

## SL11

# Importance of Drug Transporter Studies in the New Drug Discovery and Development

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Drug transporters are expressed in many tissues, such as the intestine, liver, kidney, and the brain, and play key roles in drug absorption, distribution and excretion. In this presentation, I will summarize the significant role played by drug transporters in drug disposition, focusing particularly on their potential use during the drug discovery and development process. The use of transporter function offers the possibility of delivering a drug to the target organ, avoiding distribution to other organs (thereby reducing the chance of toxic side-effects), controlling the elimination process, and/or improving oral bioavailability. It is useful to select a lead compound that may or may not interact with transporters, depending on whether such an interaction is desirable. The expression system of transporters is an efficient tool for screening the activity of individual transport processes. The changes in pharmacokinetics due to genetic polymorphisms and drug-drug interactions involving transporters can often have a direct and adverse effect on the therapeutic safety and efficacy of many important drugs.

Vectorial transport across epithelial cells is involved in the absorption/uptake and elimination of drugs in the small intestine, liver and kidney. The vectorial transport of a large number of organic anions is achieved by uptake and efflux systems. We have established double-transfected MDCK II cells where hepatic uptake transporters and efflux transporters are expressed on the basal and apical membrane, respectively, as an *in vitro* model for hepatobiliary transport. This system is useful for drug discovery and development studies and for investigating drug-drug interactions involving hepatobiliary transport.

In this presentation, I will also show you how to establish a physiologically based pharmacokinetic (PBPK) model that includes the transporter-mediated membrane transport processes and to investigate the effect of changes in transporter function on the pharmacokinetics and, ultimately, the pharmacological and/or toxicological effects. We also tried to extrapolate from *in vitro* to *in vivo* in human taking thus obtained analyses in rats into consideration. This PBPK model can then be applied to predict changes of drug concentration in plasma and target organs caused by changes in transporter function and expression level.

## REFERENCES

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