Drug-induced liver injury (DILI) is one of the major causes of liver injury. Idiosyncratic drug reactions do not occur in most patients at any dose, and they are often referred to as rare with an incidence of less than about 1/10,000. In drug development, unpredictable DILI is currently the major cause for discontinuations of new candidates in development or for withdrawals of drugs from the market. Such withdrawn drugs are generally known to produce reactive metabolites. The generation of reactive metabolites may be involved in the oxidation of cellular components or inhibition of normal cellular functions. Although many preclinical studies were performed, DILI still remained to be clarified. The mechanism would depend on three factors: (1) effect of metabolic detoxification, and metabolic activation; (2) pharmacogenetic and environmental factors; (3) immune-mediated reactions. These factors are extremely complex and vary greatly among individuals. Preclinical animal studies are still largely unsuccessful in predicting idiosyncratic DILI, as the immune-system is enormously complicated. For better understanding, a genetic polymorphism analysis by a target gene approach in patients who suffer DILI is valuable.

Recently, we tried to develop in vitro and in vivo preclinical experimental models to predict idiosyncratic DILI. Focusing on glutathione (GSH) scavenging of reactive intermediates, we developed a GSH synthetase-knockdown rat using a short hairpin RNA expressing adenovirus vector. Acute and sub-acute DILI of acetaminophen, flutamide, and diclofenac were successfully evaluated with high sensitivity. A superoxide dismutase 2-knockdown rat model was also established and evaluated. We established a cell-based assay system expressing CYP3A4 with GSH synthetase-knockdown in HepG2 cells which is useful for the prediction of CYP3A4-mediated cytotoxicity in preclinical drug development. CYP isforms (CYP2E1, CYP1A2 and CYP2C9)-expressing cytotoxicity systems were also established and used to evaluate drugs causing DILI.

DILI is occasionally accompanied by some immune reactions acting as danger signals. Immune-mediated DILI is recognized to cause an imbalance of differentiated CD4+ T cells. It has been known that halothane, an inhaled anesthetic, causes severe DILI in 1 in 30,000 patients. We recently demonstrated that IL-17 is involved in the halothane-induced liver injury in mice. IL-17 was also involved in α-naphthylisothiocyanate-induced liver injury. We also clarified that dicloxacillin-induced liver injury is mediated by Th2 dominant factors. Thus, progress has been made in clarifying the immune reactions in DILI. It is likely that animal models represent the best course of action to study immune-mediated DILI, but an in vitro cell-based HTS system should also be developed. Although difficulties exist in obtaining sufficient patient data and samples, extrapolation of the preclinical data must be confirmed in humans in the future.

References:

Biography
Dr. Tsuyoshi Yokoi has been a Professor of Drug Metabolism and Toxicology, Kanazawa University since 1997. He graduated from Gifu Pharmaceutical Univ Graduate School (1980) and was an Assis. Prof. of Gifu Univ (1980) and Tohoku Univ (1984), and an Assoc. Prof. of Hokkaido Univ (1990). He received the Ebert Prize (2008) from American Pharmaceutical Association, The Journal Award (2009) from Society of Toxicologic Pathology US and JSSX Award (2009).