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Design strategy primer for organ-on-chips

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ABSTRACT

Organ-on-a-chip (OoC) has emerged as a revolutionary technique in recent decades, capable of replicating essential aspects of physiological and pathophysiological processes of human organs *in vitro*. Serving as an effective tissue culture method for creating digital twins, OoCs show significant promise and have found applications in disease modelling, drug screening, and tissue engineering. However, there has been a lack of emphasis on the fundamental design principles of OoCs in existing literature, a crucial aspect that cannot be overlooked, especially for beginners venturing into the realm of OoCs. Therefore, this paper endeavors to provide a comprehensive overview by delving into the historical development of OoCs, outlining the characteristics of their scaffolds, presenting design strategies for both conceptualisation and fabrication processes, and offering a detailed description of design mechanisms and guidelines based on recent research publications. Furthermore, it explores future prospects and challenges within the OoC domain. Serving as a foundational guide for those new to OoC exploration, this paper aims to furnish a thorough introduction to the fabrication and design strategies employed in OoCs.

Keywords:
Design strategies; Guideline; Organ-on-a-chip; Scaffold characteristics

1. Introduction

Organ-on-a-chip (OoC), an emerging revolutionised technique in recent years, has garnered significant interest in the fields of disease modelling and drug screening worldwide due to its ability of mimicking human organs *in vitro*.[1] In 2016, it was selected as one of the "Top ten emerging technologies" in World Economic Forum held in Tianjin, China. As an effective tissue culture method for digital twins, OoC holds great potential in personalised medicine and serves as a crucial tool for tissue engineering[2] and reproductive medicine.[3]

As the name suggests, OoC means constructing human organs on a microfluidic chip *in vitro*. In contrast to the traditional two-dimensional planar cell culture technique, where human cells are cultured on the culture dishes or flasks, OoC emphasises on replicating the role and function of organs, making it more reliable for simulating and evaluating physiological and pathological process in the human body. In light of ethical concerns, time-consuming nature, high costs and species divergence with animal experiments, OoC is regarded as a novel alternative to animal tests in the human disease studies due to its inherent superiority of using human cells. Presently, OoC is been applied in human cell biology, disease physiology, and drug development for pre-clinical human disease diagnosis and treatment.[3]

A crucial aspect of OoC studies is the presence of the microfluidic chip, which serve as the predecessors and supporters of OoCs. Microfluidic chips are fabricated with micron-thin internal channels engraved on polymers, glass or silicon. Among various materials used, polydimethylsiloxane (PDMS) is commonly employed, fabricated into OoC frames through soft lithography.[4] The transparent and biocompatible characteristics of PDMS allows for real-time observation of human cells cultured in the chip. The small size accelerates biological reactions within the chip and enables high-throughput detection. The excellent physical properties of microfluidic chips, including

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thermal conductivity and mechanical strength, facilitate rapid responses to external stimuli, such as channel bending or deformation. The first OoC was proposed using PDMS base by Ingber's group in 2010,[5] in successfully reconstituting human alveoli *in vitro* on a microfluidic chip. Subsequently, with advances in techniques, a variety of OoCs has emerged.

Despite some published reviews focusing on different aspects of OoCs, like biomedicals,[6] biomaterials[7] or biosensing,[8] a comprehensive design mechanism of OoCs has been rarely reported in recent years.[9] This design aspect is essential and significant for OoCs studies, particularly for beginners. Therefore, we here introduce OoCs from the standpoint of scaffolds to analyse chip design. OoC-related academic papers regarding of articles, reviews or patents published in Web of Science have been collected and analysed. By categorising OoCs based cell compartment types, we provide an in-depth of OoCs. The aim of this review is to offer an overview of scaffold and design strategies, inspiring life scientists to explore OoCs, advance the understanding and address future perspectives and challenges to bridge the gap between *in vivo* and *in vitro* research.

2. History of organ-on-a-chip

In 2004, Schuler *et al.* first proposed the concept of *in vitro* mammalian tissue culture using different organ cells to replicate the *in vivo* microenvironment,[10] employing microfluidic compartments to culture cells for the creation of a three-chamber "lung"-"liver"-"other" microscale cell culture analog device (**Figure 1**). In this device, mammalian cells (L2 and H4IIE cell lines) are cultured in interconnected chambers connected by recirculating tissue culture medium, mimicking animal *in vivo* metabolism and aiming to estabilish a pharmacokinetic analysis model. The capabilities of conducting multiple experiments in parallel, realistically mimicking tissue culture physiologically, and monitoring the status of individual cells online provide the potentical of a human surrogate to predict human responses in clinical trials. This work is widely recognised as the earliest publication and the prototype of *in vitro* human tissue culture with microfluidic chips, making the initial development of human OoCs.

In 2010, Ingber *et al.* developed a significant and representative human OoC reconstituting organ-level human lung function on a microfluidic chip, bringing the OoC concept into reality.[5] In this groundbreaking work, they utilised a PDMS-based microfluidic chip to create two cell-culture compartments and two side chambers. Human alveolar epithelial cells and endothelial cells were positioned in seperate compartments (**Figure 2A**), separated by a porous PDMS thin membrane to allow relative independence of cell growth while facilitating small molecule communication between epithelial and endothelial cells. Side vacuum chambers were stimulated with periodic air vibration to simulate human pulmonary spontaneous breathing and surfactant production (**Figure 2A** and **B**). Schematic device fabrication details are presented in **Figure 2C** and **D**. Two PDMS layers and a PDMS membrane with a hole array were aligned and permanently bonded via Plasma treatment to form two sets of three parallel microchannels (**Figure 2C**). Subsequently, PDMS etchant was introduced into the side channels, where periodic vacuum stress induced mechanical stretching (**Figure 2D**). This design ensures barrier integrity and permeability, likely forming an air-liquid interface and maintaining alveolar-capillary barrier function. The authors evaluated the chip's response to nanoparticulate aerosols delivered into the epithelial compartment, studying the transport of nanoparticles from alveoli into the pulmonary vasculature for toxicology applications. The results demonstrated similar physiological effects of the lung-on-a-chip compared to the whole mouse lung in nanoparticle absorption, highlighting potential of OoC as an alternative to animal testing. Additionally, the compact size of the established human lung-on-a-chip (**Figure 2D**) indicated low experimental cost and the feasibility of high-throughput screening studies. This work establishes a crucial foundation for OoC advancement and is widely considered as the pioneer of the human OoCs.

What confuses new readers is the misconception that OoC involves the reconstituting a human organ on a microfluidic chip. In fact, a more precise definition of OoC is that it does not replicate the entire organ, but the repeating organic unit. For example, the lung-on-a-chip created by Ingber's group (**Figure 2**) includes layers of human alveolar epithelial cells, extracellular matrix (ECM)-coated PDMS, and endothelial cells,[5,11] mimicking the configuration of the human alveolar repeat unit. By introducing mechanical signal like cyclic stretching to simulate breathing movements and fluid shear stress to imitate blood flow, the bio-fabrication process of the lung-on-a-chip creates a biomimetic microenvironment akin to the human body's alveoli. This concept of replicating human organic units is prevalent in the construction of various OoCs. For instance, a human-airway-on-a-chip developed by the same group aimed at rapid identification of antiviral drugs, utilising a structure of bronchial-airway epithelium/ECM/pulmonary endothelium to mimic human airway physiology.[12] The focus on organic repeat units in human OoCs serves as a human surrogate, effectively capturing key features of human organs and reproducing organic physiology and pathophysiology at tissue and organ levels, as evidenced by subsequent research in the field impacting disease modelling and drug screening significantly.

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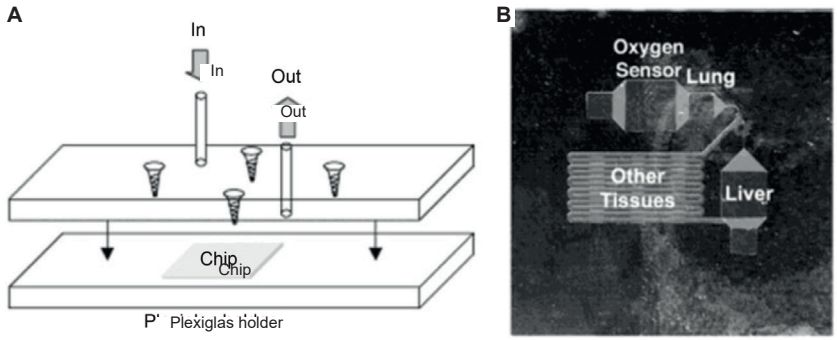

Figure 1. (A) The fabrication of the microscale cell culture analog (μCCA) device: A Plexiglas (poly(methyl metacrylate)) piece (top) and a Plexiglas sheet (down) are utilised to enclose the channels of the silicon chip, and the entire device is assembled using stainless steel screws. (B) The 1-inch square silicon chip integrates a dissolved oxygen sensor and virous cultured mammalian cells by circulating tissue culture medium within interconnected tissue compartments. Reprinted from Sin *et al.*[10] Copyright 2004, American Institute of Chemical Engineers (AIChE).

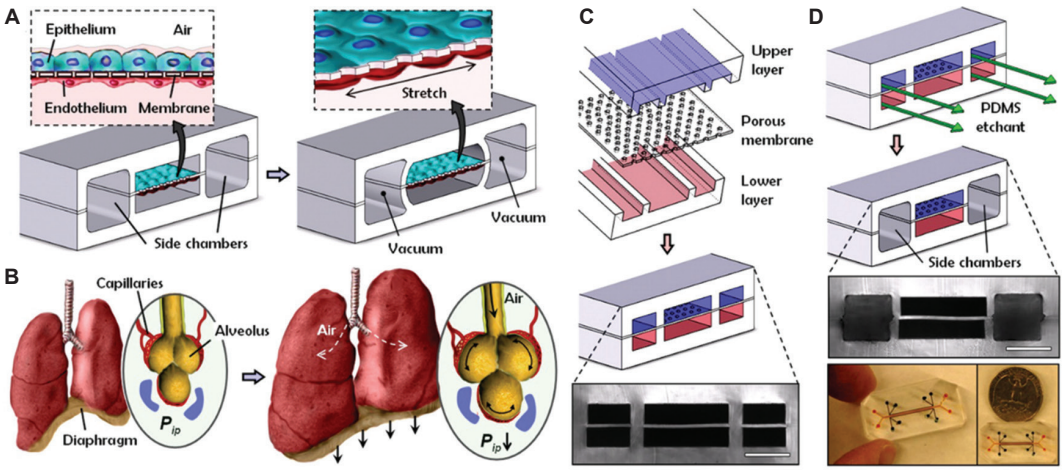

Figure 2. Design of the human lung-on-a-chip with biomimetic breathing process. (A) The microfabricated device featuring compartmentalised PDMS microchannels. (B) The spontaneous contraction and detension of the living lung. (C) Schematic diagram of the device composition with three PDMS layers. (D) Application of PDMS etchant into the side channels to create two vacuum chambers for mechanical stretching of the lung-on-a-chip, and the real images of the fabricated OoC device. Reprinted from Huh *et al.*[5] Copyright 2010, American Association for the Advancement of Science.
Abbreviations: OoC: 0rgan-on-a-chip; PDMS: Polydimethylsiloxane; P_{ip}: Intrapleural pressure.

In 2010, the National Institutes of Health and the U.S. Food and Drug Administration provided funding for regulatory science projects, including the development of a heart-lung tissue chip model to predict drug safety and efficacy in humans. Subsequently, in 2011, a collaboration between National Institutes of Health, U.S. Food and Drug Administration, and Defense Advanced Research Projects Agency led to the initiation of a microphysiological system project based on OoCs, officially launched in 2012. Researchers worldwide collaborated to develop three-dimensional (3D) human organs on chips and eventually a human-body-on-a-chip, revolutionising tissue chip technology and accelerating OoC advancements. In Europe, the Institute for Human Organ and Disease Model Technology established the European Organ-on-Chip Society in late 2018.[13] Similarly, in Asia, notably China, extensive networks for OoCs have been established, with the publication of standardised guidelines for OoCs.[14] Strong national-level funding and strategic support globally have laid a solid foundation for the OoC era, transforming new drug development by significantly reducing costs and screening times.[15]

A significant advantage of OoC design lies in its versatility, facilitating the establishment of diverse human organic models within the same microchip. Pioneers like Ingber's group have successfully applied OoC models to various organs such as kidney proximal tubules,[16] small airway,[17] liver,[18] and intestine.[19] This versatility has streamlined industry access and preclinical research, with companies like Emulate (Boston, MA, USA), TissUse (Berlin, Germany), Mimetas (Oegstgeest, The Netherlands) and CN Bio Innovations (Cambridge, UK) successfully industrialising OoCs worldwide. Additionally, the integration of advanced technologies like 3D bioprinting,[20] clustered regularly interspaced short palindromic repeats (CRISPR),[21] and organoids[22] has further fueled the broad and in-depth research development of OoCs in recent years.

3. Conceptualisation and fabrication of organ-on-a-chip

Currently, well-established OoC models can be broadly categorised into single OoCs, focusing on simulating individual organs, and multiple OoCs (also known as body-on-a-chip), aiming to replicate the systemic interactions between multiple organs in the human body. Single OoCs are designed to delve into the intricate biological processes of a specific organ, while body-on-chip models emphasise the interconnected responses between various organs, moving beyond isolated organ studies. These distinct approaches allow researchers to model both physiological and pathological responses within the body, each with its own set of emphases based on chip properties such as geometric features and the biological phenomena under investigation. Furthermore, the integration of sophisticated monitoring systems adds another layer of complexity to OoCs, making it more challenging for researchers to grasp the intricacies of chip design and fabrication. By examining OoCs from a cellular compartment perspective, irrespective of variations in cell types or organ origins, it can be found that these compartments primarily serve functions related to cell culture, introducing external stimuli, and detecting experimental parameters. Based on the number of cell compartments present, OoCs can be classified into three main categories: one cell compartment (OCC), two cell compartments (TCC), and multiple cell compartments (MCC).

3.1. One cell compartment

OCC represents the simplest form of OoC structure, serving as the fundamental unit for chip design. It typically consists of a single compartment for cell cultivation, which includes culture medium and biological hydrogels to support cell growth.[23] For example, vessels-on-a-chip models replicate structures like blood vessels,[24] lymphatic vessels,[25] and mammary ducts,[26] enabling studies on microvascular functions, vascular diseases, drug delivery assessments, and so on.[27,28] These vessels have a shared feature that they have a tubular lumen structure, typically made up of monolayer overlapping endothelium cells and surrounding matrix.[29] Notably, these microvasculatures have a structural size ranging from millimetres to submicrometers,[9] which is an important factor to be considered during the OoCs implementation. To reproduce physiological and pathophysiological features of vessels on the chip, they are always simplified into a lumen embedded by the scaffold material (**Figure 3A**).[30] Except for the simplest two-dimensional vessels-on-a-chip with endothelial cell growth in a chamber,[31] endothelial lumens circumferentially surrounded by collagen gel[32,33] or 3D spiral microvessel[34-36] are also advanced for the vessels-on-a-chip nowadays. Another common type of OCC recapitulates the function of specific organs, consisting of target organ cells and corresponding ECM. For instance, Guo *et al.*[37] used gelatin methacryloyl doped with MXene to function as ECM (**Figure 3B**). Together with cardiomyocytes, a layer-assembled heart-on-a-chip system with optical sensing capacity had been established to real-time observe the response human cardiomyocytes to drugs, in which only one kind of human cells with multi-channels were cultured in the OoC.

3.2. Two cell compartments

TCC comprises two distinct compartments interconnected by porous interface materials that facilitate physical and chemical communication between channels. Representative structures of TCC primarily consist of the top-down arrangement model (channels arranged perpendicularly) and the left-right arrangement model (channels arranged horizontally). In the schematic diagram presented in **Figure 4A**,[38] the up-down model showcases the upper compartment designated for epithelial cell culture and the lower compartment typically utilised for endothelial cell culture, thus replicating the repeat organic unit of the target organ. An example belonging to this category is the OoCs mimicking the respiratory system developed by the Ingber's group, involving two compartments separated by a porous PDMS membrane.[12] In contrast, the left-right model incorporates channels for tissue cells and endothelial cells as well, with the intermediate space usually filled with a biological hydrogel matrix. For instance, the lung-on-a-chip designed by Zhang *et al.*[39] employed alveolar epithelial cells, pulmonary vascular endothelial cells, and Matrigel to recreate the alveolar microenvironment and functions, simulating

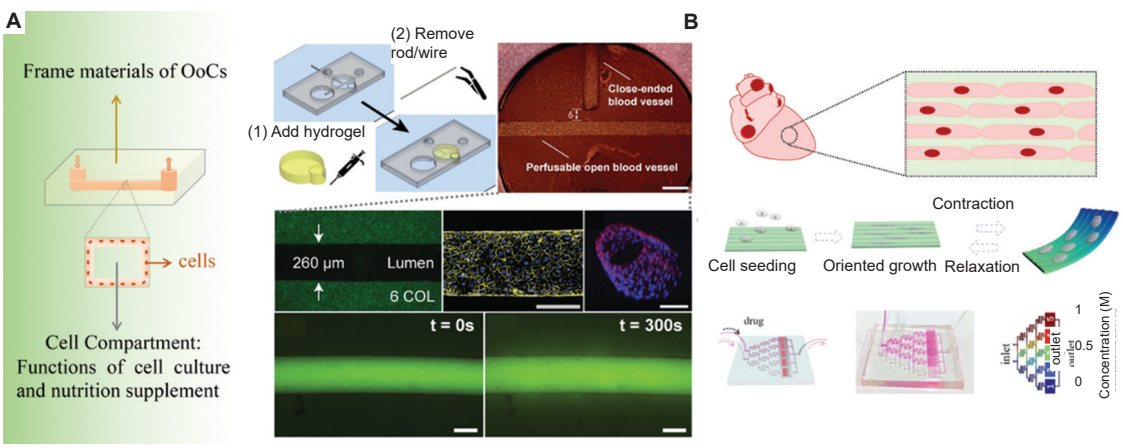

Figure 3. One cell compartment has only one cell type and can be used in OoCs for vessels or tissues. (A) Single channel of vessel-on-a-chip. Reprinted from Agarwal *et al.*[30] (B) Multiple channels of heart-on-a-chip. Reprinted from Guo *et al.*[37] Copyright 2025, Elsevier B.V. Abbreviations: COL: Collagen; OoCs: Organ-on-chips.

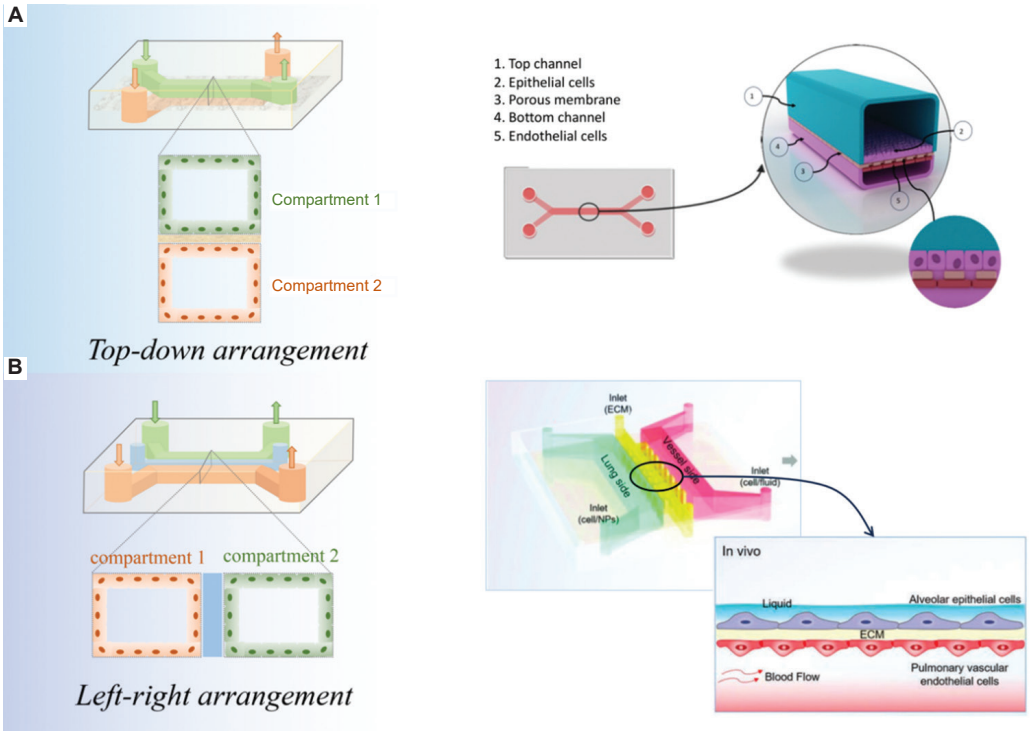

Figure 4. TCC consists of two cell compartments separated by porous interface materials or biological matrix. (A) A schematic cross section of the liver-on-a-chip with an up-down TCC configuration. Reprinted from Kennedy *et al.*[38] (B) A schematic cross section of a lung-on-a-chip device with a left-right TCC arrangement. Reprinted from Zhang *et al.*[39]
Abbreviations: TCC: Two cell compartments.

pulmonary responses in nanotoxicity testing (**Figure 4B**). The rationale behind the popularity of the left-right OoCs model likely lies in the softer nature of biological hydrogels, making it challenging to support cell growth in the top-down OoCs model due to the lower hollow compartment. However, the side walls of compartments in the left-right configuration do not provide optimal support for cell growth due to gravity, leading to occasional challenges in cell adhesion to the hydrogel. Nevertheless, most OoCs are structured in this manner owing to the natural support provided by hydrogels for organoids. TCC represents the prevalent OoCs type, encompassing lung-on-a-chip,[40] liver-on-a-chip,[41] kidney-on-a-chip,[42] heart-on-a-chip,[43] joint-on-chip,[44] and so on, where one compartment is consistently tailored for mimicking the surrounding blood vessels given their crucial role across multiple organs.[45]

3.3. Multiple cell compartments

Three or more types of human cells are integrated into a single microfluidic chip, a practice less common in conventional OoC fabrication (only one target organ) more prevalent in multi-organs-on-a-chip systems (or body-on-a-chip). In the context of conventional OoCs, MCC can be viewed as a systemic overlay or combination of OCC or TCC, featuring vertically, horizontally, or mixed stacked channels (**Figure 5**). Vertical channel stacking entails arranging the three cell compartments in a vertical manner, with or without separation interfaces. For instance, Wufuer *et al.*[46] developed a skin-on-a-chip model by co-culturing epidermal, dermal, and endothelial cells from humans to mimic skin inflammation and oedema and assess the efficacy of therapeutic drugs. Each layer was separated by PET porous membranes, facilitating interlayer communication. Song *et al.*[47] employed coaxial bioprinting to create an intestine-on-a-chip, forming closely packed multiple cells into small intestine-like tubular structures (**Figure 5A**). Similar designs can also be achieved with horizontally arranged channels, such as the endometrium-on-a-chip pioneered by Ahn *et al.*[48] (**Figure 5B**) They utilised endometrial stromal fibroblasts, endometrial epithelial cells, and endothelial cells in a 3D ECM to construct a microengineered vascularised endometrium-on-a-chip, mimicking the structure of the endometrial epithelium, stroma, and blood vessels. This model proved useful for evaluating the impact of the emergency contraceptive drug levonorgestrel. Another MCC configuration involves a hybrid model combining both horizontal and vertical arrangements, exemplified by a tumour microenvironment-on-a-chip established by Lee *et al.*[49] (**Figure 5C**). Various other compartmentalisations are also evident in OoC research, including a four-channel microfluidic model constructed by Libet *et al.*[50] to mimic the blood-brain and blood-cerebrospinal fluid barriers.

In the realm of OoC systems integrating multiple organs on a chip, MCC are typically involved to fully replicate the functional networks of their *in vivo* organ counterparts. Organs are interconnected through recirculating vascular flow with shared vascular channels (**Figure 6A**)[51] or bridged vascular tubing (**Figure 6B**).[52] Noteworthy is the concept of organoids-on-a-chip, which combines the advantages of both organoids and OoCs in emulating native organs with enhanced fidelity and is also classified as OoCs sometimes.[53] Usually derived from human induced pluripotent stem cells or tissue-resident adult

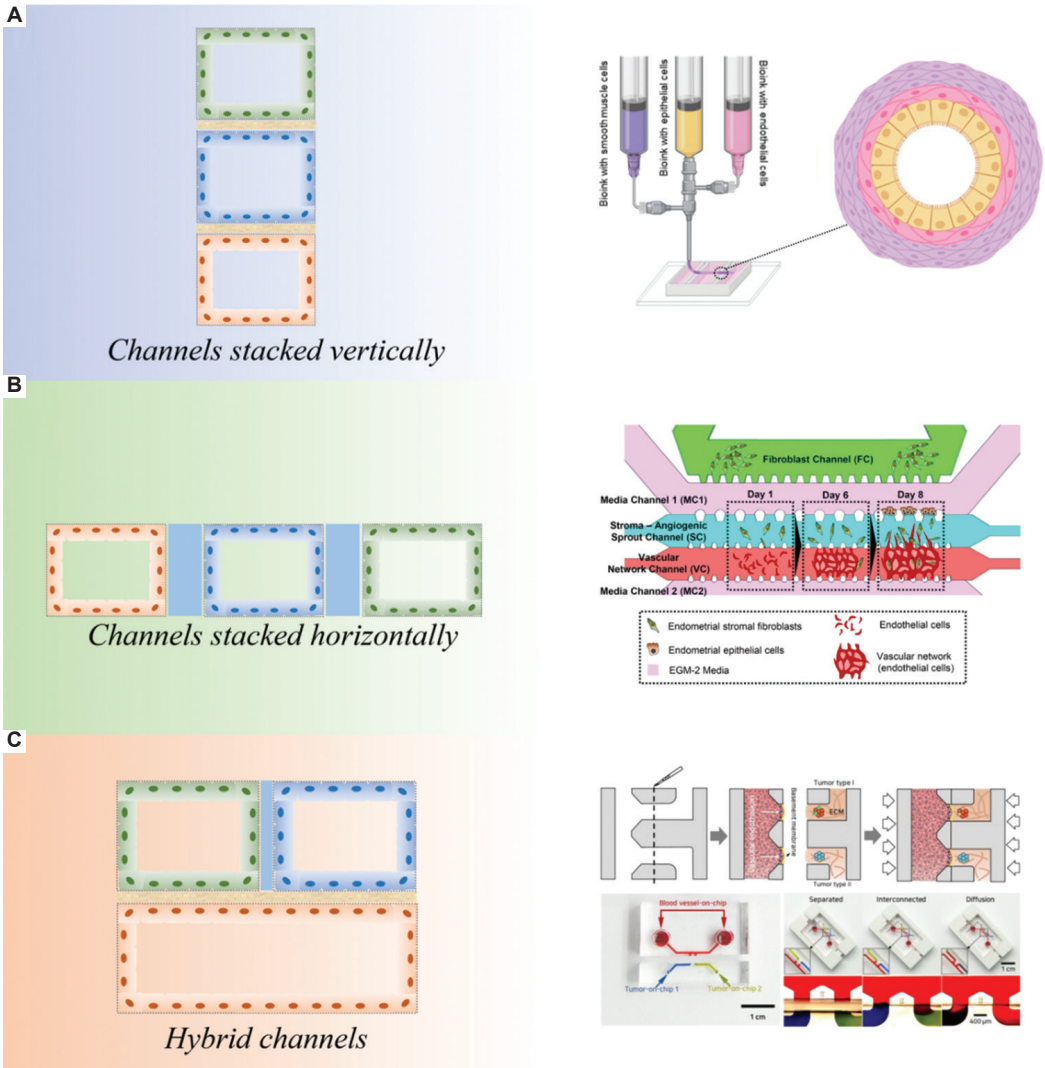

Figure 5. (A) A MCC type with the overlay of three cell compartments perpendicularly for the designed intestine-on-a-chip. Reprinted from Song *et al.*[47] Copyright 2024, Royal Society of Chemistry. (B) A MCC type with the combination of three cell compartments horizontally for an endometrium-on-a-chip. Reprinted from Ahn *et al.*[48] (C) A hybrid MCC structure for tumour microenvironment-on-a-chip with upside blood vessel cell channel and downside tumour cell channels. Reprinted from Lee *et al.*[49] Copyright 2025, Elsevier B.V.
Abbreviations: MCC: Multiple cell compartments.

stem cells via self-organisation,[54,55] organoids are commonly embedded in hydrogel channels on the chip (**Figure 6C**),[56] making a left-right chip design preferable due to the presence of a soft hydrogel matrix. Additionally, spheroids or organoids on an array chip are classified as OoCs sometimes duo to their ability of mimicking human organ functions effectively (**Figure 6D**).[57]

4. Intercellular interface between cell compartments

The interface between cell compartments plays a vital role in OoC systems, serving various functions such as facilitating cell growth, adhesion, support, regulation of cellular functions, and chemical/signal communication. It mainly contains chemical materials, biological hydrogel and cell culture medium.

Polymeric materials with a porous structure are crucial in OoCs due to their excellent permeability, enabling cell separation while maintaining the exchange of macromolecules between different cell compartments.[58] These materials serve as substrates for cell culture, mimicking the ECM or basement membrane surrounding the cells. PDMS, commonly used in pioneering OoC research, offers advantages such as optical transparency, long-term biocompatibility, high oxygen permeability, elasticity, and cost-effectiveness.[59] It remains prevalent in modern OoCs, functioning as a flexible membrane with topographical patterns to support cell responses. Poly(carbonate) (PC), widely in Transwell® inserts, is another commonly used flexible membrane in OoCs. It is transparent, hydrophobic, inert and non-biodegradable. Compared with PDMS, PC is a stiffer polymer and not suitable for OoCs requiring soft substrate or stretching stimulation.[60] Except for PDMS and PC, poly(ethylene terephthalate), poly(lactic acid), poly(l-caprolactone), and other porous are also utilised in OoCs to support cell growth and allow for nutrient transport based on experimental requirements.[60] These materials are

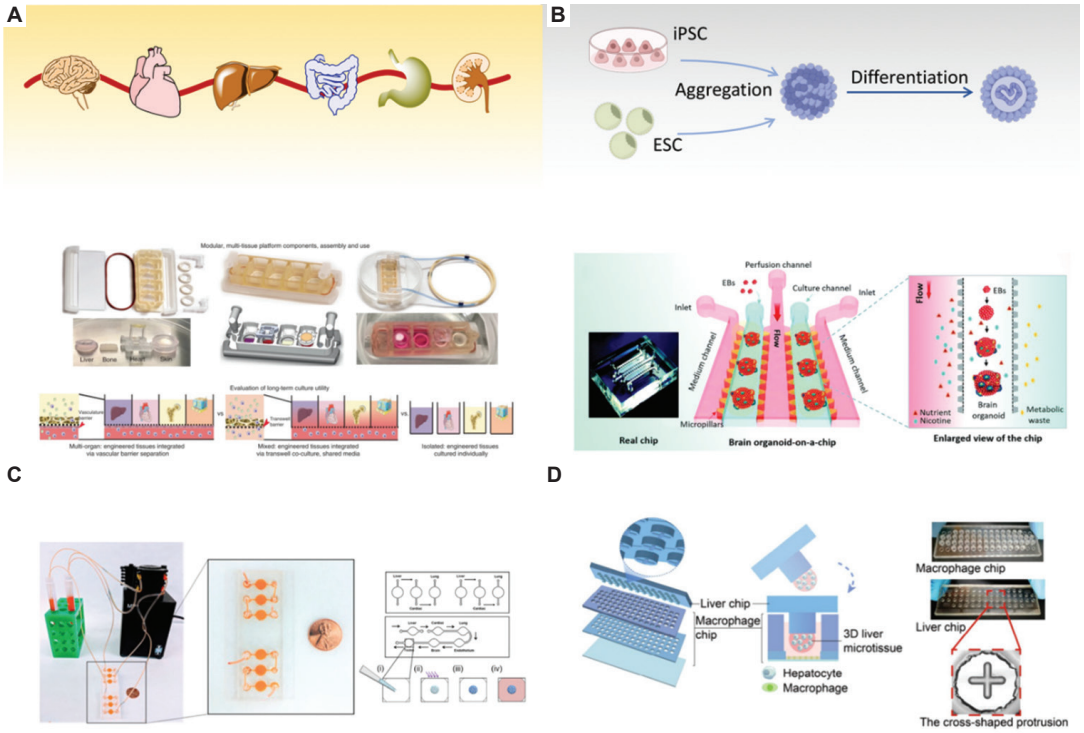

Figure 6. (A) A organoids-on-a-chip with multi-organoids involved in the chip, forming a tissue-chip system with matured human heart, liver, bone and skin tissue niches linked by recirculating vascular flow. Reprinted from Ronaldson-Bouchard *et al.*[51] (B) Multiple organoid-on-a-chip was connected by microtubes to form multi-organoids-on-chips. Reprinted from Rajan *et al.*[52] Copyright 2020, Acta Materialia Inc. (C) A representative organoids-on-a-chip with brain organoids, not cells, inoculated in the microchip, holding the strengths of both organoids and OoCs. Reprinted from Wang *et al.*[56] Copyright 2018, Royal Society of Chemistry. (D) Liver-on-a-chip with 3D liver microtissue and macrophages on a stacked array chip. Reprinted from Hou *et al.*[57] Copyright 2024, American Chemical Society. 3D: three-dimensional.

often treated with protein coatings or gas plasma to enhance cell adhesion and proliferation before cell inoculation into the chips. Chemical membrane in between always can be seen in top-down TCC.

Biological hydrogels serving as tissue scaffold materials are usually housed within a microchannel in left-right OoCs. These hydrogels, whether natural or synthetic, play a crucial role in supporting cell cultures, including stromal cells, vascular networks, or organoids.[61] Natural hydrogels, including proteins, polysaccharides and animal-derived mixtures, are obtained from nature and has a semiporous structure.[62] They have similar constitutes with natural ECM and can interact with living cells favourably, for example remodelled by cells, due to their good biodegradability and physiochemical properties.[63] Notably, collagen, a kind of thermo-gelation hydrogels at 37°C, is widely used in OoCs due to its abundance in the human body and presence in various tissues.[64] Synthetic hydrogels used in OoCs are bioinert and usually hold adjustable mechanical properties.[63] It can be chemically modified, for example, Gjorevski *et al.*[65] used Arg-Gly-Asp peptide-functionalised poly(ethylene glycol) hydrogels to govern cell morphology, to act as 3D scaffolds in customised experiments. In addition, to precisely regulate cell expansion, migration or differentiation, hybrid hydrogels with natural and Synthetic gels are utilised in OoCs to improve the effeciency.[66-68]

To supply cell nutrition, cell culture medium will be confined in a separated channel between TCC. In this situation, the cell compartment is fulfilled with organoids-embedded hydrogels in most cases. Here, the cell culture medium is also considered as a kind of cellular interface.

5. Frame microfabrication of the boundary

The selection of boundary materials depends on various factors, such as the intended functionality of the final product, microfabrication strategies, read-out methods, and biocompatibility requirements. Generally, transparent materials with good gas permeability are preferred for OoC fabrication due to the ease of culturing and monitoring the chips.

PDMS stands out as the most commonly used material in OoC fabrication. Being a silicon-based elastomer, PDMS offers numerous advantageous properties for chip fabrication and is widely utilised as both frame and interfacial materials. For instance, in pioneering work in the OoC field illustrated in **Figure 2**, researchers successfully employed PDMS to create an entire alveolus-on-a-chip model with stretchable capabilities. However, the non-specific absorption of drugs or proteins by PDMS can pose risks, particularly in drug efficacy and toxicity testing.[69-71] Alternative approaches when using PDMS in drug tests include coating it with lipids[69] or substituting PDMS with materials like polystyrene and cyclo-olefin polymers.[72] Furthermore, surface modifications such as plasma treatment and ultraviolet (UV) treatment are commonly employed to enhance the physical and chemical properties of PDMS.

Thermoplastics like PC, polystyrene, poly(methyl methacrylate), and cyclic olefin copolymer are also frequently proposed for OoC applications due to their good biocompatibility, cost-effectiveness, and ease of fabrication.[73,74] These materials exhibit low drug absorption and are thus considered alternatives to PDMS in OoCs. The high-throughput fabrication of OoCs can be achieved through injection molding of thermoplastics. However, thermoplastics have drawbacks such as non-transparency, strong autofluorescence, and poor gas permeability, which may restrict their suitability for microscopic observation and long-term cell culture.

Glass is another material commonly used in microfluidic devices for OoCs due to its lower drug absorptivity and higher mechanical durability compared to PDMS.[74] Its high transparency and good biocompatibility make it widely accepted for biological applications. Laser etching can further enhance the utilisation of glass in sub-microfluidic channel fabrication for OoCs. Nevertheless, glass's major drawback in OoCs lies in its low gas permeability.

3D printing resins enable the accurate creation of complex 3D structures through 3D printing technology.[75] However, careful attention must be paid to their biocompatibility when used for OoCs. Therefore, the use of 3D printing in OoCs often involves incorporating hydrogels as cell culture scaffolds. While hydrogels offer superior biomimicry compared to other materials, their low stiffness and biodegradability may limit their applicability for long-term cell culture in OoCs.

In short, each of these materials possesses distinct strengths and limitations. Depending on the specific experimental objectives, materials can be selected with appropriate considerations. Often, a combination of two or more materials is employed in OoC design to achieve the desired outcomes.

6. Auxiliary external stimulation

In OoCs, auxiliary external stimuli are often introduced to create a customised cell-culture environment that mimics the biological functions of specific organs, such as heartbeat, muscle contraction and lung respiration. These stimuli include chemical factors (such as ion concentration, oxygen gradient),[76,77] biological factors (such as extracellular vesicles, commensal bacteria)[78,79] and physical factors (such as mechanical force, geometric confinement).[80, 81] They assist OoCs to anchor target organs and provide a more biomimetic microenvironment for the growth and differentiation of organic cells. Unlike chemical or biological stimuli that are typically co-incubated with cells, physical stimuli are directly applied as external forces to the chip.[82] Two common types of physical stimuli are discussed here.

6.1. Mechanical stimulation

Mechanical stimuli are inherent in various organs such as blood vessels, lungs, hearts, muscles, tendons, and bones,[83] contributing to both physiological and pathological processes in organisms. They are considered the most prevalent biophysical cues due to their involvement throughout different life stages.[84] Incorporating biomechanical stimulation into OoCs can influence cellular response and cell differentiation.[85] Common types of mechanical force stimuli actively sensed by cells in OoCs include fluid shear stress, stretching, compression, hydrostatic pressure, pulsatile force, and interstitial flow (**Figure 7**).[86] By integrating mechanical stimulation into OoC designs, researchers can replicate the physical cues that cells experience *in vivo*, enabling a more accurate representation of organ functionality and response within the microfluidic system.

Fluid shear stress is commonly exerted by flat or disturbed fluidic flows (**Figure 7A**). In the context of vasculature, blood flow imposes shear stress on endothelial cells, influencing cell morphology, proliferation, and vessel permeability.[87] Generally, in blood vessel-on-chip models, shear stress induced by pumped culture media or blood flow proves beneficial for studying conditions such as atherosclerosis, thrombosis, and aneurysms. Additionally, applying shaking or orbital rotation to a culture dish exposes cells to shear stress through oscillatory movements of the medium and cells.[88]

Stretching, including cyclic stretching, can be achieved by pulling cell substrates (**Figure 7B**). An exemplar study is the lung-on-a-chip model pioneered by Ingber's group[5] and published in Science. This model utilised negative pressure in adjacent compartments to induce stretching of a PDMS chamber and subsequently stretch the cellular substrate based on the elasticity of PDMS. Alternatively, stretch carriers can assist in inducing stretching on cell substrates.

Conversely, constant or cyclic compression is typically applied by compressing cell substrates, often utilising biochemical scaffolds or flexible membranes (**Figure 7C**). For instance, Kong *et al.*[89] applied cyclic compressions onto hydrogels laden with cardiac fibroblasts to explore cardiac fibrotic remodelling. Liu *et al.*[90] reported a deformable membrane with compression force to measure hydrogel construct stiffness of 3D cell-hydrogel arrays in situ. Although cells recover to its original shape when the compression force is removed, cellular response in physiological aspects is obviously affected by the stimulation, especially in organs of skeletal muscle, skin, vasculature, and so on.

Hydrostatic pressure offers a simple means of sample injection or cellular stress sensing without external assistance (**Figure 7D**), such as an external pressure pump. It is easy to generate and maintain, making it a convenient tool in OoCs. Hydrostatic pressure can be delivered to cells via fluidic flow[91] or directly imposed on samples in models like microvasculature-on-a-chip[92] and lung-on-a-chip.[93] Notably, dynamic hydrostatic pressure generation is often accompanied by fluid shear stress in OoC systems

Blood pumped from the heart to vessels suffers from pulsatile force, leading to the formation of pulsatile flows (**Figure 7E**). Within blood vessel-on-chip models, these pulsatile forces exert shear stress on endothelial cells, enabling the study of physiological conditions in vessels, such as haemodynamic behaviour.[94] Previous research indicates that pulsatile forces can influence cell morphology, cytoskeletal organisation, and barrier formation.[95]

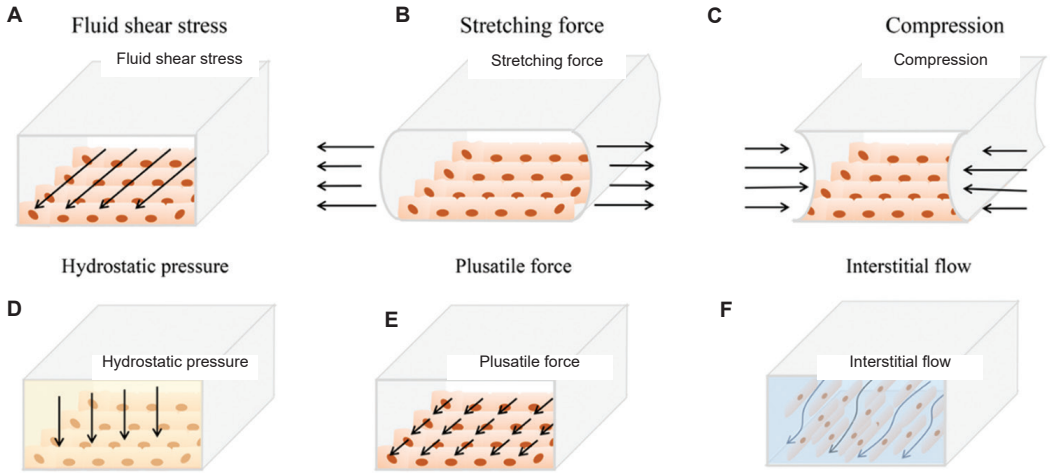

Figure 7. Cartoon illustration of the six common mechanical forces in OoCs: Fluid shear stress, stretching force, compression, hydrostatic pressure, pulsatile forces and interstitial flow.
Abbreviations: OoCs: Organ-on-chips.

Interstitial flow in OoCs typically refers to the movement of fluid around interstitial cells within a 3D porous ECM (**Figure 7F**). This flow occurs across the cell-matrix interface in various directions[96] and has been shown to impact cell migration and angiogenesis.[82] OoCs are regarded as a promising platform for introducing interstitial flow due to their capability of housing ECM within chambers consistently. It is important to note that interstitial flow often exhibits slower velocities or greater driving forces due to ECM resistance.

The flow patterns of bodily fluids are indeed complex, such as spiral laminar flow in veins, often involving a combination of mechanical force stimuli. Incorporating these stimuli undoubtedly enhances performance and fosters a more biomimetic behaviour resembling that of organs within the body. Additionally, factors like substrate stiffness, topographical patterns, and geometric constraints serve as common mechanical stimuli that passively influence cellular responses. The magnitude, duration, and frequency of these mechanical stimuli are crucial considerations that should be adjusted in OoCs to replicate cellular functions accurately.

6.2. Electrical stimulation

Electrical stimulation is also occasionally incorporated into OoCs, albeit in limited instances. For example, Vivas *et al.*[97] integrated electrical pacing into a heart-on-a-chip model using highly customisable 3D-printed pyrolytic carbon electrodes to support the maturation of cardiac microtissues. van der Helm *et al.*[98] applied electrical stimulation in a gut-on-a-chip, facilitating the normalisation of cell layer resistance in the epithelium and determination of transepithelial electrical resistance values. These stimuli are sometimes integrated in a more intricate pattern within the chip, with multiple stimuli combined to achieve specific experimental objectives effectively.[99]

7. Research trends in organ-on-chips

As an *in vitro* research method that mimics the anatomical, physiological, and pathological conditions of human organs, OoCs have significantly advanced disease modelling and drug screening capabilities. Here, academic publications related to OoCs from Web of Science database spanning from 2010 to 2024 have been collected and refined. Utilising bibliometric analysis, a comprehensive overview of OoCs was conducted to analyse the current status, distribution of research hotspots, future trends, and other pertinent aspects, which can serve as a valuable tool for researchers to assess the landscape of OoCs research to some extent.

To acquire OoC-related papers correctly and strictly, papers written in English and classified as "article" or "review" are collected with TS = ("organ-on-a-chip" OR "organ-on-chips" OR "body-on-a-chip" OR "body-on-chips" OR "human-on-a-chip" OR "body-on-a-chips" OR "organoid-on-a-chip" OR "organoids-on-a-chip" OR "spheroids on-a-chip" OR "spheroids on-chips" OR "neurovascular unit-on-a-chip" OR "NVU-on-a-chip" OR "Blood–brain barrier-on-a-chip" OR "BBB-on-a-chip" OR "BBB-on-chips" OR "retina-on-a-chip" OR "eye-on-a-chip" OR "tooth on-a-chip" OR "pulp-dentin complex-on-a-chip" OR "lung-on-a-chip" OR "lung-on-chips" OR "alveolus-on-a-chip" OR "airway-on-a-chip" OR "airway-on-chips" OR "liver-on-a-chip" OR "liver-on-chips" OR "heart-on-a-chip" OR "heart-on-chips" OR "intestine-on-a-chip" OR "gut-on-a-chip" OR "kidney-on-a-chip" OR "kidney-on-chips" OR "glomerulus-on-a-chip" OR "tubule-on-a-chip" OR "bladder cancer-on-a-chip" OR "cancer-on-a-chip" OR "carcinoma-on-a-chip" OR "cancer-on-chips" OR "placenta-on-a-chip" OR "vagina-on-a-chip" OR "endometrium-on-a-chip" OR "colon-on-a-chip" OR "progeria-on-a-chip" OR "metastasis-on-a-chip" OR "skin-on-chips" OR "WAT-on-a-chip" OR "epithelium-on-a-chip" OR "epidermis-on-a-chip" OR "endothelium-on-a-chip" OR "vessel-on-a-chip"

OR "vasculature-on-a-chip" OR "vasculature-on-chips" OR "microvasculature-on-a-chip" OR "lymphoid follicle-on-a-chip" OR "lymphangiogenesis-on-chip") in Web of Science Core Collection (citation indexes of Science Citation Index Expanded) with publication data from January 1, 2010 to December 31, 2024. A total of 2490 scientific papers were retrieved, written by 11,814 authors coming from 2570 organisations in 80 countries. They are published in 618 journals and cite 125,647 references in all.

Among these literatures, 232 authors in total are recognised as key authors with at least six published papers according Price's law, meaning OoCs is a vigorous field and hold steady co-authorship groups. Publication numbers can also reflect this point with a step-up tendency, notably a sharp increase and boost from 2016 (**Figure 8A**). We have analysed and clustered all authors based on their number of co-authored documents and total 17 clusters with connections are visualised by VOSviewer software in **Figure 8B**. Among these clusters, three groups represented by Donald E. Ingber, Yu Shrike Zhang, and Milica Radisic occupy the top three co-author network position with 34 items, 21 item, and 18 items, respectively. Besides, Donald E. Ingber, Ali Khademhosseini and Yu Shrike Zhang, and have the most OoC-related publications with 60 documents, 42 documents, and 42 documents (**Table 1**). All these papers, the three highest average citation come from Donald E. Ingber, Hyun Jung Kim, and Ali Khademhosseini (**Table 1**), which means their papers are the most popular and highly valued in OoC-focused scholars. Apparently, Donald E. Ingber is a representative researcher who gives a great contribution on OoC field development by feat of not only the foundation work of human lung-on-a-chip published in 2010[5] but also other human OoCs in following dozen years.[11,100-106] In 2020, U.S. Food and Drug Administration signed some collaborative agreements with Emulate Inc. and CN Bio, two top OoC technology companies, to evaluate lung-on-chip devices, marking the prologue of OoCs in preclinical practice.

Top keywords with minimum number of occurrences of 20 times have been analysed. After removing null words, such as OoC, microfluidics, *in vitro*, model, and so on, and merging synonyms and different variants of the same keywords as for OoCs, 124 keywords are finally obtained and sketched to form an interaction network shown in **Figure 8C.** Correspondingly, these keywords can be cataloged into five groups with items manually listed in **Table 2.** Group 1 mainly focuses on cell types and organic property in OoC. It contains cells, stem cells, organoids, organs, and organs-on-chips, from tiny cellular unit to macroscopical organ level. Group 2 mainly concentrates on microenvironment studies, mainly referring to ECM, microvascular networks, and fluid shear-stress. Other factors, such as oxygen microenvironment of cells, are also involved in OoC studies. Group 3 mainly emphasises design and fabrication of OoCs *in vitro*, consisting of fabrication methods and materials. This field tends to saturation with fewest keywords types and frequency, because the craft and scaffold materials are relatively stable for OoC studies. Group 4 centres on the realisation of cellular or organic functions for mimicking human organs of OoCs *in vitro*. For cells, it contains adhesion, proliferation, differentiation, metabolism, migration, maturation, and so on. And for organs, permeability, barrier, electrical-resistance, and angiogenesis are the most common microfunctions for recapitulating key factors of organs. Group 5 highlights the practicability and applications, for instance, disease modelling, especially cancer, toxicity research, drug testing, personalised medicine, and regenerative medicine. Few studies open paths to cooperate with other techniques, such

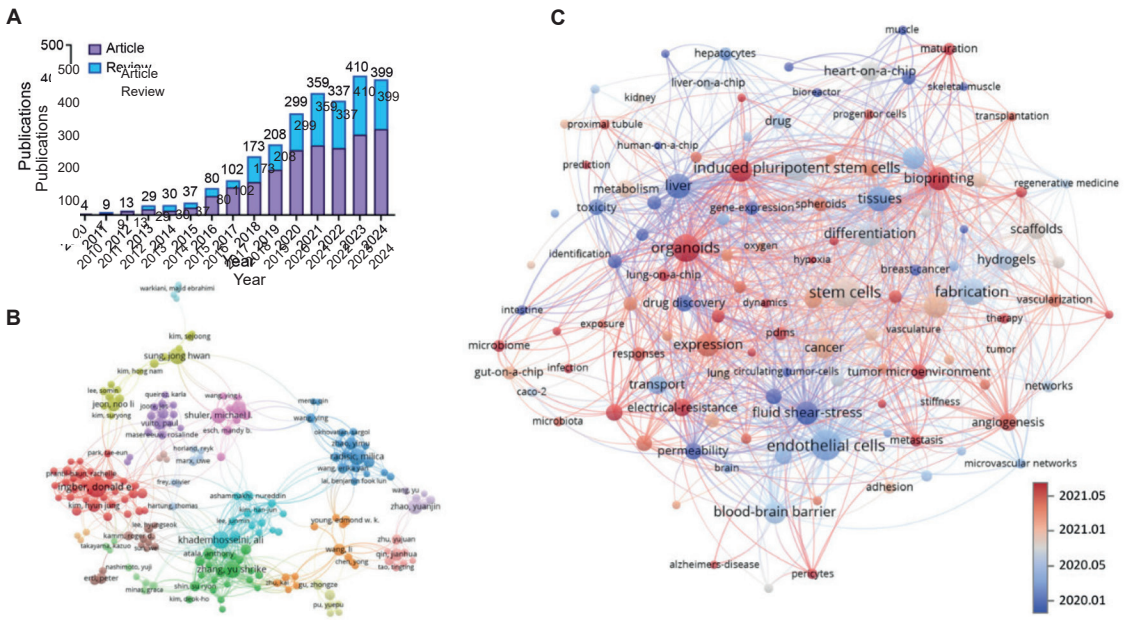

Figure 8. (A) Publications of OoCs in the year from 2010 to 2024. (B) Co-authorship analysis for key authors in OoC field. (C) Keyword (abbreviated as first five letters) analysis network in OoC field with timeline. Created with VOSviewer.
Abbreviations: OoC: organ-on-a-chip.

Table 1. Top 10 authors with most scientific documents in OoC field

Rank	Author	Document	Citation	Average citation
1	Donald E. Ingber	60	16773	280
2	Ali Khademhosseini	42	4891	116
3	Yu Shrike Zhang	42	4577	109
4	Milica Radisic	38	2607	69
5	Jong Hwan Sung	37	1634	44
6	Michael L. Shuler	32	2931	92
7	Yuanjin Zhao	31	1976	64
8	James J. Hickman	29	1728	60
9	Noo Li Jeon	25	1403	56
10	Hyun Jung Kim	23	4682	204

Ooc: Organ-on-a-chip.

Table 2. Catalogue of top keywords according to Web of Science statistical analysis

Group	Keyword
#1	endothelial cells (256, 58), stem cells (253, 39), organoids (215, 30), induced pluripotent stem cells (207, 60), liver (180, 71), tissues (171, 56), heart-on-a-chip (103, 41), epithelial cells (56, 69), spheroids (56, 27), cardiomyocytes (53, 46), lung (49, 42), fibroblasts (49, 38), liver-on-a-chip (48, 31), gut-on-a-chip (46, 57), hepatocytes (46, 49), lung-on-a-chip (44, 19), mesenchymal stem-cells (42, 30), intestine (31, 73), cerebral organoids (31, 32), Caco-2 (30, 48), pericytes (30, 26), progenitor cells (29, 20), astrocytes (28, 32), neurons (26, 31), circulating tumor-cells (26, 32), skeletal-muscle (21, 81), skin (42, 69), muscle (27, 58), proximal tubule (29, 46), vasculature (23, 39), kidney (26, 42), brain (24, 36), kidney-on-a-chip (24, 19)
#2	extracellular matrix (163, 45), fluid shear-stress (149, 54), hydrogels (129, 39), flow (73, 49), microenvironment (48, 33), networks (41, 59), mechanical-properties (37, 44), matrix (33, 41), collagen (32, 25), microvascular networks (29, 51), dynamics (26, 13), mechanotransduction (23, 60), oxygen (22, 52), hypoxia (22, 48), perfusion (22, 25), stress (21, 28), mechanobiology (20, 38)
#3	fabrication (202, 39), bioprinting (157, 37), scaffolds (111, 39), biomaterials (64, 40), design (54, 35), PDMS (47, 29), constructs (22, 64), stiffness (22, 45), surface modification (21, 13)
#4	differentiation (175, 43), expression (146, 32), blood-brain barrier (139, 48), transport (99, 47), mechanisms (89, 65), angiogenesis (87, 36), metabolism (86, 35), electrical-resistance (85, 29), permeability (80, 88), barrier (70, 76), gene-expression (58, 93), absorption (58, 51), responses (56, 51), vascularization (46, 41), metastasis (44, 20), maturation (43, 32), activation (43, 30), adhesion (42, 27), injury (38, 49), migration (35, 26), oxidative stress (32, 31), proliferation (30, 26), invasion (27, 32), inhibition (24, 51), exposure (23, 30), identification (22, 19), prediction (21, 19), long-term expansion (21, 14), barrier function (20, 26)
#5	Alzheimers-disease (22, 35), disease modeling (157, 32), tissue engineering (140, 45), cancer (131, 33), drug screening (81, 37), drug delivery (77, 59), drug discovery (76, 44), inflammation (77, 30), toxicity (75, 77), tumor microenvironment (65, 23), drug (60, 61), drug development (58, 32), nanoparticles (57, 55), biosensors (50, 31), high-throughput (44, 36), microbiome (42, 39), medicine (41, 31), breast-cancer (34 , 141), drug testing (31, 34), personalized regeneration (31, 25), therapy (30, 37), delivery (29, 35), regenerative medicine (28, 56), nephrotoxicity (27, 47), microbiota (27, 30), infection (26, 24), bioreactor (25, 69), cardiotoxicity (24, 85), fibrosis (24, 19), transplantation (24, 16), tumor (23, 26), hepatotoxicity (20, 55), pharmacokinetics (23, 44), SARS-CoV-2 (20, 32), mass-spectrometry (20, 28)

as mass-spectrometry or biosensors. These five groups nearly cover all research interests for OoC studies, which can be a great reference for OoC learners. Meanwhile, from the study timeline (Figure 8C), the OoC field have gone through three stages from reproduce of organs *in vitro*, the incorporation of ECM and microenvironment, to maturation of OoCs with the assistance of organoids and biotechniques, which gives us a direction hint for OoCs development in the future.

The first data in parentheses represents the mean occurrences of the keywords, and the second data in parentheses represents average citations of the keywords.

8. Conclusion and outlook

OoC is a cutting-edge technology that has emerged as a revolutionary technique in recent decades, capable of replicating key physiological and pathophysiological processes of human organs *in vitro*. This effective tissue culture method, serving as a form of digital twins technology, shows great promise and has found applications in disease modelling, drug screening, and tissue engineering fields. Originating from microfluidic techniques, OoCs integrate the microfunctions of human organs into microchips, showcasing rapid development and extensive research objectives over the past few decades. Through the classification of OoCs based on cell compartments, intercellular interface components, microfabrication materials, and external stimulation types, a comprehensive overview of OoC features in scaffold and design strategies has been meticulously summarised based on published academic literature. Besides, the history, current status, and future development tendency of OoCs are also introduced according to bibliometric analysis, benefiting OoC learning beginners in OoC conceptualisation, hotspots and applications. Considering that this paper does not delve into a deeper comprehensive analysis, it is suggested to establish complex out-of-context designs dynamically based on the experimental purpose.

As an emerging interdisciplinary technology, OoC presents an innovative approach to *in vitro* research models, offering vast opportunities for disease modelling, drug screening, and personalised medicine.[13] While capable of recapitulating essential organ features, OoCs fall short of fully replicating the complexity of organs or the human body.[107] For instance, OoCs usually involves monolayer cells in the chip but tissues in the body always have multilayered structure and more complex function. Primary cells in OoCs still lose partial properties to some extent compared with differentiated tissue cells. The incorporation of auxiliary operation needs more complex equipment, bringing experimental difficulty and experimental cost into OoCs. Meanwhile, the lack of analytes and data collection are also challenging needed to be addressed. To overcome these shortages and expand its usage in drug development and biological research, biological scientists are trying to enrich the functionalities of the chip to make it more bionic and more accurate, and, at the same time, engineering scientists are attempting optimise the design of the chip to make it more costless and more convenient.

Organoids-on-a-chip is the combination of organoids and OoCs. As two different yet complementary approaches, organoids self-organise stem cells and follow intrinsic developmental programmes to form miniature organs while OoCs precisely control cells and their microenvironment into a microfluidic device.[53] Thus, organoids-on-a-chip, a more powerful technique synergistically owing the best features of

organoids and OoCs,[19] is more attractive for structural and functional properties replication of *in vivo* counterpart organs with more reproducible and controllable characteristics.[108] Another increasing research field is personalised OoCs capable of involving patient-specific cells, differentiated from adult stem cells and induced pluripotent stem cells obtained from individual donors, into OoCs.[109] Personalised OoCs enable customisation of personal specific diseases and enhances relevance of human infections physiologically with high reproducibility.[1,110]

For the manufacturing of OoCs, higher throughput, low cost and automated chips[111] with user-friendliness are more attractive for, in particular, drug screening purpose. At present, OoCs in 96-well plate[112] or stackable chips[113] with a relatively higher throughput have been facilitated, showing great promise in pathogen infection and drug development. Additionally, multisensor-integrated organs-on-chips are also highly emphasised because of its ability of continuous monitoring of experimental parameters in real-time. For example, Bussooa *et al.*[114] integrated optical oxygen sensors into OoCs and real-time monitored oxygen levels within dynamic microenvironments. Other parameters, such as pH, glucose, cytokines, metabolites, and so on, can be also monitored and reflect cellular response and behaviour in real-time, a big advancement compared with endpoint analysis.[1]

OoC provides an avenue for the mimicry of human organs in life sciences, exhibiting great potential as a highly valuable research technology in bioengineering, biomaterials, and tissue engineering. Currently, in some situations, it has replaced animal models to verify drug efficiency as a preclinical tool, for instance, antibody TNT005 testing for chronic inflammatory demyelinating polyneuropathy treatment[115] and HRS-1893 for hypertrophic cardiomyopathy.[116] And the promulgation of OoC standard documents now means the wide practical application and a promising future of OoCs.

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The authors declare no conflicts of interest.
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Conceptualization: TC, PX, and FY; *Writing-original draft:* TC; *Writing-review & editing:* PX, CY, YC, YW, JZ, and FY. All authors read and approved the final version of the review.
Ethics approval and consent to participate
Not applicable.
Consent for publication
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Availability of data
Not applicable.

References

1. Alonso-Roman R, Mosig AS, Figge MT, *et al.* Organ-on-chip models for infectious disease research. *Nat Microbiol.* 2024;9:891-904. doi: 10.1038/s41564-024-01645-6
2. Möller J, Pörtner R. Digital twins for tissue culture techniques–concepts expectations and state of the art. *Processes.* 2021;9:447. doi: 10.15480/882.3387
3. Zhu Y, Kong B, Liu R, Zhao Y. Developing biomedical engineering technologies for reproductive medicine. *Smart Med.* 2022;1:e20220006. doi: 10.1002/SMMD.20220006
4. Pattanayak P, Singh SK, Gulati M, *et al.* Microfluidic chips: Recent advances critical strategies in design applications and future perspectives. *Microfluid Nanofluidics.* 2021;25:99. doi: 10.1007/s10404-021-02502-2
5. Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. Reconstituting organ-level lung functions on a chip. *Science.* 2010;328:1662-1668. doi: 10.1126/science.1188302
6. Sun L, Chen H, Xu D, Liu R, Zhao Y. Developing organs-on-chips for biomedical applications. *Smart Med.* 2024;3:e20240009. doi: 10.1002/SMMD.20240009
7. Sun L, Bian F, Xu D, Luo Y, Wang Y, Zhao Y. Tailoring biomaterials for biomimetic organs-on-chips. *Mater Horiz.* 2023;10:4724-4745. doi: 10.1039/d3mh00755c
8. Tawade P, Mastrangeli M. Integrated electrochemical and optical biosensing in organs-on-chip. *ChemBioChem.* 2024;25:e202300560. doi: 10.1002/cbic.202300560
9. Tajeddin A, Mustafaoglu N. Design and fabrication of organ-on-chips: Promises and challenges. *Micromachines (Basel).* 2021;12:1443. doi: 10.3390/mi12121443
10. Sin A, Chin KC, Jamil MF, Kostov Y, Rao G, Shuler ML. The design and fabrication of three-chamber microscale cell culture analog devices with integrated dissolved oxygen sensors. *Biotechnol Prog.* 2004;20:338-345. doi: 10.1021/bp034077d
11. Dasgupta Q, Jiang A, Wen AM, *et al.* A human lung alveolus-on-a-chip model of acute radiation-induced lung injury. *Nat Commun.* 2023;14:6506 doi: 10.1038/s41467-023-42171-z
12. Si L, Bai H, Rodas M, *et al.* A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics. *Nat Biomed Eng.* 2021;5:815-829. doi: 10.1038/s41551-021-00718-9
13. Low LA, Mummery C, Berridge BR, Austin CP, Tagle DA. Organs-on-chips: Into the next decade. *Nat Rev Drug Discov.* 2021;20:345-361. doi: 10.1038/s41573-020-0079-3
14. Group of Expert Consensus of Clinical Application about Tumor Precision Therapy Guided by Organoid-based Drug Sensitivity Testing. Expert consensus of clinical application about tumor precision therapy guided by organoid-based drug sensitivity testing (2022 edition). *Zhongguo Aizheng Fangzhi Zazhi.* 2022;14:234-239.
15. Ingber DE. Human organs-on-chips for disease modelling drug development and personalized medicine. *Nat Rev Genet.* 2022;23:467-491. doi: 10.1038/s41576-022-00466-9
16. Jang KJ, Mehr AP, Hamilton GA, *et al.* Human kidney proximal tubule-on-a-chip for drug transport and nephrotoxicity assessment. *Integr Biol (Camb).* 2013;5:1119-1129. doi: 10.1039/c3ib40049b
17. Benam KH, Villenave R, Lucchesi C, *et al.* Small airway-on-a-chip enables analysis of human lung inflammation and drug responses *in vitro*. *Nat Methods.* 2016;13:151-157. doi: 10.1038/nmeth.3697
18. Jang KJ, Otieno MA, Ronxhi J, *et al.* Reproducing human and cross-species drug toxicities using a liver-chip. *Sci Transl Med.* 2019;11:eaax5516. doi: 10.1126/scitranslmed.aax5516
19. Jalili-Firoozinezhad S, Gazzaniga FS, Calamari EL, *et al.* A complex

human gut microbiome cultured in an anaerobic intestine-on-a-chip. *Nat Biomed Eng.* 2019;3:520-531.
doi: 10.1038/s41551-019-0397-0
20. Lindner N, Mejia-Wille A, Fritschen A, Blaeser A. Development of a robotic-assisted handling and manipulation system for the high-scale bioproduction of 3D-bioprinted organ-on-a-chip devices. *HardwareX.* 2024;19:e00572.
doi: 10.1016/j.ohx.2024.e00572
21. Gautier LJC. CRISPR in 3D: Innovations in disease modelling and personalized medicine. *Biotechniques.* 2024;76:473-478.
doi: 10.1080/07366205.2024.2418748
22. Żuchowska A, Baranowska P, Flont M, Brzózka Z, Jastrzębska E. Review: 3D cell models for organ-on-a-chip applications. *Anal Chim Acta.* 2024;1301:342413.
doi: 10.1016/j.aca.2024.342413
23. Mondal MIH. *Cellulose-based Superabsorbent Hydrogels.* Cham: Springer Cham; 2019.
24. Yin H, Wang Y, Liu N, *et al.* Advances in the model structure of in vitro vascularized organ-on-a-chip. *Cyborg Bionic Syst.* 2024;5:0107.
doi: 10.34133/cbsystems.0107
25. Tronolone JJ, Mohamed N, Jain A. Engineering lymphangiogenesis-on-chip: The independent and cooperative regulation by biochemical factors gradients and interstitial fluid flow. *Adv Biol (Weinh).* 2024;8:e2400031.
doi: 10.1002/adbi.202400031
26. Song K, Zu X, Du Z, Hu Z, Wang J, Li J. Diversity models and applications of 3D breast tumor-on-a-chip. *Micromachines (Basel).* 2021;12:814.
doi: 10.3390/mi12070814
27. Moses SR, Adorno JJ, Palmer AF, Song JW. Vessel-on-a-chip models for studying microvascular physiology transport and function *in vitro*. *Am J Physiol Cell Physiol.* 2021;320:C92-C105.
doi: 10.1152/ajpcell.00355.2020
28. De Roode KE, Hashemi K, Verdurmen WPR, Brock R. Tumor-on-a-chip models for predicting *in vivo* nanoparticle behavior. *Small.* 2024;20:e2402311.
doi: 10.1002/smll.202402311
29. Zhao H, Chappell JC. Microvascular bioengineering: A focus on pericytes. *J Biol Eng.* 2019;13:26.
doi: 10.1186/s13036-019-0158-3
30. Agarwal SS, Cortes-Medina M, Holter JC, *et al.* Rapid low-cost assembly of modular microvessel-on-a-chip with benchtop xurography. *Lab Chip.* 2024;24:5065-5076.
doi: 10.1039/D4LC00565A
31. Jain A, van der Meer AD, Papa AL, *et al.* Assessment of whole blood thrombosis in a microfluidic device lined by fixed human endothelium. *Biomed Microdevices.* 2016;18:73.
doi: 10.1007/s10544-016-0095-6
32. Bischel LL, Lee S H, Beebe DJ. A practical method for patterning lumens through ECM hydrogels via viscous finger patterning. *J Lab Autom.* 2012;17:96-103.
doi: 10.1177/2211068211426694
33. Delannoy E, Tellier G, Cholet J, Leroy AM, Treizebré A, Soncin F. Multi-layered human blood vessels-on-chip design using double viscous finger patterning. *Biomedicines.* 2022;10:797.
doi: 10.3390/biomedicines10040797
34. Mandrycky C, Hadland B, Zheng Y. 3D curvature-instructed endothelial flow response and tissue vascularization. *Sci Adv.* 2020;6:eabb3629.
doi: 10.1126/sciadv.abb3629
35. Franco C, Gerhardt H. Tissue engineering: Blood vessels on a chip. *Nature.* 2012;488:465-466.
doi: 10.1038/488465a
36. Zheng Y, Chen J, Craven M, *et al. In vitro* microvessels for the study of angiogenesis and thrombosis. *Proc Natl Acad Sci U S A.* 2012;109:9342-9347.
doi: 10.1073/pnas.1201240109
37. Guo X, Sun L, Xu D, Zhao Y. Structural color heart-on-a-chip for evaluating the myocardial protection effects of traditional Chinese medicine. *Chem Eng J.* 2025;503:158261.
doi: 10.1016/j.cej.2024.158261
38. Kennedy JI, Davies SP, Hewett PW, *et al.* Organ-on-a-chip for studying immune cell adhesion to liver sinusoidal endothelial cells: The potential for testing immunotherapies and cell therapy trafficking. *Front Cell Dev Biol.* 2024;12:1359451.
doi: 10.3389/fcell.2024.1359451
39. Zhang M, Xu C, Jiang L, Qin J. A 3D human lung-on-a-chip model for nanotoxicity testing. *Toxicol Res (Camb).* 2018;7:1048-1060.
doi: 10.1039/c8tx00156a
40. You Y, Zhang C, Guo Z, *et al.* Lung-on-a-chip composed of styrene-butadiene-styrene nano-fiber/porous PDMS composite membranes with cyclic triaxial stimulation. *Microfluid Nanofluid.* 2024;28:45.
doi: 10.1007/s10404-024-02739-7
41. Liu J, Du Y, Xiao X, Tan D, He Y, Qin L. Construction of *in vitro* liver-on-a-chip models and application progress. *Biomed Eng Online.* 2024;23:33.
doi: 10.1186/s12938-024-01226-y
42. Huang W, Chen YY, He FF, Zhang C. Revolutionizing nephrology research: Expanding horizons with kidney-on-a-chip and beyond. *Front Bioeng Biotechnol.* 2024;12:1373386.
doi: 10.3389/fbioe.2024.1373386
43. Bannerman D, Pascual-Gil S, Wu Q, *et al.* Heart-on-a-chip model of epicardial-myocardial interaction in ischemia reperfusion injury. *Adv Healthc Mater.* 2024;13:e2302642.
doi: 10.1002/adhm.202302642
44. Du C, Liu J, Liu S, *et al.* Bone and joint-on-chip platforms: Construction strategies and applications. *Small Methods.* 2024;8:e2400436.
doi: 10.1002/smtd.202400436
45. Pries AR, Secomb TW. Blood flow in microvascular networks. *Compr Physiol.* 2011;9:3-36.
46. Wufuer M, Lee G, Hur W, *et al.* Skin-on-a-chip model simulating inflammation edema and drug-based treatment. *Sci Rep.* 2016;6:37471.
doi: 10.1038/srep37471
47. Song H, Hong Y, Lee H. Rapid automated production of tubular 3D intestine-on-a-chip with diverse cell types using coaxial bioprinting. *Lab Chip.* 2024;25:90-101.
doi: 10.1039/d4lc00731j
48. Ahn J, Yoon MJ, Hong SH, *et al.* Three-dimensional microengineered vascularised endometrium-on-a-chip. *Hum Reprod.* 2021;36:2720-2731.
doi: 10.1093/humrep/deab186
49. Lee J, Kim Y, Jung HI, Lim J, Kwak BS. Channel-assembling tumor microenvironment on-chip for evaluating anticancer drug efficacy. *J Control Release.* 2025;377:376-384.
doi: 10.1016/j.jconrel.2024.11.030
50. Libet PA, Polynkin LY, Saridis MR, *et al.* A four-channel microfluidic model of the blood–brain and blood–cerebrospinal fluid barriers: Fluid dynamics analysis. *Micro Nano Syst Lett.* 2024;12:28.
doi: 10.1186/s40486-024-00219-9
51. Ronaldson-Bouchard K, Teles D, Yeager K, *et al.* A multi-organ chip with matured tissue niches linked by vascular flow. *Nat Biomed Eng.* 2022;6:351-371.
doi: 10.1038/s41551-022-00882-6
52. Rajan SAP, Aleman J, Wan M, *et al.* Probing prodrug metabolism and reciprocal toxicity with an integrated and humanized multi-tissue organ-on-a-chip platform. *Acta Biomater.* 2020;106:124-135.
doi: 10.1016/j.actbio.2020.02.015
53. Park SE, Georgescu A, Huh D. Organoids-on-a-chip. *Science.* 2019;364:960-965.
doi: 10.1126/science.aaw7894
54. Mao J, Saiding Q, Qian S, *et al.* Reprogramming stem cells in regenerative medicine. *Smart Med.* 2022;1:e20220005.
doi: 10.1002/SMMD.20220005
55. Qian S, Mao J, Liu Z, *et al.* Stem cells for organoids. *Smart Med.* 2022;1:e20220007.
doi: 10.1002/SMMD.20220007
56. Wang Y, Wang L, Zhu Y, Qin J. Human brain organoid-on-a-chip to model prenatal nicotine exposure. *Lab Chip.* 2018;18:851-860.
doi: 10.1039/C7LC01084B
57. Hou Y, Gao Z, Tu P, Ai X, Jiang Y. Establishment of an idiosyncratic drug-induced liver injury model on a stacked array chip for identification of CCL5-mediated paracrine dynamics. *Anal Chem.* 2024;96:19370-19377.
doi: 10.1021/acs.analchem.4c03552
58. Corral-Nájera K, Chauhan G, Serna-Saldívar SO, Martínez-Chapa SO, Aeinehvand MM. Polymeric and biological membranes for organ-on-a-chip devices. *Microsyst Nanoeng.* 2023;9:107.

doi: 10.1038/s41378-023-00579-z
59. Radisic M, Loskill P. Beyond PDMS and membranes: New materials for organ-on-a-chip devices. *ACS Biomater Sci Eng.* 2021;7:2861-2863. doi: 10.1021/acsbiomaterials.1c00831
60. Pasman T, Grijpma D, Stamatialis D, Poot A. Flat and microstructured polymeric membranes in organs-on-chips. *J R Soc Interface.* 2018;15:20180351. doi: 10.1098/rsif.2018.0351
61. Liu H, Wang Y, Cui K, Guo Y, Zhang X, Qin J. Advances in hydrogels in organoids and organs-on-a-chip. *Adv Mater.* 2019;31:e1902042. doi: 10.1002/adma.201902042
62. Radhakrishnan J, Subramanian A, Krishnan UM, Sethuraman S. Injectable and 3D bioprinted polysaccharide hydrogels: From cartilage to osteochondral tissue engineering. *Biomacromolecules.* 2017;18:1-26. doi: 10.1021/acs.biomac.6b01619
63. Liaw CY, Ji S, Guvendiren M. Engineering 3D hydrogels for personalized *in vitro* human tissue models. *Adv Healthc Mater.* 2018;7:1701165. doi: 10.1002/adhm.201701165
64. Arık YB, de Sa Vivas A, Laarveld D, van Laar N, Gemser J, *et al.* Collagen I based enzymatically degradable membranes for organ-on-a-chip barrier models. *ACS Biomater Sci Eng.* 2021;7:2998-3005. doi: 10.1021/acsbiomaterials.0c00297
65. Gjorevski N, Sachs N, Manfrin A, *et al.* Designer matrices for intestinal stem cell and organoid culture. *Nature.* 2016;539:560-564. doi: 10.1038/nature20168
66. Sun AX, Lin H, Fritch MR, *et al.* Chondrogenesis of human bone marrow mesenchymal stem cells in 3-dimensional photocrosslinked hydrogel constructs: Effect of cell seeding density and material stiffness. *Acta Biomater.* 2017;58:302-311. doi: 10.1016/j.actbio.2017.06.016
67. Wang Z, Abdulla R, Parker B, Samanipour R, Ghosh S, Kim K. A simple and high-resolution stereolithography-based 3D bioprinting system using visible light crosslinkable bioinks. *Biofabrication.* 2015;7:045009. doi: 10.1088/1758-5090/7/4/045009
68. Wang Z, Lee SJ, Cheng HJ, Yoo JJ, Atala A. 3D bioprinted functional and contractile cardiac tissue constructs. *Acta Biomater.* 2018;70:48-56. doi: 10.1016/j.actbio.2018.02.007
69. van Meer BJ, de Vries H, Firth KSA, *et al.* Small molecule absorption by PDMS in the context of drug response bioassays. *Biochem Biophys Res Commun.* 2017;482:323-328. doi: 10.1016/j.bbrc.2016.11.062
70. Toepke MW, Beebe DJ. PDMS absorption of small molecules and consequences in microfluidic applications. *Lab Chip.* 2006;6:1484-1486. doi: 10.1039/B612140C
71. Regehr KJ, Domenech M, Koepsel JT, *et al.* Biological implications of polydimethylsiloxane-based microfluidic cell culture. *Lab Chip.* 2009;9:2132-2139. doi: 10.1039/B903043C
72. Moore TA, Brodersen P, Young EWK. Multiple myeloma cell drug responses differ in thermoplastic vs. PDMS microfluidic devices. *Anal Chem.* 2017;89:11391-11398. doi: 10.1021/acs.analchem.7b02351
73. Hassan S, Heinrich M, Cecen B, Prakash J, Zhang YS. 26 - Biomaterials for on-chip organ systems. In: Vrana NE, Knopf-Marques H, Barthes J, (eds). *Biomaterials for Organ and Tissue Regeneration.* New Delhi: Woodhead Publishing; 2020. p. 669-707.
74. Hirama H, Satoh T, Sugiura S, *et al.* Glass-based organ-on-a-chip device for restricting small molecular absorption. *J Biosci Bioeng.* 2019;127:641-646. doi: 10.1016/j.jbiosc.2018.10.019
75. Wu X, Shi W, Liu X, Gu Z. Recent advances in 3D-printing-based organ-on-a-chip. *EngMedicine.* 2024;1:100003. doi: 10.1016/j.engmed.2024.100003
76. Schwarz US. Mechanobiology by the numbers: A close relationship between biology and physics. *Nat Rev Mol Cell Biol.* 2017;18:711-712. doi: 10.1038/nrm.2017.109
77. Charelli LE, Ferreira JPD, Naveira-Cotta CP, Balbino TA. Engineering mechanobiology through organoids-on-chip: A strategy to boost therapeutics. *J Tissue Eng Regen Med.* 2021;15:883-899. doi: 10.1002/term.3234
78. Safarzadeh M, Richardson LS, Kammala AK, *et al.* A multi-organ feto-maternal interface organ-on-chip models pregnancy pathology and is a useful preclinical extracellular vesicle drug trial platform. *Extracell Vesicle.* 2024;3:100035. doi: 10.1016/j.vesic.2024.100035
79. Brasino DSK, Speese SD, Schilling K, Schutt CE, Barton MCA linkable polycarbonate gut microbiome-distal tumor chip platform for interrogating cancer promoting mechanisms. *Adv Sci (Weinh).* 2024;11:e2309220. doi: 10.1002/advs.202309220
80. Loessberg-Zahl J, Beumer J, van den Berg A, Eijkel JCT, van der Meer AD. Patterning biological gels for 3D cell culture inside microfluidic devices by local surface modification through laminar flow patterning. *Micromachines (Basel).* 2020;11:1112. doi: 10.3390/mi11121112
81. Tandon I, Woessner AE, Ferreira LA, *et al.* A three-dimensional valve-on-chip microphysiological system implicates cell cycle progression cholesterol metabolism and protein homeostasis in early calcific aortic valve disease progression. *Acta Biomater.* 2024;186:167-184. doi: 10.1016/j.actbio.2024.07.036
82. Kaarj K, Yoon JY. Methods of delivering mechanical stimuli to organ-on-a-chip. *Micromachines (Basel).* 2019;10:700. doi: 10.3390/mi10100700
83. Hoffman BD, Grashoff C, Schwartz MA. Dynamic molecular processes mediate cellular mechanotransduction. *Nature.* 2011;475:316-323. doi: 10.1038/nature10316
84. Aragona M, Panciera T, Manfrin A, *et al.* A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors. *Cell.* 2013;154:1047-1059. doi: 10.1016/j.cell.2013.07.042
85. Ingber DE. From tensegrity to human organs-on-chips: Implications for mechanobiology and mechanotherapeutics. *Biochem J.* 2023;480:243-257. doi: 10.1042/BCJ20220303
86. Zhang Y, Habibovic P. Delivering mechanical stimulation to cells: State of the art in materials and devices design. *Adv Mater.* 2022;34:e2110267. doi: 10.1002/adma.202110267
87. Thompson CL, Fu S, Knight MM, Thorpe SD. Mechanical stimulation: A crucial element of organ-on-chip models. *Front Bioeng Biotechnol.* 2020;8:602646. doi: 10.3389/fbioe.2020.602646
88. Fan Y, Jalali A, Chen A, *et al.* Skeletal loading regulates breast cancer-associated osteolysis in a loading intensity-dependent fashion. *Bone Res.* 2020;8:9. doi: 10.1038/s41413-020-0083-6
89. Kong M, Lee J, Yazdi IK, *et al.* Cardiac fibrotic remodeling on a chip with dynamic mechanical stimulation. *Adv Healthc Mater.* 2019;8:e1801146. doi: 10.1002/adhm.201801146
90. Liu H, MacQueen LA, Usprech JF, *et al.* Microdevice arrays with strain sensors for 3D mechanical stimulation and monitoring of engineered tissues. *Biomaterials.* 2018;172:30-40. doi: 10.1016/j.biomaterials.2018.04.041
91. Schlünder K, Cipriano M, Zbinden A, *et al.* Microphysiological pancreas-on-chip platform with integrated sensors to model endocrine function and metabolism. *Lab Chip.* 2024;24:2080-2093. doi: 10.1039/d3lc00838j
92. Chen SW, Blazeski A, Zhang S, Shelton SE, Offeddu GS, Kamm RD. Development of a perfusable hierarchical microvasculature-on-a-chip model. *Lab Chip.* 2023;23:4552-4564. doi: 10.1039/D3LC00512G
93. Lin TR, Yeh SL, Peng CC, Liao WH, Tung YC. Study effects of drug treatment and physiological physical stimulation on surfactant protein expression of lung epithelial cells using a biomimetic microfluidic cell culture device. *Micromachines (Basel).* 2019;10:400. doi: 10.3390/mi10060400
94. Liu XF, Yu JQ, Dalan R, Liu AQ, Luo KQ. Biological factors in plasma from diabetes mellitus patients enhance hyperglycaemia and pulsatile shear stress-induced endothelial cell apoptosis. *Integr Biol (Camb).* 2014;6:511-522. doi: 10.1039/c3ib40265g
95. Shao J, Wu L, Wu J, *et al.* Integrated microfluidic chip for endothelial cells culture and analysis exposed to a pulsatile and oscillatory shear

stress. *Lab Chip.* 2009;9:3118-3125.
doi: 10.1039/B909312E
96. Rutkowski JM, Swartz MA. A driving force for change: interstitial flow as a morphoregulator. *Trends Cell Biol.* 2007;17:44-50.
doi: 10.1016/j.tcb.2006.11.007
97. Vivas A, Ijspeert C, Pan JY, *et al.* Generation and culture of cardiac microtissues in a microfluidic chip with a reversible open top enables electrical pacing dynamic drug dosing and endothelial cell co-culture. *Adv Mater Technol.* 2022;7:2101355.
doi: 10.1002/admt.202101355
98. van der Helm MW, Henry OYF, Bein A, *et al.* Non-invasive sensing of transepithelial barrier function and tissue differentiation in organs-on-chips using impedance spectroscopy. *Lab Chip.* 2019;19:452-463.
doi: 10.1039/C8LC00129D
99. Pavesi A, Adriani G, Rasponi M, Zervantonakis IK, Fiore GB, Kamm RD. Controlled electromechanical cell stimulation on-a-chip. *Sci Rep.* 2015;5:11800.
doi: 10.1038/srep11800
100. Sontheimer-Phelps A, Chou DB, Tovaglieri A, *et al.* Human colon-on-a-chip enables continuous *in vitro* analysis of colon mucus layer accumulation and physiology. *Cell Mol Gastroenterol Hepatol.* 2020;9:507-526.
doi: 10.1016/j.jcmgh.2019.11.008
101. Goyal G, Prabhala P, Mahajan G, *et al.* Ectopic lymphoid follicle formation and human seasonal influenza vaccination responses recapitulated in an organ-on-a-chip. *Adv Sci (Weinh).* 2022;9:e2103241.
doi: 10.1002/advs.202103241
102. Ewart L, Apostolou A, Briggs SA, *et al.* Performance assessment and economic analysis of a human liver-chip for predictive toxicology. *Commun Med (Lond).* 2022;2:154.
doi: 10.1038/s43856-022-00209-1
103. Plebani R, Potla R, Soong M, *et al.* Modeling pulmonary cystic fibrosis in a human lung airway-on-a-chip. *J Cyst Fibros.* 2022;21:606-615.
doi: 10.1016/j.jcf.2021.10.004
104. Gulati A, Jorgenson A, Junaid A, Ingber DE. Modeling healthy and dysbiotic vaginal microenvironments in a human vagina-on-a-chip. *J Vis Exp.* 2024;204:e66486.
doi: 10.3791/66486
105. Kim S, Naziripour A, Prabhala P, *et al.* Direct therapeutic effect of sulfadoxine-pyrimethamine on nutritional deficiency-induced enteric dysfunction in a human intestine chip. *EBioMedicine.* 2024;99:104921.
doi: 10.1016/j.ebiom.2023.104921
106. Izadifar Z, Cotton J, Chen S, *et al.* Mucus production host-microbiome interactions hormone sensitivity and innate immune responses modeled in human cervix chips. *Nat Commun.* 2024;15:4578.
doi: 10.1038/s41467-024-48910-0
107. Leung CM, de Haan P, Ronaldson-Bouchard K, *et al.* A guide to the organ-on-a-chip. *Nat Rev Methods Primers.* 2022;2:33.
doi: 10.1038/s43586-022-00118-6
108. Liu H, Su J. Organoid and organoid extracellular vesicles for osteoporotic fractures therapy: Current status and future perspectives. *Interdiscip Med.* 2023;1:e20230011.
doi: 10.1002/INMD.20230011
109. Ramme AP, Koenig L, Hasenberg T, *et al.* Autologous induced pluripotent stem cell-derived four-organ-chip. *Future Sci OA.* 2019;5:FSO413.
doi: 10.2144/fsoa-2019-0065
110. Pushparaj K, Balasubramanian B, Pappuswamy M, *et al.* Out of box thinking to tangible science: A benchmark history of 3D bio-printing in regenerative medicine and tissues engineering. *Life (Basel).* 2023;13:954.
doi: 10.3390/life13040954
111. Li Z, Zhao Y, Lv X, Deng Y. Integrated brain on a chip and automated organ-on-chips systems. *Interdiscip Med.* 2023;1:e20220002.
doi: 10.1002/INMD.20220002
112. Junaid A, Tang H, van Reeuwijk A, *et al.* Ebola hemorrhagic shock syndrome-on-a-chip. *iScience.* 2020;23:100765.
doi: 10.1016/j.isci.2019.100765
113. Kim J, Lee KT, Lee JS, *et al.* Fungal brain infection modelled in a human-neurovascular-unit-on-a-chip with a functional blood-brain barrier. *Nat Biomed Eng.* 2021;5:830-846.
doi: 10.1038/s41551-021-00743-8
114. Bussooa A, Tubbs E, Revol-Cavalier F, *et al.* Real-time monitoring of oxygen levels within thermoplastic organ-on-chip devices. *Biosens Bioelectron X.* 2022;11:100198.
doi: 10.1016/j.biosx.2022.100198
115. Rumsey JW, Lorance C, Jackson M, *et al.* Classical complement pathway inhibition in a "human-on-a-chip" model of autoimmune demyelinating neuropathies. *Adv Ther (Weinh).* 2022;5:2200030.
doi: 10.1002/adtp.202200030
116. Yin J, Zhao M, Xu X, *et al.* A multicenter randomized open-label phase 2 clinical study of telitacicept in adult patients with generalized myasthenia gravis. *Eur J Neurol.* 2024;31:e16322.
doi: 10.1111/ene.16322

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