Developmental neurotoxicity testing with human embryonic stem cell-derived in vitro systems: the novel FP7 ESNATS tests are available

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Reproductive toxicity testing is a cutting-edge topic in toxicology (van Thriel and Stewart 2012; Coccini et al. 2012; Zimmer et al. 2012). Clearly, more accurate and faster test systems are required (Kadereit et al. 2012; van Thriel et al. 2012; Frimat et al. 2010). Therefore, the EU has initiated the FP7 research consortium, ESNATS, that aims at developing toxicity in vitro test systems based on human embryonic stem cells (hESC). In this issue of the Archives of Toxicology, the ESNATS consortium presents for the first time its novel hESC-based systems (Krug et al. 2012; Meganathan et al. 2012): the ESNATS tests for developmental neurotoxicity are finally available! The authors established protocols, which re-capitulate the different periods of differentiation of stem cells on the path to neurons: (1) establishment of the germ layers (2) neural induction (3) early neurogenesis, and (4) neurite growth. Differentiating embryonic stem cells in vitro show similar waves of gene expression as during embryonic development in vivo (Gaspar et al. 2012; Krug et al. 2012; Zimmer et al. 2011a, b). Therefore, transcriptomics represents a promising approach to detect perturbations of normal gene expression in differentiating stem cells. As a proof of concept, the authors tested two model compounds known to cause reproductive toxicity and developmental neurotoxicity in humans, namely valproic acid and methyl mercury. Indeed, both compounds caused characteristic and specific gene expression alterations in the novel test systems in contrast to D-mannitol that was used as a negative control compound. Only little overlap between genes

altered by valproic acid and methyl mercury was obtained. Interestingly, analysis of overrepresented transcription factor-binding sites demonstrated a large overlap of transcription factors involved in the response to both compounds. This led the authors to propose a novel concept of a ‘common response’ and ‘compound specific responses’. Clearly, further compounds have to be tested in the future to confirm the novel hypothesis. The manuscript of Krug and colleagues marks a historical milestone in reproductive and neurotoxicity in vitro testing. However, the hunt for the best test systems and most predictive signatures has only just begun.

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