Identification of Possible Biomarker Genes for Drug-induced Liver Injury using Chimeric PXB-Mouse® with Highly Humanized Liver

Hatsune Enomoto¹,²), Hidehisa Tachiki¹), Takashi Shimada³), Shin-Ichiro Nagatsuka⁴) and Mikiro Nakashima²)

¹)Research and Development Division, Towa Pharmaceutical Co., Ltd., Kyoto, Japan, ²)Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, ³)PhoenixBio Co., Ltd., Hiroshima, Japan, and ⁴)ADME & Tox. Research Institute, Sekisui Medical Co., Ltd., Ibaraki, Japan

Purpose. Previously we reported "T-LEX® method" involving toxicogenomic analyses of humanized liver obtained from chimeric mice to evaluate bioequivalency of the risk of drug-induced liver injury (DILI). Many generic drugs and originator products have been subjected to the T-LEX® method. In this study, we analyzed gene expression which fluctuated with hepatotoxic drugs to identify possible biomarkers in DILI using chimeric mice.

Methods. From Towa Pharmaceutical Co. products, we selected 8 drugs with relatively higher rate of hepatotoxic incidents (hTOX) and 8 drugs with negligible hepatotoxic incidents (non-hTOX) based on information shown in the package insert. The pharmaceutical products were suspended in 0.5% methylcellulose and orally administered to chimeric mice with humanized liver (PXB-mice®: PhoenixBio Co., Ltd.) three times daily. Hepatic total RNA was extracted and subjected to gene expression analyses using GeneChip® Human Genome U133 plus 2.0 Array (Affymetrix Inc.). Genes that showed statistically significant increase by 1.5 times or more and decrease by 2/3 or less were screened to obtain DILI markers.

Results & Conclusion. Cell division cycle 27 (CDC27) increased within all of 8 hTOX treatments but not in non-hTOX treatments. Other possible biomarkers such as metallothionein 1M (MT1M), solute carrier family 3 (SLC3A1), angiopoietin-like 3 (ANGPTL3), hepcidin antimicrobial peptide (HAMP), interleukin 8 (IL8) and leptin receptor (LEPR) showed higher rate of significant increase in hTOX treatments but not in non-hTOX treatments. These possible biomarkers might be of use to select pharmaceutical products and/or excipients with lower risk of DILI.