DEVELOPMENT OF QUANTITATIVE HUMAN ABSORPTION PREDICTION SYSTEM IN DRUG DISCOVERY (2) -SEPARATE EVALUATION OF PASSIVE PERMEABILITY FOR PRECISE PREDICTION OF INTESTINAL ABSORPTION INCLUDING THE ROLE OF EFFLUX TRANSPORT-
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[Purpose] It has been increasing importance of developing new compounds as oral drugs expected linear dose dependence in the desired dose range. Many commercial drugs have been suggested the non-linearity due to P-gp efflux on intestinal absorption, but the question as to whether or not a certain P-gp substrate is likely to show P-gp efflux dependent intestinal absorption in vivo is still to be addressed. The purpose of this study was to investigate the relationship between the P-gp significance on in vivo intestinal absorption and passive permeability as a useful physicochemical parameter from early drug discovery stage.

[Method] Passive permeability value was evaluated by commercially-supplied PAMPA plate by BD Biosciences. The in vivo permeability was determined by the single-pass intestinal perfusion (SPIP) model in the rat small intestine, in the presence or absence of the P-gp inhibitor verapamil.

[Results and Discussion] P-gp substrates with insufficient passive permeability showed limited permeability in rat small intestine and significantly increased in the presence of verapamil. Also, these compounds tend to exhibit the non-linear intestinal absorption in vivo. The utilization of 3-class classification of passive permeability by PAMPA and in vivo permeability by SPIP for understanding the in vivo intestinal absorption and functional role of P-gp could contribute to more precise prediction of efflux relevance and the lead optimization of drug discovery.

DEVELOPMENT OF QUANTITATIVE HUMAN ABSORPTION PREDICTION SYSTEM IN DRUG DISCOVERY (3) -PHYSICOCHEMICAL PROPERTY ORIENTED AND PHYSIOLOGICALLY BASED ABSORPTION SIMULATION PERFORMED WITH GASTROPLUS-
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[Purpose] To increase the developability of new compounds as an oral drug, reliable estimation of human oral absorption (Fa) during the drug discovery and development is important. We developed quantitative human Fa prediction system using appropriate physicochemical property and using physiologically based model simulation. The aim of this study was to illustrate our Fa prediction system with application examples taken from our work that was performed with GastroPlus™ software.

[Method] Human absorption simulations were performed with the ACAT model built in GastroPlus ver. 6.1. Physicochemical properties were estimated by ADMET Predictor™ ver. 4.0 essentially, and in some case optimized from experimental data. For poorly water-soluble compounds solubility profile was determined by thermodynamic solubility in biorelevant media (e.g., fasted state simulating intestinal fluid (FaSSIF) at pH6.5).

[Results] Retrospective analysis of Fa by GastroPlus using some compounds in clinical studies revealed that dose dependent Fa estimation is possible. For poorly water-soluble compounds, application of FaSSIF solubility for input is key point to avoid an underprediction of Fa. Current application cases of Fa estimation in our company in lead optimization, clinical read selection and clinical development are going to describe on the presentation.

[Conclusion] Quantitative simulation of drug absorption using GastroPlus can be useful from the lead optimization of drug discovery through to clinical development stage.