EXCLI Journal 2013;12:1027-1029 – ISSN 1611-2156
Received: December 10, 2013, accepted: December 11, 2013, published: December 12, 2013

Editorial:

TRANSCRIPTOMICS IN DEVELOPMENTAL TOXICITY TESTING

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Reproductive toxicity testing is one of the most complex, expensive and labor intensive fields of toxicology (Leist et al., 2013; Wobus and Löser, 2011; Hengstler, 2011; Krause et al., 2013). The catastrophic consequences of thalidomide-induced teratogenesis (Schmahl et al., 1996; Sterz et al., 1987) drastically demonstrate the fundamental importance of reliable developmental toxicity tests for human safety (van Thriel and Stewart, 2012a, b; van Thriel et al., 2012; Frimat et al., 2010; Kadereit et al., 2012; Marques et al., 2012; Duydu et al., 2011). Currently, large efforts are undertaken to establish in vitro test systems of developmental toxicity (Krug et al., 2013; Strikwold et al., 2013; Seiler et al., 2011; Bolt, 2013). Recently, human embryonic stem cell based in vitro test systems have been established that recapitulate critical periods of human early development (Krug et al., 2013; Zimmer et al., 2011;2012). During this differentiation period the differentiating stem cells are exposed to test compounds to study their influence on genome-wide expression patterns. Evaluation of the deregulated genes is usually based on methods of pattern analysis and identification of overrepresented motifs which initially has been introduced for characterization of tumor tissue (Kammers et al., 2011; Lohr et al., 2012; Botling et al., 2013; Schmidt et al., 2008, 2012; Cadenas et al., 2010). These studies have clearly shown that compounds known to induce developmental toxicity cause different alterations in gene expression than negative control compounds (Krug et al., 2013; Krause et al., 2013). Despite of this success stem cell based in vitro studies are still not broadly applied in routine toxicity testing. The majority of currently published studies are still performed in vivo (e.g. Gao et al., 2012; Saegusa et al., 2012; Ogawa et al., 2012; Romano et al., 2012; Lim et al. 2007; Burns and Korack, 2012; Shiraki et al., 2012; Balansky et al., 2012). Of course in vitro systems still have the limitation that it is difficult to derive NOAELS (Godoy et al., 2013). Although currently large efforts are undertaken to define in vivo relevant concentrations for in vitro testing (Mielke et al., 2011) and to correlate in vitro and in vivo data (Heise et al., 2012; Schug et al., 2013) the use of in vitro systems in the risk evaluation process is still controversial. Their application for harzard identification and to filter problematic compounds is more generally accepted. Although the recently published transcriptomic studies in developing stem cells represent a critical progress they still leave some important questions open:

- How are the compound induced gene expression alterations linked to adverse effects? Which expression responses represent reversible 'harmless' efforts of the cells to reestablish their equilibrium? Which genes, in contrast, indicate mechanisms leading to reversible consequences?
- What is the optimal concentration range for transcriptomics studies? Is it acceptable to use the EC_{10} as practiced

in most studies? Or do already slightly cytotoxic concentrations induce cell death associated expression signatures which dilute the specific sigals?

- Do differentiating embryonic stem cells in vitro show waves of development with susceptible periods similar to the in vivo situation?

Answers to these critical questions would certainly improve the general acceptance of the recently established FP7 ESNATS in vitro test systems (Bolt, 2013; Leist et al., 2013) in developmental toxicity.

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