The aim of preclinical studies is to evaluate the safety and pharmacological effect of new drug entities through in vitro and in vivo laboratory animal testing. However, the validity of animal testing to predict drug efficacy and safety in humans is not always guaranteed because of the existence of species differences between experimental animals and humans. Thus in vitro studies using human materials, such as human liver microsomes, human hepatocytes and liver slices, and recombinant human enzymes or transporters, have also been used in the case of ADME testing for predicting human drug metabolism and pharmacokinetics. Although results obtained from those in vitro methods are valuable, they alone are unlikely to tell us how the variable processes of drug disposition will modulate the potency of the pharmacological activity of drugs in humans. One of the ways to overcome the difficulties is to use humanized animal models.

Up to now, transgenic humanized mouse models have been developed for phase I enzymes (CYP1A1/1A2, CYP2A6, CYP2A13/2B6/2F1, CYP2C9, CYP2C18/2C19, CYP2D6, CYP2D6/3A4, CYP2E1, CYP3A4, CYP3A7 and CYP3A4/3A5/3A7/3A43), and phase II enzymes (NAT2, UGT1A and UGT2B7) for the assessment of human drug metabolism, and xenobiotic receptors (AHR, PXR, CAR and PPARα) for the assessment of gene activation. As for transporters, transgenic humanized mouse models have been developed for ABCC2 and OATP1B1/1B3. Moreover, an advanced humanized mouse model introducing multiple drug metabolizing enzymes and xenobiotic receptor genes has also been developed for the assessment of their interplay.

In addition to genetically modified mouse models, chimeric mouse models with a humanized liver have been developed and applied for drug metabolism and pharmacokinetic studies. Although transgenic mouse models carry only one or two human genes, the chimeric model mice possess all phase I and II enzymes and transporters expressed in human liver. They produce human-specific drug metabolites, show induced expression of CYP enzymes in response to the administration of prototypical human-specific inducers, and show specific inhibition of various metabolic processes including CYP-mediated oxidations by prototypical inhibitors of human drug metabolism.

Recently chimeric mice have been applied not only for ADME but also for pharmacodynamic studies. Drug candidates for viral hepatitis have been an ideal target of study, since chimeric mice can be exclusively infected with hepatitis B and C viruses. New types of direct-acting antiviral agents and their combinations were successfully evaluated by the chimeric mice, and the results mimicked those of human clinical trials. Pharmacodynamic studies have also been performed for other hepatotropic infectious diseases using chimeric mice. In addition, immunodeficient mouse models engrafted with human hematopoietic stem cells were used to study PK/PD properties of thrombopoietin receptor agonists. Moreover, an immunodeficient mouse model engrafted with glucose-6-phosphate dehydrogenase deficient (G6PD) human red blood cells was applied to the assessment of the hemolytic toxicity of drugs. This model could be a useful tool to test drugs for their potential to cause hemolytic toxicity in G6PD populations.

Genetically modified or transgenic humanized mouse models have also been applied for pharmacodynamics studies. Promyelocytic leukemia-retinoic acid receptor α transgenic mouse responded to all-trans retinoic acid therapy, suggesting that this mouse model could be a surrogate model to test therapeutic agents for human acute myelogenous leukemia. A thrombopoietin receptor humanized mouse model was also used for a thrombopoietin receptor agonist to obtain an initial estimation of the concentration that would be required for therapeutic efficacy in clinics.

At present, no regulations or guidelines are required for the use of humanized mouse models in preclinical study; however, the models would be a useful tool providing more precise information for human PK/PD and toxicity prediction. As a matter of course, development of humanized mouse models is in the early stage and substantial efforts for functional improvement of human genes in the model should be required before practical use. Nonetheless, they may become an essential tool for preclinical studies by which the gap existing between experimental animals and humans could be bridged.

References


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