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EDITORIAL

Highlight report: pluripotent stem cells in translational research

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Recently, Nina Kramer and colleagues from Vienna Medical University have published a state-of-the-art review about pluripotent stem cells in translational research (Kramer et al. 2016). Currently, many drug development programs use iPSC from patients and differentiate them to the cell type of interest to test whether drug candidates have an influence on the disease phenotype. One example of the recent developments is the eTau antibody for treatment of Alzheimer's disease or therapies of macular degeneration (reviewed in Kramer et al. 2016; Mullard 2015).

In toxicology, pluripotent stem cells are frequently applied in developmental toxicity testing (Li et al. 2016; Kumar et al. 2015; Rempel et al. 2015). Typically, pluripotent cells are exposed to test compounds during their differentiation processes, e.g., to the three germ layers or to neuronal cells (Shinde et al. 2015; Waldmann et al. 2014). This type of testing allows the sensitive identification of compounds that interfere with developmental processes (Balmer et al. 2014).

In contrast, the use of stem cell-derived mature cells, e.g., hepatocytes or neurons for evaluation of organ toxicity, still faces major challenges (Hammad et al. 2014a; Godoy et al. 2013; Hewitt et al. 2007). It has become clear that stem cell-derived hepatocyte-like cells do not achieve a fully mature status (Godoy et al. 2015; Verhulst et al. 2015; Rowe et al. 2013). This is of relevance for toxicological tests since many drug-metabolizing enzymes in stem cell-derived hepatocyte-like cells do not reach the levels of primary hepatocytes (Godoy et al. 2013; Godoy 2011). This explains why currently primary hepatocytes and even cell lines are more frequently used in toxicological studies than stem cell-derived cells (Luckert et al. 2016; Kim et al. 2015; Grinberg et al. 2014; Hammad et al. 2013, 2014a, 2015; Ghallab 2014).

Recently, it has been shown that stem cell-derived hepatocyte-like cells, besides lacking full differentiation, also show some unwanted features, such as expression of colon-specific genes (Godoy et al. 2015). Moreover, it should be considered that also primary hepatocytes lose expression of many metabolizing enzymes to some degree, when they are isolated from the liver and brought into culture. Interestingly, the same genes whose expression is partially lost in cultivated primary hepatocytes also lack upregulation in stem cell-derived hepatocyte-like cells (Godoy et al. 2016, 2015). This suggests that hepatocytes in vitro may lack the same differentiating cue which would be needed to further differentiate stem cell-derived hepatocyte-like cells. The liver has a complex architecture, optimally designed to maintain physiological parameters and local cytokine concentration within narrow ranges (Vartak et al. 2016; Friebel et al. 2015; Drasdo et al. 2014; Hammad et al. 2014b).

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Our understanding of the key factors controlling the differentiated state of hepatocytes in the organ is unfortunately still in its infancy; progress in this field may lead to novel experimental strategies required to generate fully differentiated hepatocytes (and further cell types) from stem and precursor cells.

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