Dermatotoxicological and other Safety Testing Methods without Animals – State November 2013

Session 3: New challenges for toxicological safety testing

3D in vitro methods for developmental neurotoxicity testing

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As intelligence is one of the most important capitals for society, protection of developing brains against any harm is desirable. The current standard method for testing of compounds for developmental neurotoxicity (DNT) is the rat in vivo test. To study DNT in the rat it is very expensive, time consuming and the predictivity for humans is questionable. Therefore, we have developed an in vitro method for DNT testing which is based on human neurospheres. Such neurospheres are three dimensional (3D) cell culture models consisting of neural progenitor cells (NPCs) which proliferate in culture and - under differentiating conditions – migrate and differentiate into neurons and glia cells. Thereby, they mimic the very basic processes of brain development in vitro: proliferation, migration and differentiation of premature brain cells.

We tested the effects of a variety of compounds on proliferation, migration, differentiation and viability of NPCs. Moreover, we compared data of human neurospheres to results we gained in rodent NPCs. This comparison allows an inter-species comparison of toxicodynamics. In the case of dissimilarities in effects of compounds across species we investigate the underlying signaling pathways driving compound-dependent disturbance of neurodevelopmental processes. Our results indicate that neurospheres can distinguish between positive and negative test compounds and that a variety of pathways are differentially expressed across species causing species-specific sensitivities towards different substances. Moreover, we can utilize such 3D systems for DNT testing in a medium-throughput system. More data is needed to understand to which extent such 3D systems reflect processes of human developing brains in vivo.

In summary, human and rodent neurospheres might be suitable 3D in vitro systems for assessing toxic potentials of compounds on neurodevelopment or identify compounds which are neuroprotective.