S11-3 Prediction of drug metabolism in humans by using CYP3A-HAC mice

◯Kaoru KOBAYASHI[1], Kazuma TOMIZUKA[2], Yasuhiro KAZUKI[3], Mitsuo OSHIMURA[3,4], Kan CHIBA[1]

[1]Graduate School of Pharmaceutical Sciences, Chiba University, [2]Innovative Drug Research Laboratories, Kyowa Hakko Kirin Co., Ltd., [3]Graduate School of Medical Sciences, Tottori University, [4]Chromocenter Inc.

CYP3As-humanized mice were constructed by human artificial chromosome (HAC) vector system. The CYP3A-HAC mice have the human *CYP3A* gene cluster (*CYP3A4*, *CYP3A5*, *CYP3A7*, *CYP3A43* genes and their essential regulatory regions). In the CYP3A-HAC mice, CYP3A4 and CYP3A5 are mainly expressed in both liver and intestine at mRNA levels. Hepatic CYP3A4 mRNA levels in CYP3A-HAC mice were markedly increased by treatment with typical CYP3A inducers, pregnenolone 16 alpha-carbonitrile (PCN). Hepatic CYP3A4 mRNA levels in CYP3A-HAC mice without mouse *Cyp3a* genes (CYP3A-HAC/KO mice) were also markedly increased by PCN treatment. In the CYP3A-HAC/KO mice, CYP3As were expressed in both liver and intestine at protein levels and the expression levels were increased by PCN treatment. Metabolic activities of a CYP3A substrate, triazolam, in hepatic and intestinal microsomes of CYP3A-HAC/KO mice treated with PCN were comparable to those in hepatic and intestinal microsomes of humans. In conclusion, CYP3A-HAC/KO mice were first CYP3As-humanized mice expressing CYP3As in both liver and intestine. In addition, metabolic functions of CYP3A enzymes in CYP3A-HAC/KO mice treated with PCN were comparable to those of humans. In the development of new drugs, the CYP3A-HAC/KO mice would be useful for the estimation of CYP3As-mediated metabolism in humans.