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Letter to the editor:

ADVANCES IN 2D AND 3D IN VITRO SYSTEMS FOR HEPATOTOXICITY TESTING

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Dear Editor,

Currently, much enthusiasm surrounds the establishment of hepatocyte in vitro systems as alternatives for animal experiments (Parrott et al., 2011; Schaap et al., 2012; Hammad et al., 2013; Oloyede et al., 2013). It has been shown that hepatocytes under certain culture conditions form 'microtissue' with some features similar to the in vivo situation (Rago et al., 2009; Achilli et al., 2012; Messner et al., 2013). Moreover, precursor cells including embryonic stem cells can be differentiated to share some features with primary hepatocytes (Brulport et al., 2007; Aurich et al., 2009; Gabriel et al., 2012; Seeliger et al., 2013). The transcriptome of hepatocytes in vitro has been systematically compared to the in vivo situation (Godoy et al., 2010; Zellmer et al., 2010; Doktorova et al., 2012; Godoy and Bolt, 2012; Schug et al., 2013). Despite some differences response patterns of hepatocyte in vitro nevertheless give relevant insight into the toxic mode of action of chemicals (Hewitt et al., 2007; Bauer et al., 2009; Ullrich et al., 2009; Heise et al., 2012; Knobeloch et al., 2012). Although there are large differences to primary hepatocytes, hepatoma derived cells still represent a useful and easy to handle system that can be helpful if one is aware of the limitations (Watanabe et al., 2011; Lin et al., 2012; Schreck et al., 2012; Tolosa et al., 2013). Last but not least, systems biology techniques have successfully supported the current progress in hepatotoxicity testing (Hoehme et al., 2007, 2010; Braeuning et al., 2010; Geenen et al., 2012). In this gold-rush mood currently prevailing in the field of hepatocyte in vitro systems an expert panel has recently published the probably most comprehensive review on the topic (Godoy et al., 2013). The more than 100-page article critically discusses the possibilities and limitations of liver in vitro systems with particular emphasis on hepatotoxicity testing. The reader learns how the physiological state of hepatocytes is altered when they are isolated from their in vivo microenvironment and are brought into culture (Godoy et al., 2009, 2010, 2013). Different culture systems and their advantages as well as limitations are critically reviewed, including monolayer cultures, sandwich cultures, co-cultures with non-parenchymal cells, spheroids or 'microtissue', liver slice cultures and the isolated perfused liver. A particular emphasis is given how to use these in vitro systems for studies of apoptosis and drug induced liver toxicity. Moreover, alternative hepatocyte sources, such as stem cell or hepatoma derived hepatocyte-like cells are critically discussed. The review of Godoy et al. (2013) is of high interest for anyone interested in liver physiology as well as hepatotoxicity testing.

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