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Tomorrow today: organ-on-a-chip advances towards clinically relevant pharmaceutical and medical *in vitro* models

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Organ-on-a-chip technology offers the potential to recapitulate human physiology by keeping human cells in a precisely controlled and artificial tissue-like microenvironment. The current and potential advantages of organs-on-chips over conventional cell cultures systems and animal models have captured the attention of scientists, clinicians and policymakers as well as advocacy groups in the past few years. Recent advances in tissue engineering and stem cell research are also aiding the development of clinically relevant chip-based organ and diseases models with organ level physiology for drug screening, biomedical research and personalized medicine. Here, the latest advances in organ-on-a-chip technology are reviewed and future clinical applications discussed.

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Introduction

Despite initial successes in *in vivo* and *in vitro* testing during drug trials, drug failure remains high and is accompanied by major losses in research investments. This means that, despite emerging combinatorial biochemical approaches and therapeutic strategies, regulatory approval rates for new drugs and therapies are declining. Established *in vivo* animal and *in vitro* models often do not reliably recreate the physiology of the target organ, thus poorly predicting therapeutic outcomes and possible side effects during clinical trials. To overcome these limitations, major resources have been devoted to improving experimental disease predictors to minimize patient risk and development costs. One promising strategy is chip-based organ and disease modelling. These so-called organ-on-a-chip combine recent microfluidic advances with complex three-dimensional cell biology that provide organ-like physiology and pathophysiological cellular and tissue level responses [1,2••,3]. The inherent design flexibility, tunable material properties and functionality of the microdevice allow the re-creation of characteristic biological niches found in native human tissue [4]. This aspect has direct significance for future medicine because it offers new insights into disease mechanisms as well as opportunities for advanced drug screening [5], and personalized and precision medicine [6].

This minireview looks at the progress made in organ-on-a-chip technology in the past two years, focusing on clinically relevant medical or pharmaceutical use, including latest developments in physiologic organ-on-a-chip systems, as well as high-throughput screening, disease-modelling and personalized medicine.

Human physiology on-a-chip: status quo 2018

Organ-on-a-chip technology reliably mimics the smallest functional unit of an organ with the physical, cellular and biochemical microenvironment accounting for the respective native tissue architecture for organs such as lung [7••], liver [8], gut [9], kidney [10], vasculature [11,12], heart [13,14], placenta [15•,1], and others. Until recently, on-chip monolayer cultures were predominantly used on membranes to investigate the physiology, integrity and function of human cell barriers using mostly cancer cell lines [16••]. However, since physiological responses cannot be guaranteed when using cancer cells in organ-on-a-chip systems, advanced organ-models nowadays are based on primary cells or induced pluripotent stem cells.

In the case of neurological microsystems, a variety of primary cell types and chip designs were employed to model simplified architecture and specific functions of the human brain. Under fluid shear, brain endothelial cells can be co-cultured with astrocytes on a porous hollow fiber resulting in a barrier with *in vivo*-like integrity and permeability [17]. By integrating more specialized and localized brain tissue models, such as the hippocampus, prefrontal cortex and amygdala, the permeability of potentially toxic agents can be tested

using a multi-regional brain-on-a-chip device [18]. Despite this and other proof-of-principle studies, medical applications of such complex systems are still challenging [19,20]. For instance, one major challenge is the complexity of the three-dimensional structure of a nephron in pharmacological kidney research, which still presents an insurmountable hurdle in bioengineering despite recent developments in bioprinting techniques [21–24]. Although the complexity of the nephron cannot be recreated, drug clearance can nonetheless be modeled on a chip using a simpler microfluidic cell barrier system exhibiting basic organ function [10]. Another approach employed three-dimensional culture techniques based on scaffolding collagen I matrices and cellular self-organization to establish a kidney-on-a-chip system displaying clinically relevant biomarkers for toxicity for cis-platin and doxorubicin [25]. An alternative method of mimicking the kidney is based on using pluripotent stem cells to generate organoids containing nephron-like tubular structures [26]. In this case, cells were cultured in an air-liquid interface yielding robust tubulogenesis and nephron-like renal cells with podocyte-like progenitors from the glomeruli, as well as proximal tubular-like and distal tubular-like cells. However, the presence of pre-maturity biomarkers indicated non-physiological phenotypes.

An often overlooked aspect of every organ-on-a-chip system is the fact that every tissue and organ within the human body is subjected to biophysical forces, which are also key for the development of proper physiological phenotypes [27]. Microfluidic devices containing integrated mechanical actuators have been developed with the ability to apply shear, strain, stretch and compression forces on cells to mimic mechanobiological cues [28,29]. The most straightforward strategy uses fluid flow to apply varying shear forces. For instance, fluid shear and channel curvature influence phenotype as well as the transport function of renal proximal tubule models [30,31]. The first breakthrough organ-on-a-chip model that recreated organ biomechanics was a breathing lung-on-a-chip that used a lateral vacuum to exert strain on a thin flexible membrane and stimulate the lung epithelial cell barrier [7••]. Following a period of two-weeks, increased epithelial surfactant production was induced by the continuous stretching motion, which resulted in improved barrier stability. A similar organ-on-a-chip principle was used to create a biomimetic human gut-on-a-chip mimicking the complex structure and peristaltic of native intestine tissue [32].

To overcome the technological challenge of parallelization of complex organ structures, different organ cultures were integrated in a single device to increase throughput [33]. Using pneumatic medium circulation, the pro-drug 5-fluorouracil and anti-cancer drugs capecitabine and tegafur were pumped between first, cancer, second, intestine and third, connective tissue models to simultaneously screen for the efficacy and adverse effects of drug candidates. Another micro-physiological system with higher throughput capability was developed and comprised various vascularized micro tumor models [34]. Both anti-angiogenic and anti-tumor drug activities were successfully identified by blind-screening a small compound library using hydrostatic pumping. Additionally, a microfluidic hanging drop array was established for multi-parametric monitoring of multiple spheroidal models by integration of micropumps [35] and inline electrochemical biosensors based on amperometry [36] and electric impedance sensing [37]. Highest throughput is currently achieved using a fully automated cell culture platform engineered around Mimetas' OrganoPlate® system, which is optimized for long-term maintenance and monitoring of induced pluripotent stem cell differentiation into neuronal cultures using 96 individually addressable three-dimensional microfluidic cell cultures. This system was used to monitor the onset and progression of Parkinson's disease using patient-derived neuroepithelial stem cells that were differentiated into midbrain specific dopaminergic neurons over 24 days [38].

Emulating human disease on-a-chip

Disease modeling has been largely pioneered in animal experiments and conventional monolayer cell cultures. As mentioned above, three-dimensional *in vitro* cell cultures techniques potentially obviate animal models, because *in situ* pathology can be recreated using commercially available or patient derived cells bypassing significant intra-species differences between humans and animals [39] (Table 1). An artificial bottom-up approach is frequently used to build organ-on-a-chip models with progressive complexity by exploitation of cellular differentiation, self-assembly or cell-to-cell interaction to recapitulate more features critical for disease etiology and progression [3]. For instance, organ-on-a-chip systems have been applied to investigate thrombosis and coagulation processes. A recently published pneumatic microsystem allows for quantitative spatiotemporal insights into endothelium wounding and clot formation under both physiologically and pathologic conditions [40]. Even though clinically problematic, eptifibatide showed no effect on *in*

Table 1

Overview of current advances in organ models and on-chip disease models

Organ type	Disease model	Organ model
Brain/blood–brain barrier	–	[17,19,20]
Heart	–	[13,14]
Kidney	[25,52]	[10,30,31]
Gut	[47,48]	[9,32]
Placenta	–	[1,15•]
Vasculature	[40,41,42•]	[11,12,29]
Lung	[43,46,53•]	[7••]