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Developing 3D bioprinting for organs-on-chips

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Organs-on-chips (OoCs) have significantly advanced biomedical research by precisely reconstructing human microphysiological systems with biomimetic functions. However, achieving greater structural complexity of cell cultures on-chip for enhanced biological mimicry remains a challenge. To overcome these challenges, 3D bioprinting techniques can be used in directly building complex 3D cultures on chips, facilitating the *in vitro* engineering of organ-level models. Herein, we review the distinctive features of OoCs, along with the technical and biological challenges associated with replicating complex organ structures. We discuss recent bioprinting innovations that simplify the fabrication of OoCs while increasing their architectural complexity, leading to breakthroughs in the field and enabling the investigation of previously inaccessible biological problems. We highlight the challenges for the development of 3D bioprinted OoCs, concluding with a perspective on future directions aimed at facilitating their clinical translation.

1. Introduction

The replication of the physiological structure and function of human organs is crucial for advancing biomedical research and clinical applications.[1–4] Organ reconstruction *in vitro* serves as an essential tool for studying functional mechanisms, modeling diseases, and screening drugs.[5–9] To accurately mimic human physiology, reconstructed organs must replicate the essential cell components, structures, and functionalities.[10–14] Organs-on-chips (OoCs) have emerged as a groundbreaking technology in this area.[15–22] These micro-engineered platforms combine living cells with microfluidic systems, creating dynamic environments that closely simulate organ-specific functions.[23–26] Compared to traditional 2D cell cultures, OoCs can more precisely replicate human biological features, enabling biofluid flow and spatiotemporal distribution of substances and tissues within the body.[27–33] However, OoCs face significant challenges, particularly in recreating the complex 3D structures and biological interactions present in human tissues.[34–39] Notably, OoCs are supposed to have the capacity to control the movement, placement, and form of cells grown.[40] Traditional OoCs also encounter difficulties in fabrication processes and handling, which can limit their capability in fully replicating physiology behaviors of living tissue or organs, thus hindering their broader application in biomedical research and clinical settings.[41–44] Thus, there is a crucial need to develop novel engineering approaches for advancing OoCs in fields of drug discovery and personalized medicine.

3D bioprinting has rapidly evolved into a transformative technology with the potential to overcome these challenges.[45–49] By utilizing specialized bioinks, comprising mixtures of cells, growth factors, and biomaterials, 3D bioprinting enables the precise assembly of cells and biomaterials, creating organ models on a chip or even directly printing OoCs that can mimic the biological structure and specific functionality of human organs.[50–53] Specific cell distributions in OoCs can be designated by employing 3D bioprinting techniques. 3D bioprinted OoCs is hereinafter defined as the *in situ* printing of biological structures within chips. Technically, we summarize 3D bioprinting used in OoCs into two categories: deposition-based and vat polymerization-based bioprinting. These technological advancements enhance the structural and functional fidelity of OoCs, making them more convenient in engineering.[54–56] Moreover, 3D bioprinting can provide precision, efficiency, and automation features in the control of cells, biomaterials, and extracellular matrices in OoCs. More possibilities like mass production and artificial organ manufacture could be explored in 3D bioprinted OoCs. Despite these advancements, the field remains largely conceptual, with diverse methodologies and a lack of standardization preventing widespread practical application.

In this review, we aim to discuss bioprinting techniques in combination with OoCs, focusing on how this integration can overcome existing limitations and advance the field of bioengineering. We examine the fundamental principles and

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challenges associated with OoCs and 3D bioprinting, highlighting how these technologies can be combined to enhance the structural and functional fidelity of organ models (Fig. 1). Recent successes in this integration are discussed, showcasing their potential to revolutionize biomedical research. Finally, we conclude by discussing the future directions of 3D bioprinted OoCs, emphasizing their promise in disease modeling, drug screening and precise medicine.

2. Organs-on-chips

OoCs have become an essential tool for modeling organs and their diseases, significantly enhancing our understanding of human physiology. Named one of the top ten emerging technologies by the World Economic Forum in 2016, OoCs have experienced rapid growth, driven by rising demand across the cosmetic, food, chemical, and pharmaceutical industries.[20] As their applications expand, the requirements for OoCs are becoming more complex and rigorous, calling for advancements in their design and functionality to meet these evolving needs.

2.1 OoC designs and applications

Advances in organ-on-a-chip (OoC) technology are rapidly progressing, driven by developments in engineering and biological sciences.[57] Biologically, OoC systems are becoming increasingly complex, integrating sophisticated design, diverse cell components, and intricate structures.[58–61] The transwell system, for instance, provides a straightforward method for modeling tissue barriers using a permeable membrane seeded with cells, allowing convenient cell–cell interactions and media change (Fig. 2a).[62] However, to introduce controllable fluid flow and mechanical simulation into OoCs, more advanced microfluidic chips have been developed, such as those using soft lithography and packaging techniques.[63–65] An OoC platform contained two vacuum chambers that can stretch the cell-coated membrane, resulting in the replication of lung breathing cycles (Fig. 2b).[66] Incorporating ECM components into OoCs has further enhanced their biological relevance. For example, a microfluidic chip developed by Jeon *et al.* allowed precise loading of ECMs and cells, facilitating the analysis of intricate cell–matrix interactions (Fig. 2c).[67]

Beyond traditional monocultures, OoCs have evolved to support self-organizing cultures and even multi-organ systems, which more accurately represent dynamic cell development, tissue morphogenesis, and systemic physiology.[12,72] A notable example is the organotypic angiogenesis model by Nguyen *et al.*, where endothelial cells are loaded into a collagen matrix to quantitatively study angiogenic invasion and sprouting (Fig. 2d).[68] Technical innovations continue to push the boundaries of OoC capabilities. Phan *et al.* developed a vascularized and perfused OoC platform for high-throughput drug screening (Fig. 2e),[69] while Tomasi *et al.* introduced a microfluidic droplet method to sequentially regulate the culture environment of cell spheroids, enabling multiplex operations such as co-culture, ECM encapsulation, and drug testing (Fig. 2f).[70] Recently, a multi-OoC system integrated heart, liver, bone, and skin models, all interconnected by biomimetic blood circuits (Fig. 2g).[71] This system demonstrates the potential of OoCs to model whole-body physiological interactions and systemic diseases, paving the way for more comprehensive biomedical research.

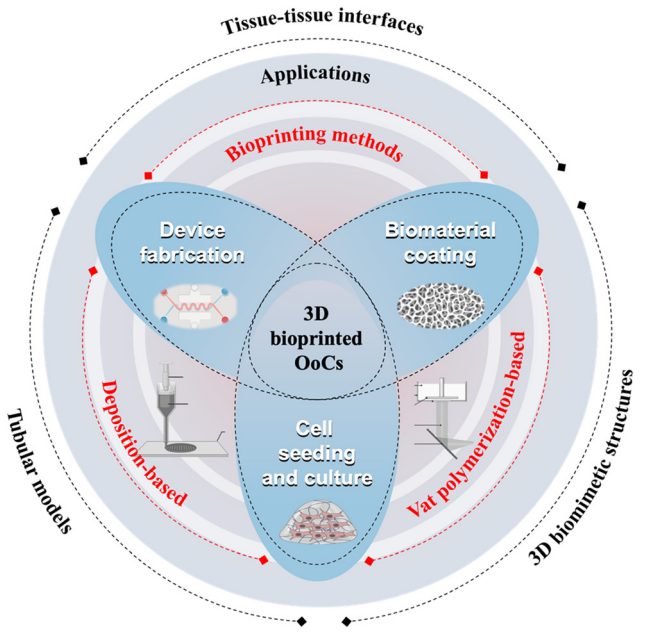

Fig. 1 A schematic illustration of 3D bioprinted organs-on-chips (OoCs). OoCs can be directly fabricated by 3D bioprinting techniques including deposition-based and vat polymerization-based bioprinting, which enhance the structural and functional fidelity of organ models and broaden the applications of OoCs.

2.2 Summary and challenges

Organ-on-a-chip (OoC) technologies have advanced significantly, gaining widespread interest and maturing rapidly in recent years. As these technologies evolve, they are increasingly recognized for their potential in replicating human physiological conditions with high fidelity. Despite the diversity in OoC designs, each system is uniquely tailored to meet specific microphysiological needs, offering distinct advantages and challenges (Table 1). Here, we categorize OoCs based on their biological complexity: designated mono-cultures, self-organizing cultures, and multi-organ systems. Mono-cultures involve cells adhering to an ECM within the OoC, providing stability for long-term culture. Conversely, self-organizing cultures enable cells to invade, spread, and grow within an ECM, creating a dynamic environment for studying cell–cell and cell–ECM interactions. Multi-organ cultures integrate multiple tissue models within a single chip, facilitating the study of organ–organ interactions. Each type of OoC offers researchers versatile options to construct tissue models for in-depth study.

Despite the remarkable progress in OoC technology, two significant challenges hinder their broader application: the complexity of the fabrication process and the difficulty of replicating 3D structures.[73] On the one hand, OoCs must become more user-friendly to be accessible to researchers without specialized engineering skills. The traditional fabrication process involves multiple steps, including microfluidic chip manufacturing, device packaging and integration, ECM modification, and cell seeding and maintenance. This complexity can be a barrier to widespread adoption. On the other hand, accurately recreating biomimetic tissues with complex 3D structures, such as vascular networks and multicellular parenchyma, remains a significant challenge. Overcoming these hurdles is essential for advancing OoC technology to the next level, where it can more effectively replicate human tissue complexity and be used in a wider range of biomedical applications.

3. 3D bioprinted organs-on-chips

To address the aforementioned challenges in the field of OoCs, 3D bioprinting has demonstrated a unique capability to recreate organ-level structures, particularly those involving complex hollow vessels, which are important parts in engineered tissue models. Bioprinting technology enables the precise shaping of bioinks into intricate tissue structures, enabling the faithful modeling of organ physiology and disease states. The integration of 3D bioprinting with OoCs has shown significant promise in enhancing the realism and functionality of these models, making them more representative of human biology. This review will explore the fundamental principles and challenges of both OoCs and 3D bioprinting, emphasizing the synergistic potential of their combination in advancing the structural and functional fidelity of organ models.

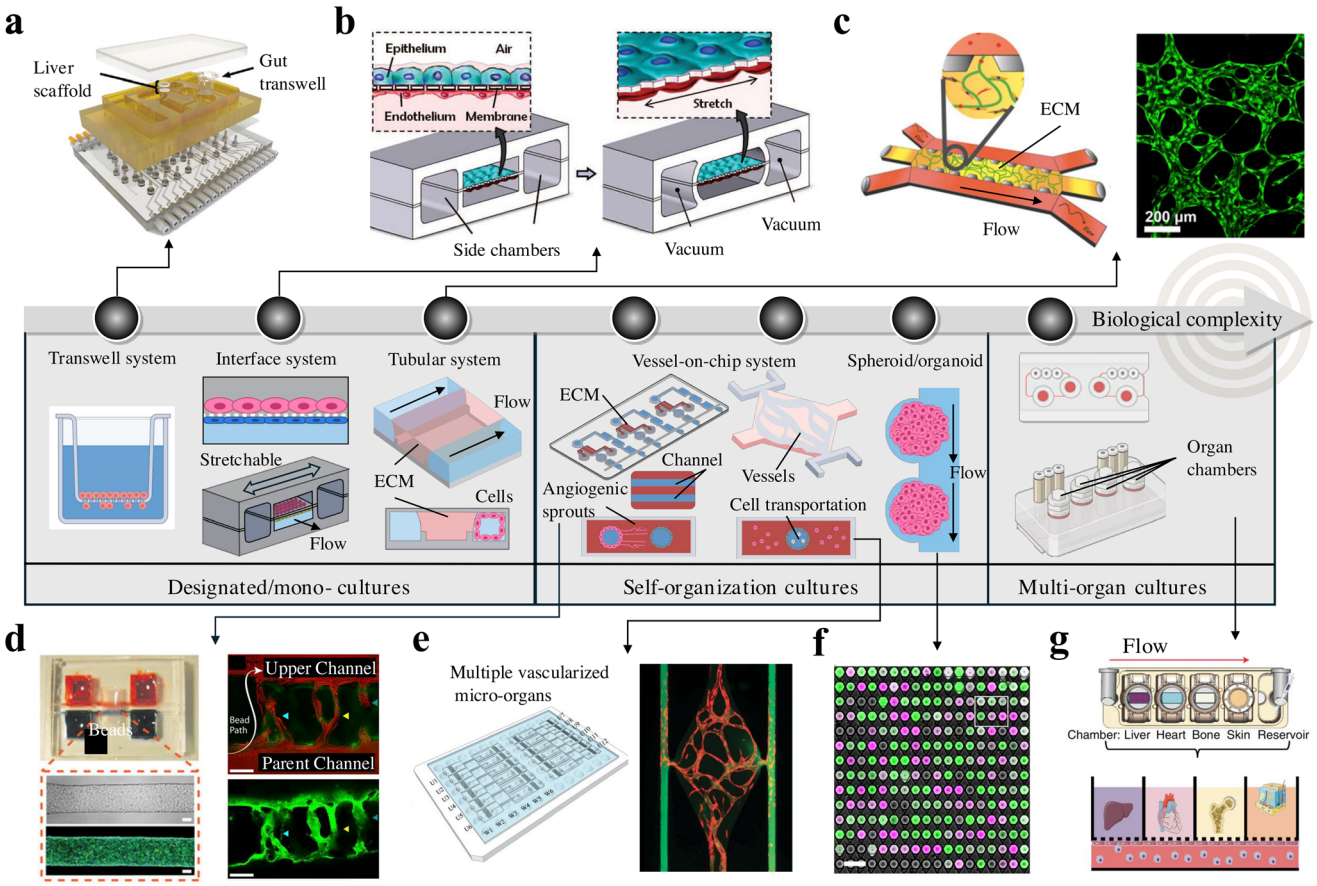

Fig. 2 Examples of diverse organ chip designs and typical applications arranged by the biological complexity of OoCs. (a) A multi-transwell system hosting immune-competent gut and liver models to quantify gut–liver interactome. Adapted with permission.[62] Copyright 2017, Wiley Inc. (b) A biomimetic platform reconstituting the functional alveolar–capillary interface of the human lung. Adapted with permission.[66] Copyright 2010, AAAS. (c) A microfluidic system containing an extracellular matrix (ECM) and pre-loaded cells. Adapted with permission.[67] Copyright 2015, National Academy of Sciences. (d) A biomimetic OoC with angiogenic sprouting and vessel origination. Scale bar, 100 μm. Adapted with permission.[68] Copyright 2013, National Academy of Sciences. (e) Vessel-on-a-chip platform showing the self-organization perfusable vasculature. Scale bar, 200 μm. Adapted with permission.[69] Copyright 2017, Royal Society of Chemistry. (f) Droplet microfluidics for forming tumor spheroids in a high-throughput manner. Scale bar, 1 mm. Adapted with permission.[70] Copyright 2020, the author(s). (g) A multi-OoC featuring various developed tissue models interconnected by vascular flow. Adapted with permission.[71] Copyright 2022, the author(s).

Table 1 Key features and challenges of OoCs. Each type of OoC offers researchers versatile options to construct tissue models

OoC designs	Platform characteristics	Advantages	Challenges
Designated cultures/mono-cultures	• Fixable arrangement of chip components and cells • Step-by-step processes: chip fabrication, chip modification, cell seeding, and cell culturing	• Stable environment for cell culturing provided by stable chips • Stable cell structures and distributions • Robust physical stimulation and stable bio-chemical regulation on cells • Highly reproducible and mass-produced chip for drug screening	• Limited cell communications in 3D level • Limited choices in cell-adhered materials • Limited in studying the dynamics of cell differentiation and proliferation • Limited in studying cell migration, invasion in 3D
Self-organization cultures	• Biomimetic ECM • Specific designs for cell aggregation, growth, invasion, and migration • Cells self-organize into biomimetic 2D or 3D structures	• Improved physiological relevance • Better cell–cell interactions • Perfusable tubular structures • Easy realization of complex tissue architectures • Real-time monitoring of the cell development dynamics	• Uncontrollable cell structures • Variability in structure formation • Limited ECM selections • Limited in synergistic self-organization of multiple types of cells • More complex tissue modeling
Multi-organ cultures	• Integration of multiple organ systems • Interconnected micro-environments • Multiple cell cultures and relative culture media	• Better systematic responses • Simulation of organ–organ interactions • Recapitulation of the pharmacokinetic and pharmacodynamic profiles of specific drugs • Clinical applicability	• Complex fabrication processes • Limited phenotypic stability • Difficulties in suitable medium preparation • Difficulties in multiplexing and standardization of multi-organ chips • Increased platform complexity and more complex tissue modeling • Difficulties in reproducibility, scaling, and automated handling

3.1 Snapshot of bioprinting strategies used in OoCs

Traditional fabrication techniques for organ-on-chips (OoCs), such as photolithography, soft lithography, and various molding processes, have been instrumental in advancing the field. However, these methods are hindered in recreating complex, three-dimensional structures characteristic of human organs and tissues. Furthermore, they often require multistep production protocols, particularly in lithographic techniques that involve several processing stages and masks. These processes not only consume significant time and resources but also require secondary cell seeding, which can increase costs and reduce selectivity for different cell types. As a result, the overall efficiency and flexibility of these traditional methods are constrained.

In contrast, 3D bioprinting offers a promising alternative, enabling the simultaneous or consecutive fabrication of complex extracellular matrix (ECM) structures and cellular components with rapid turnaround times and extensive design flexibility.[74] As a specialized branch of 3D printing, bioprinting utilizes computer-aided design (CAD) to build structures layer by layer, allowing for precise control over the architecture of the final product. When integrated with microfluidic chips, 3D bioprinting can automate the creation of reproducible, accurately positioned, and perfused multicellular cultures with customized features. This advancement significantly enhances the potential for physiological studies and drug testing at the organ level. Bioprinting techniques are broadly categorized into deposition-based and vat polymerization-based methods, each offering unique advantages in the fabrication of OoCs (Fig. 3).

Among various bioprinting techniques, inkjet-based bioprinting functions by ejecting small droplets of bioink through a nozzle using physical stimuli, precisely depositing them onto a substrate to create a 3D structure.[75] This method excels in high-resolution printing and accurate cell placement, essential for constructing intricate tissue architectures.[76] It excels in producing intricate, cell-laden patterns with resolutions as fine as 10–50 μm, making it ideal for applications requiring high spatial accuracy, such as vascular networks or thin tissue layers. However, its fabrication scale is limited to creating thin, two-dimensional constructs or small, layered three-dimensional structures. To fabricate 3D structures, extrusion-based bioprinting has been developed, which contains continuous extrusion of bioink *via* spray head to form strands, which are deposited layer by layer.[77–79] This technique is ideal for creating large, complex tissue constructs, making it widely applicable in various biomedical fields. With a typical resolution of 100–200 μm, it offers lower precision than inkjet-based methods but accommodates a wide range of bioinks, including high-

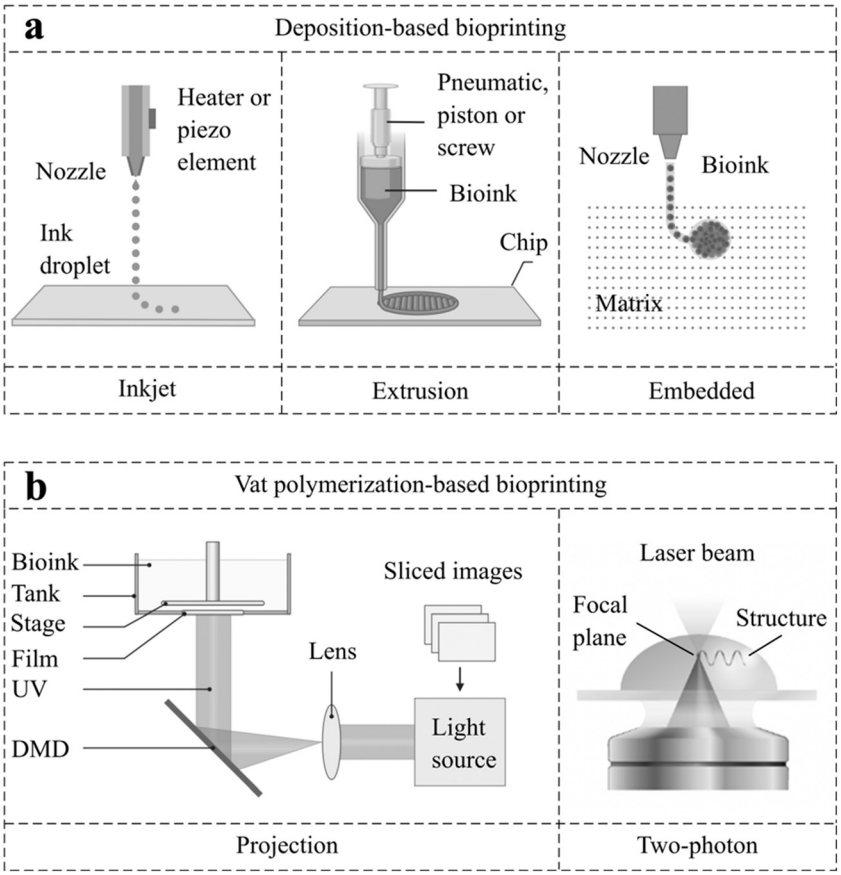

Fig. 3 Bioprinting strategies used in OoCs. (a) Schematic illustration of the deposition-based bioprinting technique, which contains inkjet-, extrusion-, and embedded-based approaches for depositing bioinks. (b) Schematic illustration of the vat polymerization-based bioprinting technique, which contains projection- and two-photon-based approaches for shaping bioinks.

viscosity hydrogels, composites, and cell-laden materials. This technique is well-suited for volumetric tissues and constructs on a centimeter scale, making it advantageous for organ-on-a-chip and scaffold fabrication. However, finer feature sizes are difficult to achieve, and the extrusion process may subject cells to shear stress. To enhance structural integrity, embedded-based bioprinting incorporated with controllable hydrogel deposition has been developed, enabling the precise fabrication of complex 3D structures within a supportive, temporary matrix.[80]

Another advanced technique, vat polymerization-based bioprinting, offers higher resolution and integration capabilities.[81] Techniques like digital light processing (DLP) and stereolithography (SLA) use light to solidify photosensitive bioinks, enabling the rapid fabrication of intricate 3D structures with precise geometric control.[82,83] This approach is particularly advantageous for applications requiring detailed tissue structures. Additionally, two-photon polymerization (2PP) bioprinting utilizes a femtosecond laser to initiate polymerization at the focal point, allowing for the generation of tissue models with complex micro- and nanoscale architectures.[84] Vat polymerization-based bioprinting achieves the highest resolution among the three methods, with feature sizes below 10 μm in cell-free constructs and sub-micron precision under ideal conditions. Besides, the fabrication scale is broad, typically supporting micron-to-centimeter-sized constructs. Particularly, vat polymerization-based bioprinting is ideal for fabricating complex microarchitectures.[85–87]

As bioprinting technologies rapidly advance, the development of biomaterials, known as bioinks, has also progressed to meet diverse bioprinting needs.[88–95] These bioinks, varying widely in composition and properties, are tailored to specific applications and tissue types.[96–100] A summary of biomaterials used in 3D bioprinting can be found in Table 2. Generally, bioinks are categorized into natural, synthetic, and composite polymers.[101,102] The selection of an appropriate biomaterial is crucial, as it must balance biocompatibility, mechanical properties, and printability to meet the specific requirements of the engineered tissue.[103–105] Different biomaterials are suitable for relevant bioprinting techniques. For example, extrusion-based bioprinting allows for robust, multi-material structures by using ion- or photo-crosslinkable bioinks but has lower resolution, suitable for vascular channels. Inkjet bioprinting provides high resolution for patterned cell layers, ideal for complex multi-cellular configurations, though limited to low-viscosity bioinks. Stereolithography (SLA)/digital light

Table 2 Biomaterials used in bioprinting and their crosslinking mechanisms. '(I)' represents 'ionic'; '(F)' represents 'free-radical chain polymerization'; '(T)' represents 'thiol-ene'; '(P)' represents 'photo-redox'

Materials	Reactive group	Cross-linking chemistry	Bioprinting technique	Printable viscosity and print fidelity
Alginate	α-L-Guluronic acid	(I)[108–110]	Inkjet, extrusion	**Printable viscosity**
Gelatin	Methacryloyl	(F)[111–114]	Inkjet, extrusion, vat polymerization	• Inkjet 3–12 mPa s • Extrusion
	Glycidyl allyl ether	(T)[115]		30 to 6×10^7 mPa s
	Norbornene	(T)[116]		• Vat polymerization
	Thiol	(T)[117,118]		1–1000 mPa s
HA	Methacrylate	(F)[119,120]	Inkjet, extrusion, vat polymerization	**Print fidelity**
	Norbornene	(T)[121]		• Inkjet
	Tyramine	(P)[122]		*Resolution:* >10 μm
	Thiol	(T)[123]		
	Acrylamide	(F)[124]		*Scale:* μm-to-mm-sized constructs
	Glycidyl methacrylate	(F)[125]		
Collagen	Methacrylate	(F), (T)[80,126]	Extrusion, vat polymerization	• Extrusion *Resolution:* >100 μm *Scale:* μm-to-cm-sized constructs • Vat polymerization *Resolution:* >6–10 μm
PEG	Acrylate	(F)[127]	Inkjet, extrusion, vat polymerization	*Scale:* nm-to-cm-sized constructs
	Methacrylate	(F)[128]		
	Thiol	(T)[129]		
	Norbornene	(T)[130]		
	Alkyne	(T)[131]		
Poly(ethylene oxide)	Methacrylate	(F)[132]	Vat polymerization	
Poly(glycidol)	Allyl glycidyl ether	(T)[133]	Inkjet, extrusion	
	Thiol	(T)[134]		
PVA	Methacrylate	(F)[135]	Vat polymerization	
Decellularized ECM	Innate proteins	(P)[136]	Vat polymerization	
Silk fibroin	Glycidyl methacrylate	(F)[137,138]	Inkjet, extrusion	
Dextran	Hydroxyethyl methacrylate	(F)[139]	Extrusion	
PEG-*co*-depsipeptide	Methacrylate	(F)[140]	Vat polymerization	

processing (DLP) offers the highest resolution for micro-scale features like capillaries, using photosensitive materials. The choice depends on balancing resolution, cell viability, and the structural needs of the OoC model. With ongoing advancements, the development of new and improved biomaterials continues to expand the potential of 3D bioprinted OoCs for biomedical applications.[106,107]

3.2 Applications – direct construction of OoCs

While soft lithography excels at producing perfusable microfluidic channels that house embedded cell constructs, its limitations in complex 3D architectures restrict its ability to fully mimic native tissue organization. To demonstrate the advantages of 3D bioprinting applied in OoCs, we hereinafter introduce typical types of 3D bioprinted OoCs according to the spatial complexity of the tissue constructs. These OoC types include tissue–tissue interfaces, tubular models, and 3D organ-level structures.

3.2.1 Tissue–tissue interfaces. Tissue–tissue interface engineering in OoCs is a complex and critical aspect of replicating the interactions between different types of tissues, such as epithelial and endothelial layers, within a single device.[141] This engineering challenge involves the precise integration of biomaterials, cellular components, and mechanical cues to recreate the dynamic environment found at tissue interfaces in the human body.[142,143] 3D bioprinting offers promising solutions to these challenges by enabling the reconstruction of multi-layered tissue frameworks, complex 3D architectures, and the integration of a biomimetic extracellular matrix (ECM) with biofluid dynamics. For instance, Yi *et al.* utilized extrusion-based bioprinting to create tumor models with compartmentalized cancer-stroma structures, maintaining a radial oxygen gradient and replicating native tumor tissue characteristics (Fig. 4a).[144] To precisely tune cellular environments while creating macroscopic morphologies, cell microgels have been incorporated into extrusion-based bioprinting (Fig. 4b).[145] The authors demonstrated that the bioprinted cell microgel-based scaffolds enhanced bioactivities of microbial consortia models. For studying cell differentiation, hiPSCs have also been employed in bioinks.[146,147] For example, one group made hiPSCs co-differentiated into diverse cell subtypes and developed into structural organoids (Fig. 4c).[148] This approach facilitated the spatial patterning of differentiated stem cells into programmable, organ-specific tissues, suitable for various therapeutic applications.

Like extrusion-based bioprinting, vat polymerization-based bioprinting has also made significant strides in fabricating

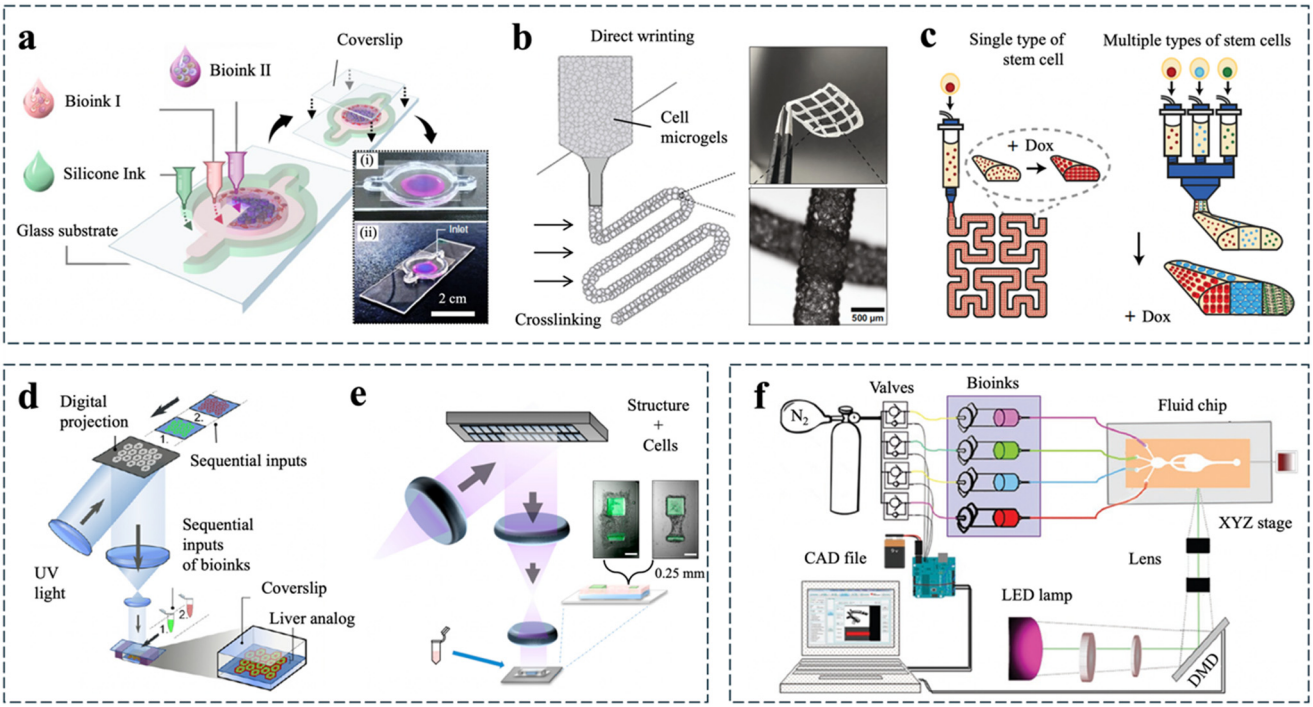

Fig. 4 3D bioprinted OoCs for reconstructing tissue–tissue interfaces. (a) Schematic illustration of the process for bioprinting glioblastoma-on-a-chip. Bioink I contains a brain decellularized ECM (BdECM) and endothelial cells; bioink II contains a BdECM and glioblastoma cells. Adapted with permission.[144] Copyright 2019, Springer Nature. (b) Extrusion-based bioprinting of functional microgel-based living materials. Adapted with permission.[145] Copyright 2023, the author(s). (c) Extrusion-based bioprinting of patterned organoids and tissues from the simultaneous co-differentiating stem cells. Adapted with permission.[148] Copyright 2022, Springer Nature. (d) DLP-based bioprinting of biomimetic liver lobule models with hepatic cells, HUVECs, and mesenchymal cells. Adapted with permission.[149] Copyright 2016, National Academy of Sciences. (e) DLP-based bioprinting of aligned cardiac cell tissues with enhanced maturity. Adapted with permission.[150] Copyright 2021, Elsevier. (f) Microfluidic-enabled multimaterial stereolithographic bioprinting of high-fidelity angiogenesis microtissues. Adapted with permission.[112] Copyright 2018, Wiley.

tissue–tissue interface OoC models. Ma *et al.* demonstrated a milestone by using DLP-based bioprinting for constructing triculture models containing physiologically and structurally relevant cell integrations. They successfully produced biomimetic lobule structures embedded with hepatic progenitor cells, HUVECs, and adipose-relevant cells (Fig. 4d).[149] To further enhance tissue functionality, Miller *et al.* used DLP-based bioprinting to fabricate alignment cues within cardiac tissues, which promoted tissue maturation and improved mRNA expression levels (Fig. 4e).[150] A critical challenge in vat polymerization bioprinting is the simultaneous printing of different materials. To address this, a microfluidics-enabled multimaterial stereolithographic bioprinting method has been used for fabricating high-fidelity inhomogeneous models (Fig. 4f).[112] These advancements in 3D bioprinting are paving the way for more sophisticated tissue–tissue interface engineering in OoCs.

3.2.2 Tubular models. Tubular tissue models are crucial for replicating the natural structures of tissues that involve biofluid flows and for mimicking tissue transportation barriers in OoCs.[151–156] Traditional methods for fabricating these tubular structures typically rely on soft lithography and endothelial cell pre-seeding in hydrogels to induce vasculogenesis and create perfusable vascular networks. However, these methods can be complex and challenging to control.[157] To address these challenges, 3D bioprinting methods have been used for fabricating biomimetic tubular structures in OoCs, allowing for cell culture in a physiologically relevant ECM under controlled hemodynamic flow. Coaxial bioprinting techniques have shown excellent ability in creating tubular living constructs (Fig. 5a).[158] Besides, template and sacrifice-based extrusion bioprinting can build multilayered hollow vessels on a chip (Fig. 5b).[159] Moreover, Kolesky *et al.* introduced an approach to print vascularized cell constructs with a thickness over 10 mm, which can be added with growth factors achieving the differentiation of mesenchymal stem cells towards an osteogenic lineage *in situ* (Fig. 5c).[160] Additionally, a projection stereolithography-based bioprinting approach can create hydrogels with functional intravascular topologies, enabling the fabrication of complex 3D transport regimes, such as vascularized alveolar models with tidal ventilation and oxygenation (Fig. 5d).[127] This approach shows great potential for creating structurally complex and functional tissues for therapeutic transplantation.

To engineer OoCs with more fidelity and functionality, cell sources used in 3D bioprinting have been developed for achieving high cell density (HCD) and diverse cellular

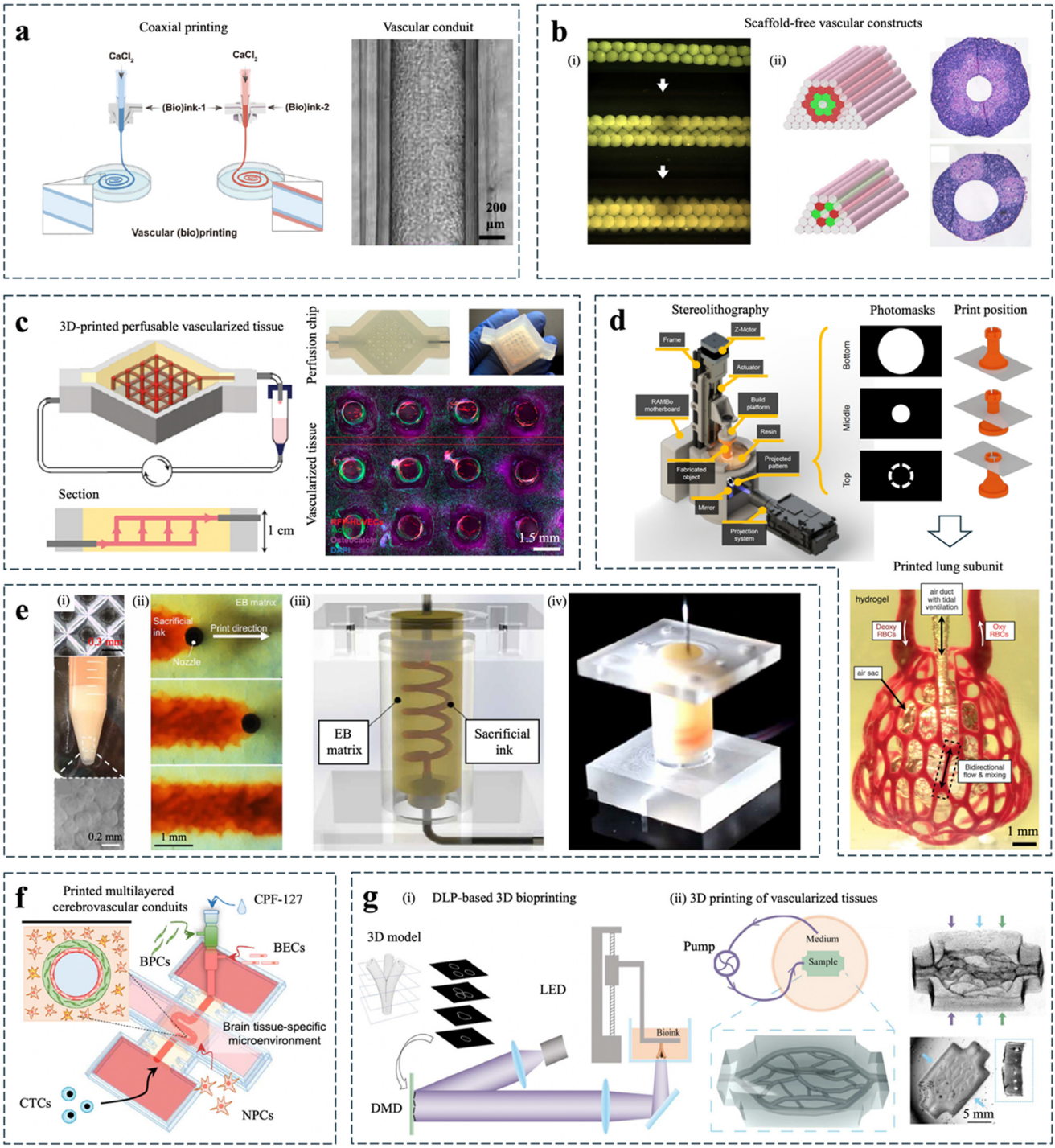

Fig. 5 3D bioprinted OoCs with tubular structures. (a) Coaxial printing of vascular constructs. Adapted with permission.[158] Copyright 2022, AAAS. (b) Prototyping bioprinting method for scaffold-free tubular vessel reconstruction. Adapted with permission.[159] Copyright 2009, Elsevier. (c) Extrusion-based bioprinting for fabricating 3D vascularized OoCs. Adapted with permission.[160] Copyright 2016, National Academy of Sciences. (d) Projection stereolithography-based bioprinting for reconstructing vascularized alveolar model topologies with tidal ventilation and oxygenation in hydrogels. Adapted with permission.[127] Copyright 2019, AAAS. (e) Embedded extrusion-based bioprinting of vascularized tissues in an organoid-based matrix. Adapted with permission.[161] Copyright 2019, AAAS. (f) A 3D triaxial bioprinting technique for the development of an on-chip brain metastasis model. Adapted with permission.[108] Copyright 2023, Springer Nature. (g) DLP-based bioprinting for fabricating OoCs with ultrahigh cell densities *via* reducing light scattering in bioinks. Adapted with permission.[162] Copyright 2023, AAAS.

components in OoCs.[13] For instance, Skylar-Scott *et al.* developed an embedded bioprinting technique to create perfusable vascular channels within an organoid-based matrix (Fig. 5e).[161] This approach successfully achieved

sacrificial writing of removable hydrogels, leading to the fabrication of organ-specific tissues with biomimetic tubular structures and HCD. To replicate complex geometries of tissue vessels and assess their role in tissue metastasis, a bioprinting approach was introduced, generating mature three-layered cerebrovascular conduits (Fig. 5f).[108] This method used the brain tissue-derived bioink with various cell types to study circulating tumor cell dissemination under specific vessel curvatures. Despite these advances, achieving tissue-level cell density in OoCs remains challenging. An improved DLP-based bioprinting technique has recently addressed this by mitigating

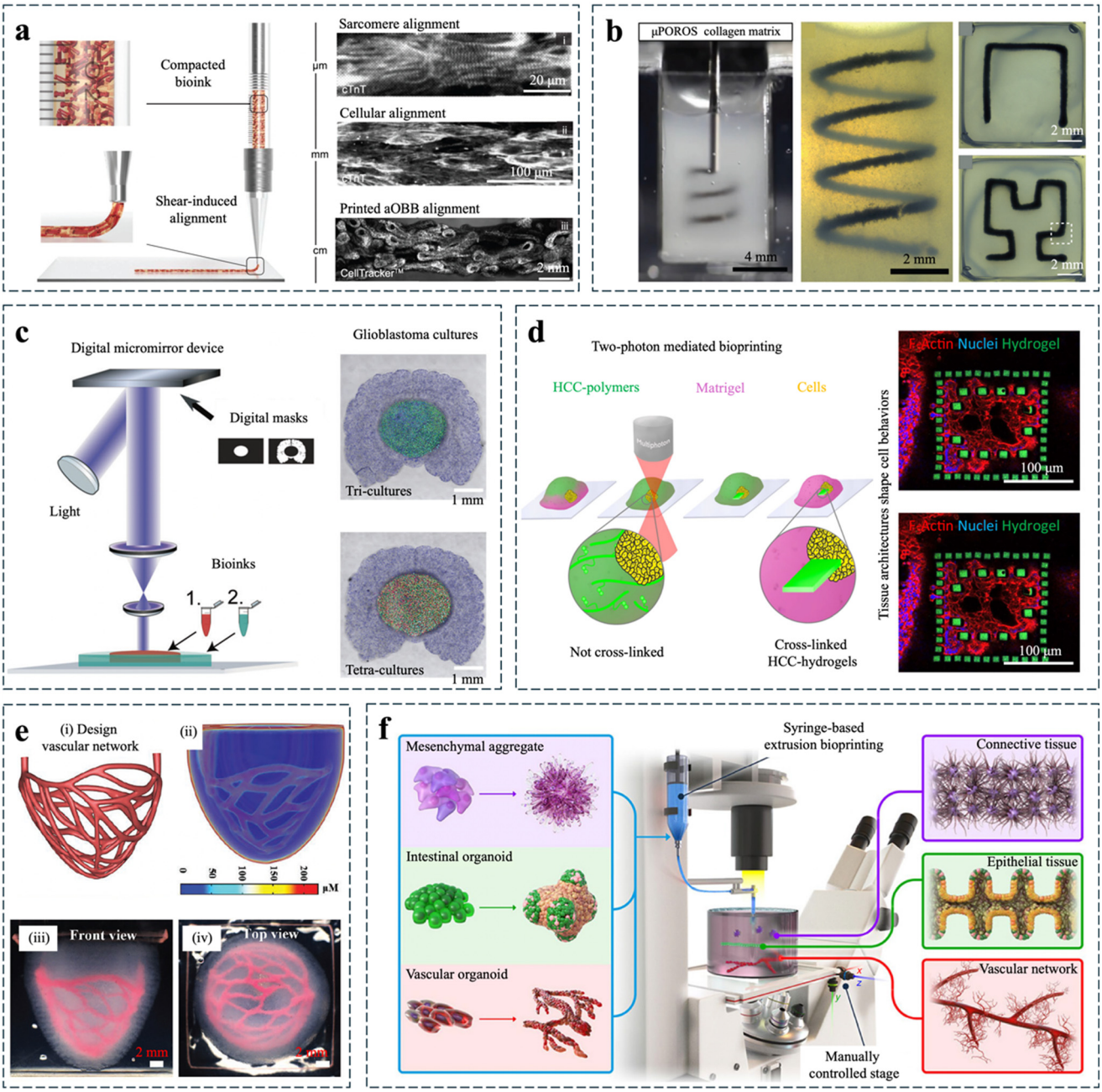

Fig. 6 3D bioprinted OoCs with 3D organ-level structures. (a) Schematic illustration of an anisotropic organ building block (OBB) orientation in bioink for forming multiscale aligned tissues on a chip. Adapted with permission.[166] Copyright 2022, Wiley. (b) Tumor ECM–mimetic matrix for supporting bioprinted constructs that can replicate 3D tumor structures. Adapted with permission.[167] Copyright 2023, Wiley. (c) 3D bioprinted brain tumor-on-a-chip with a dynamic tumor microenvironment with arranged multiple cell types. Adapted with permission.[168] Copyright 2020, Springer Nature. (d) On-chip bioprinting of hydrogel constrains for regulating organoid development. Adapted with permission.[169] Copyright 2023, Springer Nature. (e) Embedded 3D bioprinting of OoCs that replicate both the external geometry and internal vascular networks of organs. Adapted with permission.[170] Copyright 2023, Wiley. (f) Extrusion-based bioprinting of stem cell-laden bioinks for reproducing the intricate macroscale tissues with spontaneous self-organized microscale features. Adapted with permission.[171] Copyright 2021, Springer Nature.

scattering-induced deterioration of bioprinting resolution, enabling bioprinting with high cell density and fine resolution, as shown in Fig. 5g.[162] Overall, these advancements in 3D bioprinting are crucial steps toward fabricating functional, large-scale, clinically transplantable tissues or organs.

3.2.3 3D organ-level structures. 3D bioprinting offers significant design freedom for developing OoCs by enabling the generation of intricate, biomimetic architectures that reconstruct native tissues.[163] One key application of this technology is the precise printing of specific ECM structures that can program cellular growth, regulate behavior, and control functions *in vitro*.[164,165] For instance, Ahrens *et al.* demonstrated that bioprinted synthetic and biological fibers can induce shear-aligned tissue building blocks, enhancing the contractile function of cardiac tissues compared to traditional spheroid-based approaches (Fig. 6a).[166] In another study aimed at mimicking the tumor microenvironment, embedded bioprinting techniques were used to create a tumor ECM-like matrix, supporting the formation of murine melanoma models with physiologically relevant cell densities (Fig. 6b).[167] This model effectively enabled the migration of antigen-specific cytotoxic T cells through the matrix, initiating cancer cell destruction. Furthermore, DLP-based bioprinting has been used to construct complex, multicellular brain tumor models that incorporate glioblastoma cells, macrophages, astrocytes, and neural cells (Fig. 6c).[168] These biomimetic models facilitate the study of cellular interactions within the tumor microenvironment, offering a valuable platform for discovering novel therapeutic targets.

To achieve higher levels of biomimicry in 3D bioprinted OoCs, the incorporation of complex cell communication, morphogenesis, and behaviors is required. Mechanical constraints within extracellular matrix (ECM) hydrogels can significantly influence cell development and migration. For example, Urciuolo *et al.* utilized two-photon (2P) mediated bioprinting to generate hydrogels with specific physical structures around organoids, promoting cell polarity in liver organoids and guiding morphogenesis in small intestinal organoids (Fig. 6d).[169] This hydrogel-in-hydrogel live bioprinting approach enhances current *in vitro* OoC models and paves the way for more sophisticated tissue models. Additionally, embedded bioprinting have created intricate organs with biomimetic external geometries and integrated vascular networks (Fig. 6e).[170] The authors used microgel-based biphasic (MB) bioink to support bioprinted matrices. The MB bioink was used to print the tissue external structures, and then the secondary bioprinting was introduced for building vascular networks in the MB matrix. Moreover, stem cells and organoids as self-organizing building blocks were used to form interconnected cellular constructs through extrusion-based bioprinting (Fig. 6f).[171] These studies highlight the potential of 3D bioprinted OoCs in advancing cell biology and regenerative medicine.

4. Challenges and perspectives

Combining 3D bioprinting with OoCs holds promise to replicate the three-dimensional tissue structures and functional environments of natural organs more accurately. However, compared to soft lithography, 3D bioprinting faces challenges in integrating these constructs into perfusable microfluidic devices. Soft lithography excels in creating embedded microchannels essential for perfusion, nutrient delivery, and waste removal, which are critical for long-term cell viability and function. In contrast, many bioprinted constructs are standalone and require additional steps to incorporate into microfluidic systems, which can be technically demanding and may introduce structural inconsistencies. To overcome these limitations, advancements in direct bioprinting within microfluidic chips are needed. Besides, significant challenges remain in achieving true organ regeneration and clinical translation. This section discusses the hurdles and future directions for 3D bioprinted OoCs, from technical implementation to their broader capabilities.

4.1 Technical implementation

The integration of 3D bioprinting with OoC systems involves overcoming significant technical challenges, demanding a multidisciplinary approach that encompasses physics, chemistry, engineering, and biology. A clear understanding of the biological questions at hand is vital for determining the appropriate bioprinting strategy. The suitable biomaterials and bioprinting methods are also crucial for OoC fabrication, as these factors directly influence the functionality and reliability of the models. Additionally, the detailed design is required for the configuration of the device and the accurate deposition of cells within the OoC framework, ensuring that the resulting system mimics the physiological environment as closely as possible. The development of standardized and commercialized 3D bioprinted OoCs is anticipated to address these challenges, facilitating broader applications in both research laboratories and clinical settings. This progress could ultimately lead to more sophisticated, reliable, and accessible OoC platforms, advancing both basic research and therapeutic applications.

4.2 Complex structure and functionality of tissue models

The next significant challenge in the field of 3D printed OoC is to demonstrate clear superiority over traditional animal models, a shift that could revolutionize clinical trial design by reducing reliance on animal testing and enabling more personalized approaches to medicine.[172] To make a breakthrough in translation applications, OoCs should incorporate complex structures and mature functionalities that closely mimic natural tissues. Recent advancements include the integration of patient-derived cells into bioinks, which more accurately represent native human physiology and enhance the potential for personalized medicine.[173,174]

Additionally, the biomimetic arrangement of various cell types is crucial for replicating the spatial constraints and tissue morphologies found *in vivo*. Internal structures, such as vascular networks, are equally important for sustaining tissue function.[175] The future trajectory of this field involves the creation of personalized tissues or organs on miniaturized chips, offering significant promise for regenerative studies and clinical translation.

4.3 Multi-organ cultures

In multi-organ systems like those in humans, organs interact simultaneously and in complex ways with other organ systems. Replicating these interactions in OoC models, particularly during stages like disease development where target, vascular, and nerve tissues interplay, could lead to more accurate simulations of systemic interactions.[176–178] However, significant challenges arise when attempting to construct barriers between different organs and in maintaining the functionality of multiple organs within a single OoC system.[179–182] Addressing these challenges is critical for advancing multi-organ chip technologies, which could offer more physiologically relevant models for studying human health and disease.[183] As research progresses, overcoming these hurdles will be essential for creating integrated, functional multi-organ chips that can faithfully replicate the dynamic environment of the human body, thereby enhancing the utility of OoCs in both research and clinical applications.

5. Conclusion

Given that OoCs still can't meet the requirements in replicating complex functional and organizational tissue features for translational applications, bioprinting techniques offer new strategies and powerful tools for advancing OoC development and biomedical applications. This review aims to inspire researchers from various disciplines to address challenges of 3D bioprinting used in OoCs. With continued effort, 3D bioprinted OoCs may eventually achieve true organ regeneration and become widely used in personalized medicine, disease treatment, regenerative medicine, and clinical applications.

Data availability

This review article did not generate any new data. All data discussed within the manuscript are derived from previously published studies, which are well-cited throughout the text. The referenced datasets and sources can be accessed *via* the original publications listed in the reference section. No new datasets were created or analyzed in this study.

Conflicts of interest

The authors declare no competing financial interests.

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