The Cytochrome P450 Catalyzed Drug Metabolism in Drug Development: Pharmacogenetics and Drug Interactions

Jae-Gook Shin, MD, PhD

Department of Pharmacology and Clinical Pharmacology, Inje University College of Medicine

Drug metabolism and pharmacokinetics (DM/PK) are one of the major issue to be evaluated throughout the whole drug discovery and drug development. Now a days, the knowledge based drug discovery and developments ask us lots of informations on the target compounds, and DM/PK and pharmacogenomics are one of the major areas to be considered in the drug R&D. Since many of drugs are metabolized mainly by CYP isoforms, it is not surprising to evaluate the metabolic stability drug interaction potential, and involvement of CYP isoforms that are genetically polymorphic. These factors, causing wide interindividual variation of drug responses, increase of difficulty in predicting the personalized optimum dose regimen of individual patients.

From the introduction of human liver microsomal incubation study and cDNA expressed CYP enzymes, it is very usual that the drug metabolism and drug interaction potentials are evaluated in the early phase of drug discovery and development. Inhibitory interactions are one of the serious issue of drug development since several therapeutic drugs including terfenadine and cisapride were withdrawn from market due to the problem of drug interaction. We developed high throughput screening method for the inhibitory interaction potential of target compound on nine CYP isoforms using cassette dose and LC/MS/MS assay. The *in vitro* inhibitory interaction data is highly useful to predict the *in vivo* drug interaction potential in a clinical setting, and a related FDA guidance suggest to submit the inhibitory interaction data *in vitro* before the phase 2 clinical trial, but it is no unusual that the drug interaction studies using human liver microsome are completed before or during the preclinical development. Among the screening methods of the induction potential, the promotor luciferase assay and the expression profiling of the enzymes in animal will be discussed in the lecture.

The *in vivo* drug interaction in human subjects is frequently evaluated by mechanism based approaches using CYP isoform specific probes. In this aspect, high throughput cocktail approach seems to be a good tool to investigate the interaction of a candidate compounds with any of CYP isoform substrates. In the lecture, newly developed "Inje cocktail" will be introduced in comparison with several previous reported cocktails. In addition, several examples of clinically relevant drug

interactions will be discussed.

In addition to drug interaction, pharmacogenetics/pharmacogenomics is another major factor causing wide interindividual variation of the drug responses. The genetic polymorphisms of drug metabolizing enzymes and drug transporters cause wide variation of drug disposition in human subjects. This should be considered in the drug discovery and development. Many of CYP enzymes are well known to be genetically polymorphic, which is significantly taken into account in the early DM/PK screening and study design of clinical drug development. The study subjects are routinely pre-genotyped for the CYP isoforms especially for new drug candidate that are metabolized by the genetically polymorphic CYP isoform(s). The author will present the pharmacogenetics/ pharmacogenomics of CYP isoforms in a Korean populations and issues in the pharmacogenetics/ pharmacogenomics in the application to the drug development. In addition, the combined effect of pharmacogenetics and drug interaction should be evaluated if the candidate drug has a such potential of drug interaction as well as pharmacogenetics related problems.