

Poster: free communications

## Human HepaRG<sup>®</sup> hepatocytes for the detection of toxic metabolic pathways

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Human HepaRG<sup>®</sup> cells from a human hepatic cell line are able to differentiate *in vitro* into hepatocyte-like cells and display hepatic functions: HepaRG<sup>®</sup> cells exhibit (i) a hepatocyte-like morphology; (ii) a metabolic competence for phase I and II enzyme activities; (iii) a concomitant expression of hepatic influx and efflux transporters (Le Vee et al., 2006); (iv) a good response to standard inducers of drug metabolizing enzymes (Aninat et al., 2006; Le Vee et al., 2007; Kanebratt et al., 2008).

In this study, HepaRG<sup>®</sup> cells were used to set up a cytotoxicity screening protocol that modulates the metabolic pathways and uses rezasurin transformation as a single toxicity endpoint. Three model xenobiotics, flutamide, tamoxifen and amitriptyline were chosen to investigate the relevance of the protocol. Differentiated HepaRG<sup>®</sup> hepatocytes were produced following our standard process. Their metabolic pathways were induced or inhibited as follows: CYP1A2 was induced by omeprazole and DMSO. CYP1A2, CYP3A4, phase II enzymes like NAT were inhibited by co-incubation of furafyllin, ketoconazole, salicylamide or acetaminophen with each xenobiotic.

A comparison of the results obtained with HepaRG<sup>®</sup> cells, with primary culture of human hepatocytes or with HepG2 cells (+ or - S9) was also done.

We found: (i) The specific cytotoxic profiles of each xenobiotic were comparable in human hepatocytes, HepaRG<sup>®</sup> cells and HepG2 cells + S9; (ii) The addition of the CYP inhibitors or the phase II enzymes inhibitors either increased or decreased the toxicity of the compounds as was expected from the literature (Seva et al., 2007) and (iii) from our human hepatocyte data.

These results suggest that HepaRG<sup>®</sup> hepatocytes are a promising tool for the screening of toxic metabolism pathways.

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