BIOCELL
2022 46(5): 1177-1180

Tech Science Press

# From organ-on-a-chip towards body-on-a-chip

Jong Hwan SUNG*

Hongik University, Seoul, 04066, Korea

**Key words:** Multi-organ-on-a-chip, Disease models, Drug development, *In vitro* model system

**Abstract:** Organ-on-a-chip technology aims to reproduce the key physiological features of human organs and tissues, even complex actions of multi-organ interaction. While organ-on-a-chips at single-organ level has made notable achievement during the last decade, multi-organ-on-a-chips, which manifests unique advantages, has started gathering attention only recently. In this viewpoint, we discuss the current status of organ-on-a-chip technology, with a specific emphasis on multi-organ-on-a-chip. Key technological advances contributing to the maturation of the field, and challenges that need to be addressed before wider adoption in relevant fields are discussed. We will share our perspectives on how the multi-organ-on-a-chip can improve the drug development process.

## Introduction

The difficulties associated with drug development (Scannell *et al.*, 2012) mainly comes from the fact that the model systems used in the process show limited physiological relevance to humans. Cell-based *in vitro* systems can partially reflects cellular physiology, often decaying rapidly after separation from the body (Freires *et al.*, 2017), and animal to human extrapolation is often inaccurate (Seok *et al.*, 2013; Pound and Ritskes-Hoitinga, 2018).

As suggested by recent review articles, organ-on-a-chip technology is considered as a promising solution to this problem (Ingber, 2020; Jalili-Firoozinezhad *et al.*, 2021). Organ-on-a-chips, also known as tissue chips or microphysiological systems (MPS), offer advantages over conventional cell-based *in vitro* models. The precise control over three-dimensional geometries, flow of fluids, and transport of molecules in microscales allows recreation of the tissue microenvironment. It allows manipulation of experimental conditions, enabling hypothesis-driven research. For example, the effect of fluid flow on cell physiology can be studied by applying flow with controlled flow rates (Chi *et al.*, 2015; Lee *et al.*, 2019). The most prominent advantage is that it can connect multiple organs and allow communication between them. So-called multi-organ-on-a-chip, also often termed body-on-a-chip or human-on-a-chip, enables realization of complex and dynamic interactions between multiple organs, analogous to what happens in the human body (Lee and Sung, 2018a; Sung *et al.*, 2019b; Sung, 2021).

## Advance of Organ-on-a-Chip

The conception of organ-on-a-chip technology came with the development of soft lithography, which uses elastic silicone materials, polydimethylsiloxane (PDMS), to create microscale devices (McDonald *et al.*, 2000) in the field of microfluidics, which uses precise handling of microscale liquids. The application of microfluidics in biological context was demonstrated in early 2000s (Allen and Bhatia, 2003; Sia and Whitesides, 2003).

The concept of multi-organ-on-a-chip was conceived in its preliminary form as macroscale bioreactors fluidically connected using pumps to transfer cell culture media between different organ modules (Shuler *et al.*, 1996). Termed by the authors as a 'cell culture analog', this system was used to probe the metabolism-dependent toxicity of naphthalene toxicology (Sweeney *et al.*, 1995). With the advance of microfluidic technology, the cell culture analog became microscale, fabricated on a silicon wafer and connected via microfluidic channels (Sin *et al.*, 2004; Viravaidya *et al.*, 2004). These proof-of-concept studies proved that organ-organ interaction can be reproduced *in vitro* (Sung and Shuler, 2009; Tatosian and Shuler, 2009; Sung *et al.*, 2010).

Advancing from these studies, a seminal paper was published in 2010, where recapitulation of organ-level functionality of the lung by creating alveolar-capillary interface and applying cyclic stretching was demonstrated,

*Address correspondence to: Jong Hwan Sung, jhsung22@hongik.ac.kr
Received: 31 August 2021; Accepted: 13 December 2021

Doi: 10.32604/biocell.2022.019055

to study pathological mechanism underlying pulmonary diseases (Huh *et al.*, 2010). Collaborative multi-year research funding effort from multiple institutes such as US Food and Drug Administration (FDA), National Institutes of Health (NIH), and Defense Advanced Research Projects Agency (DARPA), was initiated in US, and similar funding effort was initiated in Europe as well (Low *et al.*, 2021). Recent research works are aimed towards building multi-organ systems for mimicking complex pathophysiological processes in the body (Miller and Shuler, 2016).

In addition to the funding effort tin the public sector, recent effort in commercialization in the industrial sector is also noteworthy (Ewart *et al.*, 2017; Ribas *et al.*, 2018; Low *et al.*, 2021). Many US and Eurpose-based companies, including Mimetas, TissUse, CNBio, Emulate, and Hesperos are collaborating with major pharmaceutical companies seeking ways to incorporate organ-on-a-chip technologies in drug development process.

## Key Technologies of Organ-on-a-Chip

Early works on organ-on-a-chip focused on development of microfluidic devices or fabrication methods for recreating the tissue microenvironment. For example, a novel method for fabricating silicon substrate or soft hydrogel into 3D villi structure of intestinal epithelium was developed to culture gut epithelial cell line in 3D shape (Sung *et al.*, 2011; Esch *et al.*, 2012). Cyclic stretching of a porous membrane structure mimicking the alveolar-capillary interface using pneumatic vacuum control enabled realization of breathing motion (Huh *et al.*, 2010) and peristaltic movement of the intestine (Kim *et al.*, 2012). Control of convection and diffusion process at microscale enabled spontaneous formation of perfusable, vascular structure within extracellular matrix (ECM) (Kim *et al.*, 2013).

One of the most important technological advances required for organ-on-a-chip systems are improving the physiological relevance of the system, by incorporating stem cells, primary cells, or even organoids (Kasendra *et al.*, 2018). Some obstacles need to be overcome, such as the high cost of cells and media, and insufficient supply with inconsistent quality of cell phenotypes. The use of organoids can be limited, since organoids are self-organized multicellular 3D tissue models and it is difficult to create barrier structures commonly seen in the epithelial tissue of the intestine, skin, and alveolar.

3D bioprinting is another area that has made significant contribution to organ-on-a-chip field. Early organ-on-a-chip works relied heavily on photolithography-based fabrication methods, which is useful for fabricating inorganic materials, but inadequate for mimicking the extracellular matrix (ECM) environment of *in vivo* tissues. The ability to fabricate natural and synthetic hydrogels in microscale structures has offered great opportunities for organ-on-a-chip fields (Zhang *et al.*, 2016).

Real-time, noninvasive detection in organ-on-a-chip devices is important, and various optical and electrochemical sensing methodologies have been integrated with organ-on-a-chip systems (Choi *et al.*, 2016). Thorough validation with conventional detection methods and standardization efforts may be needed. Acquisition of a large set of data will also allow a deeper insight in the interpretation of the experimental results, particularly when combined with artificial intelligence technology (de Chiara *et al.*, 2021).

## Towards Multi-Organ-on-a-Chip

Organ-on-a-chips offer the possibilities that conventional *in vitro* methods cannot. Multi-organ-on-a-chips enable simulation of dynamic, complex interaction of multiple organs, which is impossible to achieve with conventional static systems, as illustrated in Fig. 1 (Lee and Sung, 2018a; Sung, 2021). Early proof-of-concept studies demonstrated that pharmacokinetic-pharmacodynamic (PK-PD) profiles of drugs can be simulated (Sung *et al.*, 2010). A suitable mathematical framework may be necessary to interpret the chip data and extrapolation to humans (Sung *et al.*, 2018; Sung *et al.*, 2019a). More recent studies have demonstrated the practical ability of multi-organ-on-a-chips to predict the PK profiles of drugs (Maass *et al.*, 2017; Tsamandouras *et al.*, 2017; Edington *et al.*, 2018; Herland *et al.*, 2020).

The multi-organ-on-a-chip can be a powerful *in vitro* platform for modeling complex diseases. Many diseases, including obesity, diabetes, metabolic syndromes, and immune-related diseases show complex mechanisms involving different organs, and in many cases conventional static *in vitro* systems are inadequate for modeling such diseases. Multi-organ-on-a-chips can be useful for screening therapeutics for such diseases, as well as probing the unknown mechanisms of disease progression. For example, non-alcoholic fatty liver disease (NALFD) manifests its symptoms with excessive fat accumulation in the liver, but treatment of NAFLD may be possible by improving the barrier integrity of the gut epithelium (Lee and Sung, 2018b; Jeon *et al.*, 2021). Lastly, incorporation of patient-originated cells into the multi-organ-on-a-chip will lead to personalized humans-on-a-chip.

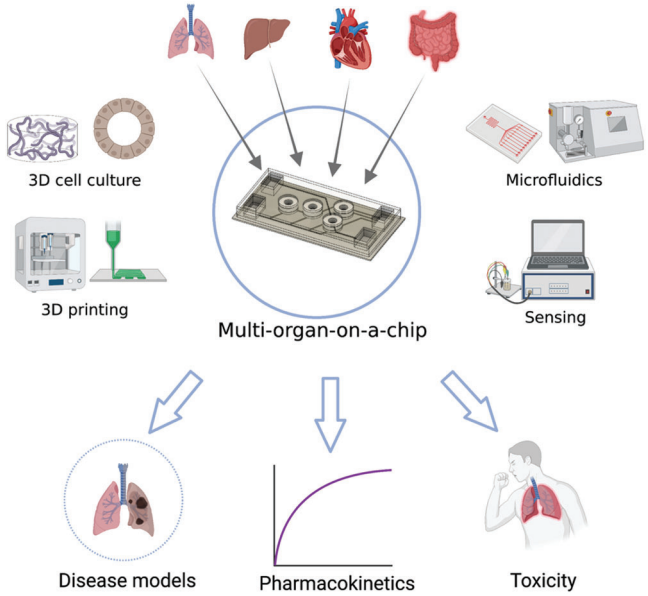


**FIGURE 1.** Schematics of the concept of multi-organ-on-a-chip with constituting technical components and potential applications. The image was created with BioRender.com.

Several challenges remain before wider adoption of this technology will be seen. Validation of physiological relevance has always been a major target that many researchers have been addressing. Recent progress seems promising, as evidences are accumulating that shows pathophysiological processes can be simulated (Benam *et al.*, 2020; Tang *et al.*, 2020), with increasing availability of stem cells, organoids, and primary cells. Improvement of chip fabrication material is necessary. While polydimethylsiloxane (PDMS) is ideal material with many advantages in lab scale, industrial applications will require material with easier mass production and reduced adsorption. Connecting multiple organ modules may require complex fluidic system for recirculation, where novel perfusion methods such as pneumatic pumping may be useful (Rebelo *et al.*, 2016), or gravity-induced perfusion (Lee *et al.*, 2017). This may offer additional advantages by eliminating the need for tubes, and consequently reducing the possibility of bubbles and dead volumes in the system.

As the multi-organ-on-a-chip systems grow in its complexity with increasing number of organs, the importance of mathematical framework for designing and interpreting the system will also increase. One aspect that needs special attention is how to 'scale' different organs to reflect how the human body works. As allometric scaling law suggests, organisms with different masses have different organ masses, as well as other physiological parameters (West *et al.*, 1997). Since the multi-organ-on-a-chip is an extremely miniaturized version of the human body in terms of its size, direct application of allometric scaling law may not be sufficient and rigorous mathematical approach for chip design may be needed (Abaci and Shuler, 2015). At least for the early phase of multi-organ-on-a-chip technology, it will be important to accurately define which physiological functionalities need to be mimicked. For example, the intestine chip may be needed to model the absorption of drugs, or inflammation in response to external stimulation, or *in vitro* milieu for commensal bacteria. Depending on which aspect is being focused on, the optimal ratio of the intestine relative to organs, for example the liver may be different (Lee *et al.*, 2017; Maass *et al.*, 2017). Despite these challenges remaining, the future multi-organ-on-a-chip technology looks very promising, and recent progress in commercialization has been impressive with major pharmaceutical companies actively participating in the movement.

**Authors' Contribution:** The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

**Funding Statement:** This work was supported by National Research Foundation of Korea, under Grant (Basic Research Lab, 2019R1A4A1025958), and by the Ministry of Trade, Industry & Energy (MOTIE), Republic of Korea, under the Technology Innovation Program, Grant 20008414 (Development of intestine-liver-kidney multiorgan tissue chip mimicking absorption distribution metabolism excretion of drug), Hongik University Research Fund.

**Conflicts of Interest:** The author declares that they have no conflicts of interest to report regarding the present study.

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