

Ingenuity[®] Science Spotlight:

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Underlying Mechanisms of Pharmacology and Toxicity of a Novel PPAR Agonist Revealed Using Rodent and Canine Hepatocytes

Yin Guo, Robert A. Jolly, Bartley W. Halstead, Thomas K. Baker, John P. Stutz, Melanie Huffman, John N. Calley, Adam West, Hong Gao, George H. Searfoss, Shuyu Li, Armando R. Irizarry, Hui-rong Qian, James L. Stevens and Timothy P. Ryan. *Toxicological Sciences* 96(2), 294–309 (2007).

<http://toxsci.oxfordjournals.org/cgi/content/abstract/96/2/294>

A research team led by Timothy Ryan in the Department of Investigative Toxicology at Eli Lilly set out to understand the mechanisms underlying species differences in the pharmacological and toxicological responses to a novel PPAR agonist, LY465608, observed *in vivo*. IPA analysis of global gene expression changes induced by LY465608 in dog and rat hepatocytes identified species-specific abnormalities in toxicity-related pathways and cellular processes. The novel insights generated by IPA helped the team propose a mechanism of species-specific toxic effects, which may have a significant impact on the development of compounds to treat metabolic disorders.

Primary dog and rat hepatocytes treated with the novel PPAR agonist LY465608 were used as an *in vitro* model to explore mechanisms of toxicity. IPA Functional Analysis of global drug-induced gene expression changes was used to understand which biological functions were most significantly and differentially affected by compound treatment in rat and dog hepatocytes. In rat hepatocytes, IPA identified Lipid Metabolism as the most significantly perturbed process, a finding that was consistent with the known pharmacology of LY465608. In contrast, IPA identified Cell Death as the most significantly perturbed biological process in dog hepatocytes, a finding that was consistent with the liver toxicity observed in LY465608-treated dogs. Importantly, the team found that expression changes in individual genes were subtle, but when viewed collectively in the context of pathways and functions, these data pointed to specific mechanisms of toxicity.

IPA analysis of expression-based studies, in combination with biochemical studies, provided the Lily team with a better understanding of the differential pharmacology and toxicity observed in rats and dogs in response to a novel PPAR agonist, and represents a valuable approach to future development of compounds to treat metabolic disorders.