Recent advances and challenges in organoid-on-a-chip technology

Intan Rosalina Suhito, Tae-Hyung Kim
School of Integrative Engineering, Chung-Ang University, Seoul, Korea

Conventional 2-dimensional cell culture poorly mimics human-relevant models, which is considered a major challenge in biological research. Organoids are a recent breakthrough in 3-dimensional (3D) in vitro tissue engineering that better reflect the physiological, morphological, and functional properties of in vivo organs (e.g., brain, heart, kidney, lung, and liver). Consequently, organoids are extensively used in various impactful biomedical applications including organ development, disease modeling, and clinical drug testing. However, organoid technology still has several limitations, including low reproducibility, vascularization, limited nutrient uptake and distribution (affecting the level of organoid maturation), lack of standardization, and intra-clonal variability. Efforts have been made to overcome these shortcomings of organoid culture. Microfluidic technology has successfully facilitated the establishment of organoid-on-a-chip systems, which effectively improve the structural and physiological features of organoids in a controlled manner. This review discusses the recent advances and developments in organoid-on-a-chip technology. We hope that this study will motivate researchers to explore the possible engagement between microfluidic devices and self-assembled 3D cell cultures to leverage the enhanced quality of organoids, which will have favorable impacts on future tissue regeneration and regenerative therapies.

Keywords: Pluripotent stem cells; Organoid culture; Organoid-on-a-chip; Multi-organoids-on-chip

Introduction

Tremendous scientific advances in stem cell research and regenerative therapies have led to the in vitro development of organoids. Organoids have complex self-organized three-dimensional (3D) multicellular structures that recapitulate the function, architecture, and complexity of their corresponding in vivo organs [1–3]. Apart from animal models, human organoids possess unique properties and details to facilitate better investigation of human disease with few ethical concerns [4]. They also have excellent potential applications in other areas of biomedical research, such as mimicking physiological characteristics of human organs for molecular medicine and drug discovery, or understanding the mechanisms underlying organ regeneration and development [5–9].

Organoids can be established either from tissue-resident adult stem cells, primary cells, and pluripotent stem cells, including embryonic stem cells and patient-derived induced pluripotent stem cells [10–14]. Various protocols, tools, and methods to develop specific types of organoids for particular purposes have been reported [15–17]. A technique called the "sandwich method" has been commonly employed, which depends on the
involvement of extracellular matrix (ECM) materials (i.e., Matrigel) to induce 3D confinement [18,19]. Organoids can also be developed using agitation in bioreactors to create embryoid bodies in the initial stage [20–22]. Brandenberg et al. [23] successfully established a hydrogel-based microengineering cell culture to develop gastrointestinal organoids, which serves as a proof-of-concept for the underlying cellular aggregation in microwell arrays.

Although some of these aforementioned methods are capable of generating viable organoids, their limitations hinder their application at an industrial scale [24–26]. For instance, methodological standardization is difficult and often causes poor reproducibility and uniformity, including high variability in the shape, size, and cell-type ratio of the developed organoids [27–30]. Another obstacle stems from a lack of access to nutrient supply and waste elimination, which limits organoid functionality, maturation, and vascularization [31–35]. The sequential induction processes involved in in vitro organogenesis mostly produce only one tissue-specific organoid, and scarce inter-organ communication is also a significant issue [4,36]. Therefore, a high-fidelity organogenesis approach is essential to accommodate the full range of stochastic phenomena in organoid research.

The microfluidic system is an emerging strategy that involves the integration of physics, chemistry, engineering, and biotechnology, covering a wide range of applications in science and technology [37–40]. This system usually comprises microchannel platforms with dimensions ranging from 10 to 100 μm to ensure bioanalytical performance of the microscale sample volume [41]. In recent research, microfluidic technology has been aligned with 3D cell culture because it allows the improvement of both structural and physiological aspects of organoids in controlled environments [42–46]. This combination, which can be popularly termed “organoid-on-a-chip,” enables the rapid and complex growth of organoids on a platform with multiple parameters and biomimetic environments that are similar to in vivo conditions [47,48]. Due to their favorable characteristics, organoids-on-a-chip are promising for solving the problems faced by conventional techniques, thereby facilitating the scale-up of organoid quality and features for either commercial use or high-throughput analysis.

This review focuses on recent advances in organoid-on-a-chip development, as presented in Fig. 1. Numerous studies related to organoid-on-a-chip models are comprehensively discussed. We also discuss the potential of constructing multi-organ chips based on organoid-on-a-chip systems to elaborately demonstrate interactions between different organs in the human body. Overall, organoids-on-a-chip are extremely useful to study actual organ development, with consequent advantages in future research on biomedicine, disease mechanisms, drug discovery, and tissue regeneration.

**Organoid-on-a-chip models**

The generation of organoids in vitro has excellent potential in biomedical research because of organoids’ outstanding ability to mimic the structural, physiological, and functional characteristics of relevant organs at a miniature scale [49–52]. Numerous organoid development protocols have been established over the past few decades [11,53–58]. Nevertheless, low reproducibility and the lack of standardization of conventional methods lead to huge variations in the morphology (shape, size, and dimensions) and specific cell-type distributions involved in the self-organized growth of organoids [59,60]. In addition to variability issues, non-standardized protocols also lead to instability in organoid maturation and vascularization [61–64]. These challenges should all be taken into account in organoid development.

Engineered 3D cell cultures have recently increased in popularity as the most advanced system in organoid research. Various attempts to obtain robust organoid properties from an engineering perspective have resulted in the development of these 3D cultures. A microfluidic system integrated with in vitro organoid culture is termed an organoid-on-a-chip, which is highly promising because it facilitates the self-organization of cells into a miniature organ in controlled environments (e.g., pH, gas, nutrient supply, and physical or chemical stimulation) [65,66]. Additional sensors could also be incorporated into an organoid-on-a-chip device to allow access for monitoring of organoid responses and behaviors, which would eventually help minimize culture variations [67,68].

Numerous papers have demonstrated the development of organoids-on-a-chip with distinct characteristics for the corresponding organs. To date, several types of organoids have been successfully grown using a microfluidic platform that yields improved organoid characteristics, such as brain, kidney, intestine, and liver organoids-on-a-chip [44,48,69–71]. This section will highlight some reported organoid-on-a-chip models that can make excellent contributions to bioengineering research.

**Ethics statement:** This study was a literature review of previously published studies and was therefore exempt from institutional review board approval.
1. Brain organoids-on-a-chip

The brain is a vital organ of the body and the central nervous system. Understanding the physiological properties of the human brain is highly challenging, and most neurological disorders occur within its complex structure and organization. Animal models are insufficient to capture the unique features and complexity of human brain development. Therefore, progressive research with stem cells has facilitated the construction of miniature organs in vitro termed organoids—customizing the details of human brain pathology in a way that is ultimately informative for neurobiological studies.

In early 2013, Lancaster et al. [72] reported the formation of human pluripotent stem cell (hPSC)-derived cerebral organoids to model microcephaly. This development paved the way for brain organoids to gain attention in the field of neurology. Moreover, this motivated the research group to establish a basic protocol for cerebral in vitro organogenesis from hPSCs [58]. Research in this field is always progressing because its main goal is to accurately recapitulate the complex structural and functional properties of the developing brain in vivo, which was thought to be impossible.

Advances in stem cell research have brought about the development of microfluidic technology, resulting in a high-fidelity model referred to as a brain organoid-on-a-chip (Fig. 2) [71,73]. Wang et al. [71] successfully developed engineered stem cell-derived 3D brain organoids using an organ-on-a-chip system. An illustration of a microfluidic device used for the growth and differentiation of brain organoids is depicted in Fig. 2A, where the preceding embryoid bodies derived from human-induced pluripotent stem cells (hiPSCs) were immobilized in Matrigel, followed by their infusion into the cell culture channel. Neural differentiation of self-organized embryoid bodies into brain or-
Fig. 2. Brain organoid-on-a-chip development. (A) Schematic illustration representing the configuration of the brain organoid-on-a-chip device. (B) Immunohistochemical analysis for TUJ1 and SOX2 markers (indicated by arrows) in 33-day organoids grown on a chip compared with petri dish. (C) Light-sheet microscopic bright-field images of 3-dimensional (3D) brain organoids encapsulated in Matrigel and brain extracellular matrix (BEM) cultured in a plate and microfluidic device at 60 days of cultivation period (scale bar=500 μm, n=3). (D) Quantification analyses for the 3D organoid volume (n=3, 9, and 13 for Matrigel plate, BEM-plate, and BEM-device groups, respectively, Matrigel plate versus BEM-device p=0.0007, BEM-plate versus BEM-device p=0.0014, n=3) and sphericity (n=3 per group, independent replicates=3) of brain organoids using IMARIS software. (E) Expression of the radial glial marker PAX6 and extracellular glycoprotein marker Reelin in BEM-device organoids (left panel, scale bars=200 μm, n=2) and 3D imaging of Reelin expression in BEM-device organoids at day 30 (right panel, scale bars=200 μm, n=5). (F) 3D plotting and (G) quantification of deep-layer marker TBR1-expressing cells in Matrigel plate, BEM-plate, and BEM-device organoids at day 30 using IMARIS software (n=3 for Matrigel plate and BEM-plate groups, and n=4 for BEM-device group, independent replicates=3). (H) 3D plotting analysis of TBR1+ cells in BEM-device organoids on different z-positions in the radiometric color spectrum (scale bar=200 μm, n=3). EBs, embryoid bodies. All data are presented as mean±standard deviation. Statistical differences between the groups were determined with unpaired two-tailed t-test (**p< 0.01, ***p< 0.001). (A, B) Adapted from Wang et al. RSC Adv 2018;8:1677–85, with permission from Royal Society of Chemistry [71]. (C–H) Adapted from Cho et al. Nat Commun 2021;12:4730, with permission from Nature Research [73].
ganoids was performed in perfused culture conditions. According to the immunohistochemical staining results of this study, the brain organoids grown on a chip for 33 days contained higher proportions of cells positive for SOX2 and TUJ1, which are neural progenitor and neuronal markers, respectively, than those obtained from the conventional method in petri dish culture (Fig. 2B).

In a recent study, Cho et al. [73] achieved an advancement in brain organoid-on-a-chip, wherein a modified microfluidic platform allowed dynamic culture of brain extracellular matrix (BEM)-embedded brain organoids. The microfluidic BEM system was shown to enhance radial glial growth and corticogenesis, as shown in Fig. 2C–H. Observations from 3D light-sheet microscopy and morphological analysis demonstrated that the speed of surface structure growth and development was significantly higher in brain organoids on microfluidic BEM devices than in those on either Matrigel or BEM plates, which were used as control groups (Fig. 2C). Furthermore, the average volume of organoids in all three groups dramatically increased from 0.14±0.02 mm^3 (Matrigel plate) to 0.31±0.14 mm^3 (BEM plate) and 0.56±0.17 mm^3 (microfluidic BEM), whereas their degree of sphericity decreased from 0.57±0.03 to 0.47±0.14 and 0.35±0.11 for BEM and microfluidic BEM, respectively (Fig. 2D). These phenomena indicated that BEM can promote better volume expansion, maturation, and epithelial tissue elongation in brain organoids, while the microfluidic chip supports the dynamic microenvironment for brain organoid growth.

Other results highlighted the superiority of microfluidic BEM for brain organoid generation including immunostaining for Reelin+ expression, which corresponds to Cajal-Retzius cells—the main cell type in neuronal migration and cortical lamination (Fig. 2E) [74]. Confocal visualization and quantification, as shown in Fig. 2F and 2G, exhibited that BEM-device organoids contained a higher TBR1+ cell population than those in Matrigel plate organoids. In microfluidic BEM organoids, TBR1 expression was also detected in a radiometric color spectrum along with the cortical layer (Fig. 2H). The data from this study indicate that the microfluidic BEM device significantly enhances cortical organization in brain organoids, further validating the enormous value of microfluidic technology to achieve any progress in human organ-relevant organoid culture.

2. Kidney organoids-on-a-chip

Chronic kidney disease (CKD) is among the most deadly diseases globally, affecting 11% to 13% of people worldwide [75]. There is an urgent need to find solutions for the high mortality rate and socioeconomic issues related to CKD rehabilitation (i.e., hemodialysis or renal transplantation). Stem cell and regenerative therapies based on hPSC-derived kidney organoids have been proposed as alternatives. Another application of interest in organoid research is their potential to model diseases. For instance, studies on patient-specific CKD can be conducted by growing kidney organoids from both healthy donor- and patient-derived hPSCs to mimic in vivo kidney development.

Several methods have been established for kidney organoid generation with varying induction compositions and cultivation durations. In 2014, Taguchi et al. [76] reported a multi-step protocol to form kidney organoids derived from metanephric mesenchyme through long-term treatment with high concentrations of CHIR99021 (CHIR, a WNT agonist), followed by treatment with a combination of other bioactive molecules (e.g., retinoic acid, activin, and BMP4). Takasato et al. [77] also established the generation of spherical kidney cells from human embryonic stem cells using a protocol based on CHIR treatment onto 2-dimensional (2D) nephron progenitor cells (NPCs) at various time-points to facilitate self-assembly of the 3D kidney organoid culture. The third protocol, which was reported by Morizane et al. [19], contained a shorter induction process than that in the Takasato protocol, which involved inducing NPCs only from the posterior intermediate mesoderm.

Although in vitro kidney organogenesis could be achieved using different differentiation protocols, the challenges of using hPSC-derived kidney organoids for regenerative medicine remain significant. Examples include the lack of maturation and vascularization, the low scalability and reproducibility of the differentiation protocol, and the presence of non-renal off-target cells [78]. These challenges have hindered the use of kidney organoids for renal replacement therapy. Therefore, recent advancements in bioengineering have provided a solution involving the generation of various organoid types on a microfluidic platform, including kidney organoids-on-a-chip, to ensure better translation of laboratory-scale organoid-based approaches.

In order to overcome the limitations of static culture conditions, Homan et al. [61] successfully achieved in vitro kidney organoid generation using microfluidic chips. Specifically, a microfluidic culture system was constructed that accounts for multiple parameters including the ECM, media composition, fluidic shear stress (FSS), and co-cultured human endothelial cells. Their results demonstrated that kidney organoids developed under high FSS conditions exhibited remarkably enhanced vasculature and maturity of the tubular and glomerular subdivisions, including improved morphology of tubular epithelial cells and podocytes. Controlling the fluid flow onto the microfluidic
chip allowed significant effects of environmental cues on simultaneous organoid maturation and vascularization.

Subsequently, the effects of biochemical and biomechanical factors on vascularization of the kidney organoid-on-a-chip have been extensively investigated [70]. Lee et al. [70] presented their experimental setup of a kidney organoid-on-a-chip with an optimized ECM and controlled shear stress, as shown in Fig. 3A. Kidney organoids were cultured on a device coated with 1.5% Matrigel containing 100 ng/mL vascular endothelial growth factor (VEGF) to ensure their maturation during fluidic flow (10 µL/min flow rate). As shown in Fig. 3B and 3D, kidney organoids under shear stress and VEGF supplementation exhibited higher NPHS1 and PECAM expression, demonstrating that combining biomechanical stimuli with blood vessel-promoted growth factors can synergistically enhance blood vessel formation in kidney organoids. The population of PECAM endothelial cells in the Matrigel/VEGF-coated chip was also found to have increased to 8.82%, compared to the 0.18% in the Matrigel-coated kidney organoid-on-a-chip (Fig. 3C). Further investigations into dynamic micro-vascularization networks in kidney organoids-on-a-chip will provide more insights for organ regeneration and developmental studies.

3. Liver organoids-on-a-chip
The liver is considered the most varied and largest immunologically complex organ, accounting for 2% to 5% of the human body weight. It is involved in metabolic processes including bile production, protein synthesis and digestion, xenobiotic detoxification, and regulation of the major chemical compounds in the bloodstream [79]. The liver comprises several cell types including hepatocytes, stellate cells, Kupffer cells, and liver sinusoidal endothelial cells. Any damage to these cells caused by drug toxicity, excessive alcohol consumption, infectious agents (hepatitis virus), or physical trauma, can result in hepatic fibrosis and even cirrhosis, which leads to one million annual deaths globally [80,81]. Notably, the generation of liver or hepatic organoids is motivating mechanistic studies of liver diseases and efforts to identify potential drugs for organ therapies using in vitro models.

Broutier et al. [11] established a protocol for the long-term expansion of self-renewing human and mouse adult liver organoids along with genetic modifications. They developed the organoid by providing an ECM microenvironment along with various growth factors for liver development, including hepatocyte growth factor, epidermal growth factor, fibroblast growth factor, and R-spondin-1. This liver organoid model combined with genetic engineering is extremely useful for a better understanding of the non-transformed and physiologically relevant human liver. Furthermore, advanced microengineering has been widely integrated with organoid technology, which allows the construction of liver organoids in controlled microfluidic systems.

In 2018, Wang et al. [69] reported an in vitro liver model based on hepatic differentiation of hiPSCs into liver organoids on a 3D perfusable micropillar chip. The liver organoid-on-a-chip was found to favorably differentiate into cholangiocytes and hepatocytes, which recapitulate the main features of heterogeneous liver formation. Compared to static conditions, fluid flow into the organoid-on-a-chip resulted in higher expression levels of SOX17 and FOXA2, which are markers attributed to the improvement of endodermal differentiation, as well as ALB and CYP3A4, markers associated with liver organoids. Interestingly, the organoid in the dynamic culture system demonstrated hepatic-specific functional enhancement and morphological properties, as indicated by higher levels of albumin and urea compared to those in static culture.

Recently, Michielin et al. [82] have studied the role of accumulative soluble ECM in developing hiPSC-derived hepatic organoids in microfluidic environments (Fig. 4A). As shown in Fig. 4B, an effective hepatic differentiation protocol of hiPSCs has been developed to guide them towards definitive endoderm, hepatic endoderm, immature hepatocytes (IHs), and mature hepatocytes in a microfluidic channel (µF), confocal images shown in Fig. 4C confirmed an increase in structural basal lamina protein deposition (COL4 and LAM) and fibrillar protein accumulation (COL1 and FN) in hiPSC-derived IH cells developed in µF compared with those in conventional culture conditions. Net-like structures were observed in µF samples because of potential ECM deposition and remodeling activity that forms junctions, branches, and a mesh-like structure. Moreover, the quantitative polymerase chain reaction analysis identified the overexpression of ECM receptors (i.e., FNI, ITGA5, ITGA6, and ITGB1) and epithelial markers (E-CAD and c-MET) genes in IH-containing organoids-on-a-chip, which strongly correlated with the increased ECM protein levels (Fig. 4D). Overall, this study provides a good understanding of accommodating external regulation of cell-secreted factors to accelerate stem cell differentiation, including organoid generation for disease modeling.

Multi-organoids-on-a-chip systems
Clinical practices in drug discovery have mostly leaned on in vivo animal models or conventional in vitro cell culture, both
Fig. 3. Kidney organoid-on-a-chip model. (A) Schematic illustration showing the experimental setup of human pluripotent stem cell (hPSC)-derived kidney organoid-on-a-chip under optimized extracellular matrix (ECM) and controlled shear stress conditions. (B) Immunofluorescence images demonstrating the effects of shear stress on the kidney organoid differentiation in a kidney organoid-on-a-chip within 6 days of culture time. Each sample was stained for NPHS1 (podocyte, red), PECAM1 (vascular endothelial cell, green), LTL (proximal tubules, white), and DAPI (nuclei, blue) to identify the kidney-related cells, accordingly. (C) Cell coverage area and (D) antibody-positive area analysis of the kidney-related markers in organoid samples. *p<0.05 for LTL expression of Matrigel-coated group vs. Matrigel/vascular endothelial growth factor (VEGF)-coated group, ***p<0.001 for PECAM expression of Matrigel-coated group vs. Matrigel/VEGF-coated group). Scale bars are 100 μm. Adapted from Lee et al. Nano Converg 2021;8:35, with permission from Springer Open [70].
Fig. 4. Hepatic organoid culture on a microfluidic system. (A) An illustration depicting a proof-of-concept for the study of microfluidic environmental roles in hepatic organoid differentiation from human pluripotent stem cells (hPSCs). (B) Two-phase hepatic differentiation strategy tested by adapting different published hepatic differentiation protocols. hPSCs are committed to definitive endoderm cells in conventional culture conditions (CCC), i.e., a standard Petri dish, during the first phase, and then injected in microfluidic channels (μF) upon cell splitting. During the second phase cells are differentiated to mature hepatocyte cells by maintaining a fixed low frequency of medium change (2 times per day). (C) COL1, FN, LAM, and COL4 expression of IH cells derived from H0-193 human induced pluripotent stem cells (hiPSCs) in CCC and μF. (D) Real-time PCR analysis of Integrin receptors (ITGA5, ITGA6, ITGB1, and ITGB4), FN1, epithelial markers (E-CAD and cMET) of IH cells derived from H0-193 hiPSCs in CCC and μF. DE, definitive endoderm; ECM, extracellular matrix; HE, hepatic endoderm; MH, functional hepatocyte. Mean±standard error, n=6, t-test, *p<0.01, **p<0.005. Scale bar, 10 mm. Adapted from Michielin et al. Cell Rep 2020;33:108453, with permission from Elsevier [82].
Fig. 5. Multi-organoid combinations on a microfluidic platform. (A) Graphical illustration and (B) real images of the modular multi-organoids-on-a-chip hardware system setup to maintain the 3-tissue model. Individual microfluidic micro-reactor units house each organoid or tissue model, and are connected via a central fluid routing breadboard, allowing for straightforward "plug-and-play" system preparation initialization. (C) Viability of lung, liver, and cardiac constructs under following conditions: (i) no drug control and (ii) bleomycin after maintenance in the 3-organoid platform for 9 days. Bleomycin was added on day 3. Little cell death was observed; however, cardiac organoids in the bleomycin group appeared somewhat disaggregated. Green, calcein AM-stained viable cells; Red, ethidium homodimer-stained dead cells. (D) Cardiac organoid beating plots on day 9 of the sample groups as follows: The three-organoid platform cardiac organoids under (i) no drug control and (ii) bleomycin treatment, and (iii) Single cardiac organoids under bleomycin treatment. Adapted from Skardal et al. Sci Rep 2017;7:8837, with permission from Nature Research [83].
of which cannot precisely mimic human physiological organs. Compared to 2D cell models, stem cell-derived 3D organoid generation is currently favored to screen and examine the toxicity of various drug candidates. However, real tissues in the human body exist in a dynamic microenvironment with multiple tissue interactions that affect other downstream processes. Therefore, a microengineering system is an excellent tool to improve organoid technology that can further reflect multi-organ interactions inside the body, called multi-organoids-on-a-chip.

Briefly, multi-organoids-on-a-chip refer to attempts to culture several types of organoids on a microfabricated device that is specifically designed to mimic the functional properties and interactions of human organs in vitro. Skardal et al. [83] developed bioengineered tissue constructs using multiple organoids-on-a-chip that facilitate inter-organ reactions for drug screening. As depicted in Fig. 5A and 5B, a perfusion-driven and highly functional multi-tissue microfluidic chip containing heart, liver, and lung organoids was developed. The circulatory perfusion system enables modular “plug and play” abilities in the platform configuration, along with fluid flow using a micro-peristaltic pump. This multi-organoid platform can prevent drug testing failures because of unanticipated toxicity towards non-targeted tissues, which is crucial for its future applications in humans.

As a model study, bleomycin was selected to target the lung without harming the liver or cardiac organoids on the three-organoids-on-a-chip system; this drug is commonly used to treat some cancers that simultaneously induce severe lung fibrosis and inflammation. Based on the live/dead staining results shown in Fig. 5C, the no-drug control group and the bleomycin-treated group presented relatively low dead-cell numbers. In fact, cardiac organoid morphology was slightly changed along with its terminated beating rate because of bleomycin exposure (Fig. 5D). This evidence explained an unanticipated side effect of bleomycin because it does not cause cardiotoxicity. Therefore, the cardiac organoid alone was treated with bleomycin, and the beating plots data showed that bleomycin did not suppress the cardiac beat. Referring to all the data, it was suggested that bleomycin may have indirect effects on cardiac organoids through the production of possible secondary factors from one of the other organoids in the platform.

Three years later, the same research group successfully expanded their work by integrating six organoids instead of three on one integrated platform to better reflect complex native human organ interactions [84]. Briefly, the microfluidic device they reported allows the growth of multiple organoid types—cardiac, liver, vascular, testis, lung, and brain or colon—under the same recirculating perfusion system. It was clearly observed that one organoid functionality triggered the appropriate response from other organoids, especially in the presence of particular drugs. This complex 3D human-based mini-organoid system makes a remarkable contribution to validate the usefulness of advanced in vitro models in drug screening and future toxicological studies.

Conclusion and future perspectives

In summary, this paper reviews various studies focusing on the progress and challenges in organoid technology. Organoids are a well-known 3D self-organizing cellular model capable of accurately mimicking the corresponding in vivo organ. Organoids can overcome many limitations of animal models in biomedical research and clinical therapies. Integration with a microengineering system has been recently introduced into a bioengineered tissue model, named the organoid-on-a-chip. It has been proven that some organoid drawbacks could be solved by combining organoid culture with microfluidic devices (e.g., organoid maturation and vascularization). Meanwhile, more detailed and complex microfluidic-based organoid platforms should be developed to understand multiple organoid interactions that could better imitate human organs in vivo; such platforms are referred to as multi-organoids-on-a-chip. These advanced tissue engineering miniature models are widely applicable in various biological and biomedical fields, such as disease modeling and clinical drug screening.

Using a typical organoid-on-a-chip is rather challenging because of the need to accelerate its usability in a large quantity of human-oriented research. As a concrete example, the multi-organoid platform has been already known to be impactful for in vitro drug testing; however, the regulatory mechanism of drug efficacy relating to each mini-organ response remains unclear. Therefore, we hope to motivate researchers to utilize multi-organoids-on-a-chip for further investigations in interdisciplinary biomedical sciences. This advancement in organoid engineering can open up avenues to shorten the time needed for studies in the development of new future drugs, which usually takes more than a decade from the preclinical stages until commercialization in the market.

Notes

Conflict of interest
No potential conflict of interest relevant to this article was reported.
Funding
This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (Grant No. NRF-2019R1C1C1007633).

ORCID
Intan Rosalina Suhito, https://orcid.org/0000-0003-3268-6732
Tae-Hyung Kim, https://orcid.org/0000-0003-3671-3830

Data availability
Please contact the corresponding author for data availability.

References


