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Guest editorial:

HIGHLIGHT REPORT: METABOLOMICS IN HEPATOTOXICITY TESTING

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Hepatotoxicity is one of the most frequent forms of systemic toxicity of drugs and a leading cause for drug withdrawal from the market. To improve the possibilities to predict hepatotoxicity, Tzutzuy Ramirez and colleagues from BASF in Ludwigshafen recently tested a metabolomics based *in vitro* system (Ramirez et al., 2017). They exposed HepG2 cells to 35 test compounds and applied LC-MS/MS as well as GC-MS to quantify 89 metabolites in the culture medium supernatant and 194 intracellular metabolites. A main focus was to determine quality criteria, such as reproducibility and concentration dependency of the test system. The relative standard deviations of technical replicates were in the range of 5-10 %, while controls from different days were between 10 and 15 % (Ramirez et al., 2017). This is an excellent reproducibility for an *in vitro* system. Moreover, convincing concentration-response relationships were obtained and metabolite patterns could be associated with specific mechanisms of toxicity, such as peroxisome proliferation and liver enzyme induction or inhibition (Ramirez et al., 2017). Therefore, the HepG2 metabolomics technique represents a promising new candidate in the field of *in vitro* hepatotoxicity prediction. Limitations are that the HepG2 cells show major metabolic differences compared to human hepatocytes. Moreover, the present study did not yet include a systematic comparison of negative and positive controls at *in vivo* relevant concentrations, which remains a challenge for the future.

Currently, mechanisms of hepatotoxicity represent a major focus in toxicological research (Kyriakides et al., 2016; Ghallab, 2015c; Ramachandran et al., 2015; Chen et al., 2015; Campos et al., 2014; Hammad et al., 2014; Hassan, 2016; Stöber, 2015). Despite progress in the field of stem cell research (Gómez-Lechón and Tolosa, 2016; Godoy et al., 2016; Cameron et al., 2015) and studies with cell lines (Tolosa et al., 2015; Hewitt et al., 2007; Godoy et al., 2013), primary hepatocytes still remain a gold standard (Reif et al., 2015; Grinberg et al., 2014; Stöber, 2015; Ghallab, 2015a; Arbo et al., 2016). Moreover PBPK modeling (Ghallab, 2015b; Reif et al., 2017; Thiel et al., 2015) and spatio-temporal models (Ghallab et al., 2016; Vartak et al., 2016; Jansen et al., 2017; Friebel et al., 2015) have supported our understanding of the mechanisms of liver toxicity. The next year will show whether the novel HepG2 metabolomics assay can be integrated into useful test batteries for a better prediction of human hepatotoxicity.

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