

## STUDY ON SPECIES DIFFERENCES OF DRUG METABOLISM IN CHIMERIC MICE WITH HUMAN AND RAT HEPATOCYTES

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Humanized model animals are needed for prediction of *in vivo* human drug pharmacokinetics, metabolic disposition, safety, and clinical efficacy of anti-viral agents, and as a source of biological materials for *in vitro* studies. Through transplantation, we have established strains of chimeric mice with humanized liver (human-chimeric mice) in which more than 80% of the liver is repopulated with human hepatocytes<sup>1</sup>. Human-chimeric mice express major human cytochrome P450s (CYPs) species and major human phase II enzymes in the liver, and the expression levels are similar to those in humans<sup>2</sup>. Previously, we compared the drug-metabolizing ability of human-chimeric mice and humans by evaluating the absorption, metabolism and excretion of *S*-warfarin. The data obtained from human-chimeric mice showed good agreement with reported human data<sup>3</sup>.

We recently produced rat hepatocyte-engrafted chimeric mice (rat-chimeric mice). We then conducted comparative metabolism studies in human-chimeric mice and rat-chimeric mice using the model drugs diazepam, zaleplon (ZAL) and M-5 (amino derivative metabolite of 5-*n*-butyl-7-(3,4,5-trimethoxybenzoylamino)pyrazolo[1,5-*a*]pyrimidine, OT-7100 with potential analgesic effect), which were reported to show marked species differences in their metabolic pathways. In preclinical ADME studies, rats are generally used as an *in vivo* model, and we aimed in this study to clarify the relationship of the pharmacokinetics and metabolism in rat-chimeric mice to those in rats. Diazepam is a psychoactive drug, which undergoes either *N*-dealkylation by CYP2C19 to afford nordiazepam, or 3-hydroxylation by CYP3A4 to afford temazepam in humans, whereas in rats it is metabolized to oxazepam and polar 3-hydroxylated, *N*-demethylated, and *p*-hydroxylated metabolites, chiefly catalyzed by CYP3A2, CYP2C11, and CYP2D1, respectively<sup>4, 5</sup>. ZAL is a non-benzodiazepine sedative-hypnotic agent used for the treatment of insomnia. Preclinical studies have shown that the major metabolite of ZAL in humans is aldehyde oxidase-generated 5-oxo-ZAL, an aromatic ring oxidation product at the position adjacent to the nitrogen atom of the pyrimidine ring, while in mice and rats, it is *N*-desethyl-ZAL<sup>6</sup>. The difference in the metabolic functions of human and rat CYP1A2 is thought to be responsible for the human-specific metabolic activation of M-5. Human CYP1A2 catalyzes only C-3 hydroxylation of M-5. However, rat CYP1A2 catalyzes both C-6 and C-3 hydroxylation of M-5, as well as unknown metabolite formation<sup>7</sup>. The results from the two strains of chimeric mice well reflect the reported human and rat data.

In conclusion, human-chimeric and rat-chimeric mice are useful tool for examination of species differences of pharmacokinetics and disposition.

### References:

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