RESEARCH ON TRANSPORTERS IN DRUG DISCOVERY AND DEVELOPMENT
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In the past, transporter (TP) research in the industries was mainly focused on explaining the PK properties observed during clinical development or on the differentiation with competitors to support sales after launch. Many of these studies were conducted under the tuition of academia.

Recently, the International Transporter Consortium (ITC) provided integrated information on the methodology of TP research, including in vitro experiment systems and data analysis (Ref. 1). They also provided the decision trees to guide which types of preclinical observations trigger clinical studies. In response to this recommendation, pharmaceutical industries in Japan are preparing for the TP studies required as part of IND and NDA submission.

Evaluations of a drug candidate as an inhibitor are conducted during the drug discovery and development stages using cell lines, hepatocytes, membrane vesicles and tissue slices. Typical probe compounds, though they may not be specific, are used to evaluate the potential of DDI caused by the inhibition of TPs. On the other hand, it is not easy to assess a drug candidate as a victim of DDI, even if uptake studies using animal and human tissues suggest that the compound is a substrate of TPs. This is because lipophylic and/or insoluble compounds often give indistinct results, and supplies of experimental materials such as cell lines or Xenopus oocytes expressing TPs, which are required to conclude if the compound is a substrate of a specific TP isoform, still require improvement. Another issue in TP research is the difficulty in evaluating the in vitro transport data with the physicochemical properties and predicting the in vivo contribution with the pharmacokinetic properties. In the case of P-gp, there are more than 300 compounds reported as substrates (Ref. 2), but only a few P-gp substrates are known to be victims of DDI caused by the inhibition of P-gp, and the reason for this is still not clearly explained. Accumulation, sharing the experimental background data and theoretical and quantitative considerations are expected.

In pharmaceutical industries, ADME researchers are experts of quantitative considerations. When TP is a target of pharmacology, the pharmacological effect could be analyzed as DDI between a drug candidate and an endogenous compound. Thus, our kinetic analysis and in vitro-in vivo extrapolation techniques are expected to be utilized in the evaluation of TPs as targets of pharmacological and toxicological effect.

Ref. 2 Metabolism and Transport, Drug Interaction Database (University of Washington)

Biography
1985-1991 Nippon Roche
1991-1992 Postgraduate researcher, UCSF
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