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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.

REFERENCES

Balmer NV, Klima S, Rempel E, Ivanova VN, Kolde R, Weng MK, et al. From transient transcriptome responses to disturbed neurodevelopment: role of histone acetylation and methylation as epigenetic switch between reversible and irreversible drug effects. Arch Toxicol. 2014;88:1451-68. doi: 10.1007/s00204-014-1279-6.

Bolt HM. Transcriptomics in developmental toxicity testing. EXCLI J. 2013;12:1027-9.

Cordova FM, Aguiar AS Jr, Peres TV, Lopes MW, Gonçalves FM, Pedro DZ, et al. Manganese-exposed developing rats display motor deficits and striatal oxidative stress that are reversed by Trolox. Arch Toxicol. 2013;87:1231-44.

Driessen M, Kienhuis AS, Pennings JL, Pronk TE, van de Brandhof EJ, Roodbergen M, et al. Exploring the zebrafish embryo as an alternative model for the evaluation of liver toxicity by histopathology and expression profiling. Arch Toxicol. 2013;87:807-23.

Frimat JP, Sisnaiske J, Subbiah S, Menne H, Godoy P, Lampen P, et al. The network formation assay: a spatially standardized neurite outgrowth analytical display for neurotoxicity screening. Lab Chip. 2010;10:701-9.

Ghallab A. In vitro test systems and their limitations. EXCLI J. 2013;12:1024-6.

Godoy P, Hewitt NJ, Albrecht U, Andersen ME, Ansari N, Bhattacharya S, et al. Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME. Arch Toxicol. 2013;87:1315-530. doi: 10.1007/s00204-013-1078-5.

Grinberg M, Stöber RM, Edlund K, Rempel E, Godoy P, Reif R, et al. Toxicogenomics directory of chemically exposed human hepatocytes. Arch Toxicol. 2014;88:2261-87. doi: 10.1007/s00204-014-1400-x.

Hengstler JG, Marchan R, Leist M. Towards the replacement of in vivo repeated dose systemic toxicity testing. (Highlight report). Arch Toxicol 2012;86:13-5.

Hoelting L, Scheinhardt B, Bondarenko O, Schildknecht S, Kapitza M, Tanavde V, et al. A 3-dimensional human embryonic stem cell (hESC)-derived model to detect developmental neurotoxicity of nanoparticles. Arch Toxicol. 2013;87:721-33. doi: 10.1007/s00204-012-0984-2.

Krug AK, Kolde R, Gaspar JA, Rempel E, Balmer NV, Meganathan K, et al. Human embryonic stem cell-derived test systems for developmental neurotoxicity: a transcriptomics approach. Arch Toxicol. 2013;87:123-43.

Leist M, Ringwald A, Kolde R, Bremer S, van Thriel C, Krause KH, et al. Test systems of developmental toxicity: state-of-the art and future perspectives. Arch Toxicol. 2013;87:2037-42.

Mariussen E. Neurotoxic effects of perfluoroalkylated compounds: mechanisms of action and environmental relevance. Arch Toxicol. 2012;86:1349-67.

Sisnaiske J, Hausherr V, Krug AK, Zimmer B, Hengstler JG, Leist M, et al. Acrylamide alters neurotransmitter induced calcium responses in murine ESC-derived and primary neurons. Neurotoxicology. 2014;43:117-26.

Stern M, Gierse A, Tan S, Bicker G. Human Ntera2 cells as a predictive in vitro test system for developmental neurotoxicity. Arch Toxicol. 2014;88:127-36. doi: 10.1007/s00204-013-1098-1.

Stewart JD, Marchan R. Current developments in toxicology. EXCLI J. 2012;11:692-702.

Strikwold M, Spenkelink B, Woutersen RA, Rietjens IM, Punt A. Combining in vitro embryotoxicity data with physiologically based kinetic (PBK) modelling to define in vivo dose-response curves for developmental toxicity of phenol in rat and human. Arch Toxicol. 2013;87:1709-23.

Tonk EC, de Groot DM, Wolterbeek AP, Penninks AH, Waalkens-Berendsen ID, Piersma AH, et al. Developmental immunotoxicity of ethanol in an extended one-generation reproductive toxicity study. Arch Toxicol. 2013;87:323-35.

Van Thriel C, Stewart JD. Developmental neurotoxicity: the case of perfluoroalkylated compounds. Arch Toxicol. 2012;86:1333-4.

Waldmann T, Rempel E, Balmer NV, König A, Kolde R, Gaspar JA, et al. Design principles of concentration-dependent transcriptome deviations in drug-exposed differentiating stem cells. Chem Res Toxicol. 2014;27:408-20. doi: 10.1021/tx400402j.

Weng MK, Natarajan K, Scholz D, Ivanova VN, Sachinidis A, Hengstler JG, et al. Lineage-specific regulation of epigenetic modifier genes in human liver and brain. PLoS One. 2014;9(7):e102035.

Zimmer B, Pallocca G, Dreser N, Foerster S, Waldmann T, Westerhout J, et al. Profiling of drugs and environmental chemicals for functional impairment of neural crest migration in a novel stem cell-based test battery. Arch Toxicol. 2014;88:1109-26.