

P231 Prediction of Drug-induced Liver Injury in Humans by Using Chimeric PXB-mice® with Highly Humanized Liver

Shin-Ichiro Nagatsuka , ADME & Tox. Research Institute, Sekisui Medical Co., Ltd., Tokai-mura, Ibaraki, Japan

Darina Hynes , ADME & Tox. Research Institute, Sekisui Medical Co., Ltd., Tokai-mura, Ibaraki, Japan

Shin-Ichi Ninomiya , ADME & Tox. Research Institute, Sekisui Medical Co., Ltd., Tokai-mura, Ibaraki, Japan

Masakazu Kakuni , PhoenixBio Co., Ltd., Higashihiroshima, Japan

Chise Tateno , PhoenixBio Co., Ltd., Higashihiroshima, Japan

Takashi Shimada , PhoenixBio Co., Ltd., Higashihiroshima, Japan

Yasushi Yamazoe , Division of Drug Metabolism and Molecular Toxicology, Graduate school of Pharmaceutical Sciences, Tohoku University, Sendai, Japan

Drug-induced liver injury (DILI) takes a significant position in the leading causes of withdrawal or black-box warning of a newly developed drug. In order to find out promising biomarkers for the early prediction of DILI in humans, omics approaches have been employed using in vivo (experimental animals, mainly rats) or in vitro (human hepatocytes or hepatoma cell lines) systems. However, there are significant species and in vitro/in vivo differences that make the prediction unreliable. We have been using chimeric PXB-mice®, in which more than 70% of hepatic parenchymal cells are replaced by human hepatocytes, for the toxicogenomic analyses of hepatotoxicants. This animal model, which mimics human-type drug metabolism and disposition, has a potential to bridge the gap between rodent-type and human-type livers and to explain the difference of in vivo and in vitro response of human hepatocytes against hepatotoxicant treatments. By using 23 different hepatotoxicants (acetaminophen, amiodarone, diclofenac, d-penicillamine, flutamide, erythromycin, valproate, sulindac, indomethacin, perhexilene, methyldopa, amitriptyline, tamoxifen, acetylsalicylic acid, methotrexate, demeclocycline, hydrazine, hydroxyurea, imipramine, orotic acid, troglitazone, tolcapone and ibufenac) and 10 non-hepatotoxicants, we have analyzed changes in hepatic gene expression in PXB-mice®. These drugs were orally administered to PXB-mice® three-times daily at relatively high doses (ca. 20% of reported LD50), followed by hepatic total RNA preparation and gene expression analyses using oligonucleotide microarray chips. For each of hepatotoxicants and non-hepatotoxicants treatments, positive and negative incidents of significant change in expression were analyzed, e.g. when statistically significant induction (or reduction) of a gene expression occurred in 8 out of 10 tested hepatotoxicants, the positive incident was expressed as 80% and negative incident was expressed as 20%. For the prediction of DILI susceptibility due to the drug-treatment, true positive rate was calculated for each gene as the product of positive incident in hepatotoxicant treatment and negative incident in non-hepatotoxicant treatment. Genes which showed the true positive rate of larger or equal to 0.5 were selected as biomarkers for DILI. About 1000 genes were extracted as biomarker candidates for DILI prediction. The method for score calculation for DILI prediction and lot-to-lot difference of chimeric mice on the effectiveness of score method will be discussed.