Identification of MicroRNA as Possible Risk Marker for Drug-induced Liver Injury using Chimeric PXB-Mouse® with Highly Humanized Liver

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Purpose. Recently, microRNAs (miRNAs) have emerged as risk marker of drug-induced liver injury (DILI) in clinical. We developed a novel method to identify miRNAs as possible risk markers for DILI. We analyzed expression of miRNAs which fluctuated under the treatment of drugs with relatively higher rate of hepatotoxic incidents (hTOX) and those with negligible hepatotoxic incidents (non-hTOX) using chimeric mice with highly humanized liver.

Methods. We selected 8 hTOX (Amiodarone, Acetaminophen, Ticlopidine, Terbinafine, Methotrexate, Valproate, Diclofenac, Benzbromarone) drugs and 8 non-hTOX (Dipyridamole, Cefalexin, Eperisone, Propranolol, Pirenzepine, Trihexyphenidyl, Dapagliflozin, Bumetanide) drugs based on information shown in the package insert. The drugs were administered to chimeric mice with humanized liver (PXB-mice®: PhoenixBio Co., Ltd.) three-times daily. Hepatic miRNAs were analysed using GeneChip® miRNA 3.0 array (Affymetrix Inc.), in order to select miRNAs that increased by 1.5 times or more in hTOX drugs and not increased in the non-hTOX drugs.

Results & Conclusion. We found 7 miRNAs (miR-10a, miR-183, miR-557, miR-1202, miR-3065-5p, miR-3195 and miR-4535) that increased only in hTOX treatments and not in non-hTOX treatments. Previous studies revealed the role of miR-10a, miR-183 and miR-1202 in non-hepatic tissues. This is the first report showing these 7 miRNAs might be involved in DILI. The present method is useful for discovery of new miRNAs as risk marker of DILI without clinical trials.