S12-1 A strategy to avoid intestinal first pass metabolism and drug-drug interactions

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Many drug candidates are developed as oral drugs and some of those candidates exhibit low bioavailability, considered to be a result of low solubility, low permeability and hepatic first pass metabolism. Other causes include CYP3A4 and P-glycoprotein present in the intestine, both of which act as a barrier against xenobiotics. Some CYP3A4 substrates exhibit low bioavailability due to intestinal first pass metabolism and the plasma concentrations of such substrates are remarkably increased by CYP3A4 inhibition from other drugs or foods such as grapefruit juice. Additionally, the pharmacokinetics of such CYP3A4 substrates exhibit wide variability. Prediction of intestinal first pass metabolism is important for drug development but no standard method has been established. We recently developed a method for predicting intestinal first pass metabolism and drug-drug interaction that will enable better selection of drug candidates. In this symposium, we will describe a strategy to avoid developing drugs with intestinal first pass metabolism and drug-drug interactions.