

Evaluation of Score Methods for the Prediction of Drug-induced Liver Injury in Humans by Using Chimeric PXB-mice[®] with Highly Humanized Liver.

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Of the leading causes of withdrawal of a newly developed drug, drug-induced liver injury (DILI) takes a significant position. Toxicogenomic approaches have been employed using *in vivo* (experimental animals, mainly rats) or *in vitro* (human hepatocytes or hepatoma cells) systems in order to find of promising biomarkers for DILI. We have used 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, 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 hepatotoxicants. By using 20 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) and seven non-hepatotoxicants, we have analyzed changes in hepatic gene expression in rats and PXB-mice[®]. These drugs were orally administered to rats and PXB-mice[®] three-times daily at high doses (ca. 20% of reported LD₅₀), followed by hepatic total RNA preparation and gene expression analyses using oligonucleotide microarray chips. Several marker gene candidates, which specifically responded to the hepatotoxicants, were extracted and evaluation of DILI susceptibility due to the drug-treatment was analyzed by using two different score methods. Lot-to-lot difference of chimeric mice on the effectiveness of score methods will be discussed.