our purpose, we should perform 5 studies: (1) Developing transporter-specific probes (substrates) and inhibitors which are useful for the evaluation of transporter functions in human. (2) Constructing methods for the quantitative prediction of transporter polymorphism effects on PK (Fig. 1). (3) Analyzing alteration in transporter functions in patients with hepatic/renal disorders, and constructing prediction methods for PK alteration. (4) Establishing quantitative prediction methods of DDI based on PBPK modeling and simulation (Fig. 2), performing several clinical studies. (5) Developing PET/SPECT probes which are useful for real-time and non-invasive analyses of drug distribution. Predicting effects at the target organs and toxicity more precisely using transporter probes.

Expected Research Achievements and Scientific Significance
Our achievements will contribute to understanding variations in PK parameters and DDI mechanisms in drug development, and also contribute to improving efficacy and safety of clinical drug uses.

Publications Relevant to the Project

Term of Project] FY2012-2016
Budget Allocation] 148,500 Thousand Yen
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