

Guest editorial:

TRANSCRIPTOME BASED DIFFERENTIATION OF HARMLESS, TERATOGENETIC AND CYTOTOXIC CONCENTRATION RANGES OF VALPROIC ACID

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Currently, much effort is invested in the development and optimization of *in vitro* systems for toxicity testing (Godoy et al., 2013; Sisnaiske et al., 2014; Grinberg et al., 2014; Stewart and Marchan, 2012; Hengstler et al., 2012). However, one major problem in this field of research is the difficulty to link observations made *in vitro* to adverse effects *in vivo* (Ghallab, 2013; Bolt, 2013). To come closer to a solution of this fundamental problem, Waldmann et al. (2014) performed a study in which they systematically analysed concentration-dependent transcriptome alterations of valproic acid in relation to human blood concentrations known to cause teratogenic effects. Waldmann and colleagues used human stem cells that differentiate to neuronal precursor cells during a 6-days period, a test system recently developed for developmental neurotoxicity testing (Krug et al., 2013; Weng et al., 2014; Balmer et al., 2014; Zimmer et al., 2014; Leist et al., 2013). Based on the results of genome-wide expression alterations the authors identified three concentration ranges: (1) A range of tolerance below 25 μM valproic acid, where no gene expression deregulation was observed; (2) a range of deregulation between 15 and 550 μM valproic acid. In this concentration range numerous genes involved in regulation of neuronal development were deregulated. Interestingly, this represents the range of VPA concentrations in blood, where

developmental toxicity has been observed in humans. (3) The concentration range above 800 μM valproic acid, where cytotoxic effects were observed. However, such high concentrations are usually not obtained in patients.

Currently, developmental toxicity testing *in vitro* represents a cutting-edge topic, because animal tests are extremely cost- and labor- intensive (Strikwold et al., 2013; Stern et al., 2014; Driessen et al., 2013; Cordova et al., 2013; Hoelting et al., 2013; Tonk et al., 2013; van Thriel and Stewart, 2012; Mariussen, 2012; Frimat et al., 2010). However, only few studies systematically compared how concentration ranges that induce (or do not induce) adverse effects *in vivo* influence biomarkers in *in vitro* systems. The study of Waldmann et al. (2014) sets an example how this type of study can be designed. Of course, future work is required to see whether the good *in vitro/in vivo* correlation observed for valproic acid will be confirmed for further chemicals known to induce developmental toxicity.

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