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Guest editorial:

HUMAN NON-PARENCHYMAL LIVER CELLS FOR CO-CULTIVATION SYSTEMS

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Recently, Pfeiffer and colleagues have published protocols that allow the isolation of human hepatocytes and non-parenchymal liver cells from the same donor (Pfeiffer et al., 2014). Cell isolation is performed with resected liver tissue, usually obtained from hepatectomy because of metastasis from colon cancer. Human liver cells are initially isolated by the conventional two-step EDTA/ collagenase perfusion technique. Next, hepatocytes and non-parenchymal cells are separated by low-speed centrifugation. After purification by Percoll density gradient centrifugation, Kupffer cells, sinusoidal endothelial cells and stellate cells are further separated by specific adhesion and by magnetic bead sorting. Typical yields of a single isolation are $1.9x10^6$ Kupffer cells, $2.7x10^5$ sinusoidal endothelial cells and $4.7x10^5$ stellate cells. All cell types can be cultivated either as mono- or co-cultures.

Co-cultivation of non-parenchymal cells and hepatocytes from the same donor may become an important approach of hepatotoxicity testing in future. It is well known that non-parenchymal cells play a critical role in hepatotoxicity (Laskin, 1996; Kantari-Mimoun et al., 2014; Krell et al., 1987). Sinusoidal endothelial cells have been shown to support liver regeneration, where they serve as 'guide-rails' for regenerating hepatocytes and guarantee the rapid re-establishment of functional liver tissue (Hoehme et al., 2010; Schliess et al., 2014). Moreover, sinusoidal endothelial cells have been shown to secrete HGF and Wnt factors during liver regeneration, which stimulate hepatocytes to proliferate (Ding et al., 2010). They condition the vascular niche by angiocrine signals which can be disturbed after repeated administration of hepatotoxic compounds, leading to activation of stellate cells and fibrosis (Ding et al., 2014). Currently, *in vitro* systems for hepatotoxicity testing are in the focus of toxicological research (Ghallab, 2013; Krell et al., 1987; Schyschka et al., 2013; Grinberg et al., 2014). Although the important role of non-parenchymal cells is out of question (Liu et al., 2013; Hammad et al., 2014; McCuskey et al., 2005; Yee et al., 2003), currently mostly hepatocyte monocultures are tested (Miszczuk et al., 2014; Rodrigues et al., 2013; Watzek et al., 2013; Vinken et al., 2013; Huang et al., 2013). An explanation probably is that cultivation of non-parenchymal cells is still challenging. For example stellate cells tend to be activated spontaneously in culture and sinusoidal endothelial cells may lose capacity to secrete cytokines. Although there is still a long way to go, the technique of Pfeiffer et al. (2014) will improve the availability of human non-parenchymal cells and may facilitate the development of *in vitro* systems that recapitulate the communication between hepatocytes and non-parenchymal cells.

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