PREFACE

Application of Drug Metabolism and Pharmacokinetics for New Drug Development

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Preclinical drug discovery is a time- and labor-consuming work and unfortunately very small number of compounds can be applicable to patients. Moreover, though the cost of new drug development has been increasing for the past many years, the number of approved new drug is relatively fixed (Kola and Landis, 2004). Theoretically it is not possible to develop new drug with complete safety and high efficacy, so the pharmaceutical companies always try to pre-screen potential toxicity of drug candidates. Approximately 50% of lead compounds failed because of insufficient efficacy and 40% attrition of lead compounds is due to safety issues (DiMasi, 1995). *In vivo* low efficacy and unexpected toxicity are frequently associated with poor drug metabolism and pharmacokinetic profiles (Masimirembwa et al., 2003; Kuppens et al., 2005). Hence, big portion of clinical success of drug candidates could be dependent on DMPK properties of compounds. In fact, DMPK assessment is done at many steps in new drug development procedures, and initial decision could be an important factor for successful drug development. In this special issue, we provide nine outstanding review articles and eleven original articles covering several fields of DMPK and practical pharmaceutics and these articles may strengthen our understanding of current progress in these important research areas.

A series of the reviews start with two papers covering animal and human pharmacokinetics: Predicting approaches for human pharmacokinetics using interspecies pharmacokinetic scaling, and accelerated mass spectrometry-based microdosing studies. Kang and Lee introduced the reliable interspecies scaling and prediction methods for various pharmacokinetic parameters

and plasma concentration-time (C_p) profiles. The detailed equations were well summarized in tables for the interspecies scaling of total body clearance (CL), volume of distribution at steady state ($V_{d,ss}$) and C_p profiles. The main purpose of interspecies pharmacokinetic scaling is selection of first-in-human dose which is low enough to be safe. Several approaches had been published for this purpose, and the authors thoroughly compared their advantages and limitations in this review. Finally, the authors pointed that these approaches are still highly empirical, so the reliable method improvements are further required for the prediction of human pharmacokinetics (Kang and Lee, 2011). Because of severe temporal and economic standstill in the new drug development, the FDA has made an effort to enhance the productivity by Critical Path Initiative Project since 2004. Exploratory investigational new drug (eIND) studies were introduced for this purpose, and microdosing study (Phase 0 study) could be the core study in this aspect. The purpose of microdosing study is the prediction of human pharmacokinetics in therapeutic doses as early stage as possible. However, since microdosing study is first human study, the usual dose should not exceed 1/100 of the dose, at which the pharmacological effects can be predicted. Because of this dosing limitation, both the highly-sensitive analysis equipment and the reliable *in silico* modeling method are required for the exact prediction of pharmacokinetics in therapeutic dose. Bae and Shon introduced the current development and application of analysis equipments in microdosing study, focusing on accelerator mass spectrometry (AMS). The authors also discussed the limitation of AMS-based microdosing study such as questionable predicting ability and the high cost of AMS application (Bae and Shon, 2011).

Inter-individual variabilities of drug absorption, distribution, metabolism and excretion are common in clinics and can result in poor drug response, adverse

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drug reaction and unfavorable drug-drug interaction. Genetic variations in metabolic enzymes and transporters are common causes of inter-individual variability, and the progress of pharmacogenomics and pharmacogenetics provides the scientific basis for personalized medicine which optimizes drug therapy on the basis of each patient's genetic constitution. In this special issue, we invited two review articles introducing genetic polymorphism of cytochrome P450 (CYP) and ABCB1 transporter which are representative metabolic enzyme and drug transporter, respectively. The current knowledge on the polymorphism by nonsynonymous SNPs in CYP subtypes is provided (Lee and Kim, 2011). With brief explanation about each subtype of CYP, clinically important substrates of each subtype were listed in the text. Moreover, allelic variants of CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6 and 3A4 located in the coding regions and their effects on phenotype were summarized in five tables. In order to evaluate the effects of genetic polymorphism in CYP enzymes and ABCB1 transporter, Yoo and Lee focused on meaningful genetic polymorphisms with recently conducted clinical studies. They further introduced some examples of interplay of ABCB1 transporters and CYP enzymes according to genetic polymorphisms (Yoo and Lee, 2011). They pointed out that even though the theoretical basis of interplay between efflux transporter and metabolic enzymes has been previously suggested (Benet, 2010; Benet and Cummins, 2001), only the limited numbers of therapeutic drugs may be applicable to this theory. The authors explained the result of clinical studies for risperidone according to genetic polymorphisms in *CYP2D6* and *ABCB1*, and insisted that the mechanism suggested by Benet could not properly interpret their clinical results. Finally, the authors emphasized the need of new convincing pharmacokinetic models to estimate interplay between ABCB1 transporters and CYP enzymes.

As the uses of herbal medicines increase in clinics, their unexpected adverse effects should be considered in health care systems. Because herbal medicines are usually used as multiple drug therapy with other synthetic drugs, many of adverse drug reactions can be caused by herb-drug interactions. In this special issue, there are three review articles introducing herb-drug interaction and its clinical implications. Na et al. introduce the useful *in vitro* methodology for CYPs and UGTs-mediated metabolism study. The detailed description for the methodological aspect is included in the text. *In vitro* cocktail probe substrate of CYP subtypes and specific probe for UGT activity were well listed in two tables. Finally, many of *in vivo* and *in vitro* examples of drug interactions about Ginkgo biloba

and St. John's wort were described. Choi et al. selected nice botanicals (ginkgo, green tea, grape, licorice, saw palmetto, garlic milk thistle, ginseng and St. John's wort) and summarized the literatures focusing on their effects on metabolic enzymes and transporters. The published effects of each botanical extract and its active components were clearly demonstrated in nine tables. The source of plant samples (extracts and individual components), the species difference (human and animal) and the effect difference between *in vitro* and *in vivo* system were separately reviewed. Han focused on the role of some selected drug transporters in drug interactions as well as their clinical implications. The current updated results of drug-drug interactions caused by p-glycoprotein (p-gp), organic anion transporters (OATs) and organic anion transporting polypeptides (OATPs) were described with the data of recently conducted clinical trials. The draft drug interaction guidance for p-gp substrate or inhibitor was introduced in the text. The author further explained the technologies to evaluate transporter interactions and discussed need for the new experimental approaches considering development stage (discovery versus clinical development).

In the past few years, the number of new drugs reaching the market has decreased. One of the main reasons for the failure of drug candidates is unexpected toxicity. Hepatotoxicity was ranked first in the frequency of drug-induced adverse events, and it seems to be a common reason for withdrawal of new drug from the market by the FDA. The most important cause for drug-induced liver injury is production of toxic metabolites. In fact, 71% of drugs are known to produce reactive metabolites. Lee et al. summarized the current methods used for the determination of reactive metabolites necessary for predicting drug-induced liver injury in drug discovery and development. They described a general overview of the relationship between drug metabolism and liver injury and introduced *in vitro* methods for the assessment of reactive metabolites (Lee et al., 2011).

The last review paper in this special issue deals with a practical designing and strategy of drug formulation to treat chronic disease. Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation in joints through leukocyte sequestration and destruction of cartilage and bone, which may cause disability and negative socioeconomic impacts. Despite the rapid advances in therapeutic options for RA, systemic adverse effects may arise from frequent and long-term dosing and limitation of administration route. Mitragotri and Yoo described current treatment options of RA, explaining new methods for delivery to

inflamed joints. They suggested that micro and nano-particle systems selectively delivering drugs to inflamed synovium have the potential to improve the drug efficacy and summarized key design parameters of RA-targeted drug carriers (Mitragotri and Yoo, 2011).

In conclusion, nine reviews in this special issue provide valuable information on many of the important advances in the clinical application of DMPK and practical pharmaceuticals. We expect that this special issue will be helpful to understand recent progress of DMPK field for the new drug development.

REFERENCES

- Bae, S. K. and Shon, J.-H., Microdosing studies using accelerated mass spectrometry as exploratory investigational new drug trials. *Arch. Pharm. Res.*, 34, 1789-1797 (2011).
- Benet, L. Z. and Cummins, C. L., The drug efflux-metabolism alliance: biochemical aspects. *Adv. Drug Deliv. Rev.*, 50 Suppl 1, S3-S11 (2001).
- Benet, L. Z., Predicting drug disposition via application of a Biopharmaceutics Drug Disposition Classification System. *Basic Clin. Pharmacol. Toxicol.*, 106, 162-167 (2010).
- Choi, Y. H., Chin, Y. W., and Kim, Y. G., Herb-drug interactions: focus on metabolic enzymes and transporters. *Arch. Pharm. Res.*, 34, 1843-1863 (2011).
- DiMasi, J. A., Success rates for new drugs entering clinical testing in the United States. *Clin. Pharmacol. Ther.*, 58, 1-14 (1995).
- Han, H.-K., Role of transporters in drug interactions. *Arch. Pharm. Res.*, 34, 1865-1877 (2011).
- Kang, H. E. and Lee, M. G., Approaches for predicting human pharmacokinetics using interspecies pharmacokinetic scaling. *Arch. Pharm. Res.*, 34, 1779-1788 (2011).
- Kola, I. and Landis, J., Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.*, 3, 711-715 (2004).
- Kuppens, I. E., Breedveld, P., Beijnen, J. H., and Schellens, J. H., Modulation of oral drug bioavailability: from pre-clinical mechanism to therapeutic application. *Cancer Invest.*, 23, 443-464 (2005).
- Lee, I.-S. and Kim, D., Polymorphic metabolism by functional alterations of human cytochrome P450 enzymes. *Arch. Pharm. Res.*, 34, 1799-1816 (2011).
- Lee, K. S., Oh, S. J., Kim, H. M., Lee, K. H., and Kim, S. K., Assessment of reactive metabolites in drug-induced liver injury. *Arch. Pharm. Res.*, 34, 1879-1886 (2011).
- Masimirembwa, C. M., Bredberg, U., and Andersson, T. B., Metabolic stability for drug discovery and development: pharmacokinetic and biochemical challenges. *Clin. Pharmacokinet.*, 42, 515-528 (2003).
- Mitragotri, S. and Yoo, J.-W., Designing micro- and nanoparticles for treating rheumatoid arthritis. *Arch. Pharm. Res.*, 34, 1887-1897 (2011).
- Na, D. H., Ji, H. Y., Park, E. J., Kim, M. S., Liu, K.-H., and Lee, H. S., Evaluation of metabolism-mediated herb-drug interactions. *Arch. Pharm. Res.*, 34, 1829-1842 (2011).
- Yoo, H.-D. and Lee, Y.-B., Interplay of pharmacogenetic variations in ABCB1 transporters and cytochrome P450 enzymes. *Arch. Pharm. Res.*, 34, 1817-1828 (2011).