Abstracts of poster presentations at the DDT World Congress

1) Toxicogenomics in Flutamide-treated Rats and Chimeric PXB-mice with highly humanized liver

Chimeric PXB-mouse with highly humanized liver is a unique animal model to mimic human-type drug metabolism. This animal model has the potential to explain the difference of drug-induced hepatotoxicity in rodents and humans. Flutamide, which causes idiosyncratic hepatotoxicity in humans, was used to examine changes in hepatic gene expression in rats and PXB-mice. After a single oral administration of 300mg/kg flutamide to rats and PXB-mice, hepatic gene expression profiles were analyzed by using oligonucleotide microarray. In nuclear receptor regulated genes such as aryl hydrocarbon receptor signaling or oxidative stress response, genes responsible for xenobiotic metabolism were strongly induced in flutamide-treated rats. In flutamide-treated PXB-mice, however, induction of such genes was very weak. In apoptotic pathway, gene expression profiles in rats and PXB-mice were in an inverse relationship. These results suggest species difference of flutamide-induced heptocelluar injury and its regeneration processes in rodents and humans.

Take home message:
Flutamide-induced changes in hepatic gene expression in various biological pathways were analyzed in rats and chimeric mice with highly humanized liver.

Corresponding Author:
Takashi Shimada (PhoenixBio Co. Ltd.)

Additional authors:
1) Shin-ichiro Nagatsuka, (Sekisui Medical ADME & Tox. Research Institute)
2) Gaku Onishi, (Sekisui Medical ADME & Tox. Research Institute)
3) Shin-ichi Ninomiya (Sekisui Medical ADME & Tox. Research Institute)
4) Masakazu Kakuni (PhoenixBio Co. Ltd.)
5) Chise Tateno-Mukaidani (PhoenixBio Co. Ltd.)

2) Retinopathy induced in rats by BAC transgenics of a human derived rhodopsin gene mutant

Retinitis pigmentosa (RP) represents the most common mendelian degenerative retinopathy of man, involving death of rod photoreceptors, cone cell degeneration, retinal vessel attenuation and pigmentary deposits. To better understand the functional and structural role of rhodopsin in the pathogenesis of retinal disease, we generated a [P347L]rhodopsin mutant BAC transgenic construct harboring C-to-T transition into the exon 5 of the rat rhodopsin gene locus and transgenic rats carrying the recombinant BAC DNA. [P347L]Rho rats do not elaborate rod outer segments, losing their photoreceptors within 4 months, hence there is no rod ERG response in 4-month-old animals. These animals provide a useful genetic model on which to analyze the human mutant opsin pathology, and for assessing the therapeutic potential of introducing functional rhodopsin genes into degenerating retinal tissues or the transplantation of an artificial retina. The recombineering-based BAC transgenic rats will become promising tools for drug discovery and in vivo screening.

Take home message
We generated a novel transgenic rat model for a retinitis pigmentosa which carries [P347L] rhodopsin mutant recombinant BAC DNA.

Corresponding Author:
Akira Shiota (PhoenixBio Co. Ltd.)

Additional Authors:
Mineo Kondo (Department of Ophthalmology, Nagoya University School of Medicine)
Masatsugu Ueda (PhoenixBio Co. Ltd.)