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Letter to the editor:

THE BODY-ON-A-CHIP CONCEPT: POSSIBILITIES AND LIMITATIONS

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Dear Editor,

Recently, Frey et al. (2014) have established a reconfigurable microfluidic platform to study multi-tissue interactions. This platform contains multiple spheroids of different cell types in hanging drops. The hanging drops are connected by microfluidic networks. The path of the liquid flow through the hanging drops is precisely controlled and offers the possibility to perfuse them either sequently or parallelized. For example culture media may first pass a hanging drop with a liver spheroid and subsequently pass kidney, heart, bone marrow, or neuronal tissues (Frey et al., 2014). Currently, many groups work on the optimization of 'body-on-a-chip' systems (Kelm and Marchan, 2014; Sung et al., 2014; Williamson et al., 2013). Currently, 'organ-on-a-chip' concepts are developed for many tissues including heart (Zweigerdt et al., 2014; Agarwal et al., 2013), kidney (Jang et al., 2013), lung (Punde et al., 2014; Weis et al., 2013; Huh et al., 2012) and intestine (Esch et al., 2014, 2012). Years before the 'body-on-a-chip movement' much work has been invested in the optimization of three dimensional culture systems (Xie et al., 2006; Marquette et al., 2007; De Kock et al., 2011; Teichmann et al., 2014; Ramaiahgari et al., 2014). Among the easiest and most efficient methods of 3D culture are the collagen sandwich technique, where cells are cultivated between two layers of soft gel collagen (Schug et al., 2008; 2013; O'Brien, 2006) or cell spheroids which can be generated by hanging drop cultures (Messner et al., 2013; Godoy et al., 2013). Today organotypical in vitro systems are frequently used to study mechanisms of toxicity, particularly in the fields of hepatotoxicity (Schyschka et al., 2013; Rodriques et al., 2013; Watzek et al., 2013; Ilkavets, 2013), nephrotoxicity (Limonciel et al., 2012; Jennings et al., 2012) and developmental toxicity (Bolt, 2013; Balmer et al., 2014; Zimmer et al., 2014; Stern et al., 2014; Krug et al., 2013a, b). These organotypical in vitro systems are now used in 'body-on-a-chip' devices if they can be transferred to cell culture microdevices.

Nevertheless, despite of recent progress in 'body-on-a-chip' research it is clear that this concept is still in its infancy. For example, the overall quality of the 'body-on-a-chip' is limited by the quality of its 'microorgans'. Although multiple publications claim that three dimensional (3D) culture systems represent higher levels of tissue organization, this is certainly not correct. Correct would be that 3D culture systems represent some aspects of real tissue but many tissue functions are not represented. For example liver microtissues establish bile canaliculi between the hepatocytes. Therefore, these model systems may be used to study excretion of compounds from hepatocytes into bile canaliculi. However, liver microtissues currently do not establish sinusoids, the liver's microvessels (Hammad et al., 2014). This causes numerous differences to real liver tissue. For example the sinusoidal tissue unit is not correctly established. Liver sinusoidal endothelial cells (LSECs) with Kupffer cells at their luminal and stellate cells at the parenchymal side are responsible for numerous mechanisms in toxicology,

ranging from interactions with circulating immune cells to pathogenesis of liver fibrosis. Obviously, this sinusoidal tissue unit is not correctly recapitulated by the currently available artificial microtissues. Similar critical limitations could be described for microtissues representing other organs. In conclusion, microfluidics offer the prospect to establish complex physiological scenarios under accurately 'reproducible *in vitro* conditions'. However, the hunt for a 'body-on-a-chip' or even an 'organ-on-a-chip' that really deserves this name has only just begun.

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