Progress in ‘body-on-a-chip’ research

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Published online: 9 September 2014
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Advanced cell culture technologies have gained a new momentum in recent years. Currently, large research projects have been initiated to mimic not only tissue structure and function in vitro but rather creating networks of organs and tissues using a ‘body-on-a-chip’ or multi-organ approach (Esch et al. 2014; Zhang et al. 2009; Choucha-Snouber et al. 2013; Imura et al. 2010; Huh et al. 2012; Wagner et al. 2013; Sonntag et al. 2010; Sung and Shuler 2010; Sin et al. 2004). In contrast to multi-organ devices, body-on-a-chip concepts attempt to down scale required tissue size and fluidics to enable broader applicability. However, communication between artificial organs/tissues with an exchange of toxic metabolites originating from liver metabolism has not yet been successfully achieved. To bridge this gap, Olivier Frey and colleagues have established a technology, which connects microtissues in a multiwell setup by a laminar flow ‘microvessel’ system, as recently described in *Nature Communications* (Frey et al. 2014). Their technical layout consists of interconnected hanging drops, each with a base diameter of 3.5 mm that is applicable for a 96- or 384-well format. With a single pipetting step, suspended cells are loaded onto the plates and consequently form gravity-enforced spheroids in hanging drops. These can be loaded with different cell types, resulting in microtissues with the properties of different organs. Next, this static configuration is interconnected through

200-µm-wide channels that are themselves connected via tubing. An important feature of this elegant, microscale and user-friendly device is that it connects the individual drops by laminar flow, which develops its highest flow speed at the bottom of the individual drops—the position where the microtissues are located. The path and flow direction of these ‘microvessels’ can be manipulated, thus allowing sequential perfusion of the microtissues originating from different cell types including liver, heart, brain and different types of tumors, thereby mimicking the metabolite exchange seen in vivo.

A proof-of-principle experiment demonstrated that the chemotherapeutic prodrug, cyclophosphamide could be activated to its active metabolites, 4-hydroxyphosphamide and aldophosphamide in a liver microtissue. These metabolites were then transported via the ‘microvessels’ to a tumor microtissue where it formed the toxic phosphoramidate mustard and blocked further growth. In contrast, static experiments where supernatants from cyclophosphamide-treated liver microtissues were pipetted to tumor microtissues did not efficiently block tumor growth, indicating the superiority of the ‘laminar flow microvessels,’ where metabolites are produced in very small volumes, resulting in relatively high concentrations at the target tissue.

The novel reconfigurable hanging drop network interconnected by ‘laminar flow microvessels’ has elegantly and robustly solved the problem of how to functionally interconnect the individual organ compartments of a ‘body-on-a-chip.’ A limitation is—of course, that a ‘body-on-a-chip’ system is only as good as its individual tissues. For example, a ‘liver microtissue’ still differs from a real liver as it lacks the sinusoidal architecture that functionally links each individual hepatocyte to the blood stream with almost 50 % of its surface (Hoehme et al. 2010, 2007; Hammad et al. 2014; Drasdo et al. 2014). It will be exciting to see

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whether microfluidic technologies will be able to mimic also the sinusoidal structures in the near future.

Recent results make it quite apparent that there is still a disconnect between in vitro systems and the in vivo situation, which have to be addressed in order to advance toxicological profiling for human beings (Godoy et al. 2009, 2011; Hengstler et al. 2009; Bolt 2011; Ghallab 2013; Hammad et al. 2013). Due to a strong need, great efforts are on their way toward improving in vitro prediction of human toxicity, for example, by the EU Seurat-1 research network (Godoy et al. 2013; Messner et al. 2013; Driessen et al. 2013; Fabian et al. 2013; Strikwold et al. 2013; Schug et al. 2013; Krug et al. 2013; Balmer et al. 2014; Zimmer et al. 2014). The present ‘body-on-a-chip with microvessels’ system offers an elegant solution to assess not only tissue-/cell-specific toxicology but rather acquiring a more systemic-like response toward a given substance. However, the hunt for in vitro systems that quantitatively predict human toxicity with sufficient accuracy to establish, for example, non-observed adverse effect levels (NOAELs), has only just begun.

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