Materials Today Bio 30 (2025) 101438

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Biomaterial-assisted organoid technology for disease modeling and drug screening

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ARTICLE INFO

Keywords:
Biomaterial
Organoid technology
Disease modeling
Drug screening

ABSTRACT

Developing disease models and screening for effective drugs are key areas of modern medical research. Traditional methodologies frequently fall short in precisely replicating the intricate architecture of bodily tissues and organs. Nevertheless, recent advancements in biomaterial-assisted organoid technology have ushered in a paradigm shift in biomedical research. This innovative approach enables the cultivation of three-dimensional cellular structures *in vitro* that closely emulate the structural and functional attributes of organs, offering physiologically superior models compared to conventional techniques. The evolution of biomaterials plays a pivotal role in supporting the culture and development of organ tissues, thereby facilitating more accurate disease state modeling and the rigorous evaluation of drug efficacy and safety profiles. In this review, we will explore the roles that various biomaterials play in organoid development, examine the fundamental principles and advantages of utilizing these technologies in constructing disease models, and highlight recent advances and practical applications in drug screening using disease-specific organoid models. Additionally, the challenges and future directions of organoid technology are discussed. Through continued research and innovation, we aim to make remarkable strides in disease treatment and drug development, ultimately enhancing patient quality of life.

1. Introduction

Precision therapy is increasingly recognized as a cutting-edge approach in modern medical practice. Modeling diseases and conducting drug testing are indispensable for the progression of precision medicine. By simulating the initiation and progression of diseases, these models offer vital insights into the underlying mechanisms and pathophysiological pathways of illnesses. Through the establishment of various disease models, researchers can comprehensively study disease etiology, progression, and prognosis, offering a theoretical basis for precision treatment. In contrast, drug screening involves selecting the most promising therapeutic agents from a large pool of candidates [1]. Advanced technologies facilitate drug screening at multiple levels, such as cellular and animal models, thereby enhancing the efficiency of drug discovery, aiding in the identification of effective treatments for specific patient groups, and improving treatment precision and efficacy [2]. However, disease models have inherent limitations and cannot fully replicate complex conditions; additionally, drug screening outcomes can be influenced by numerous factors, potentially leading to inaccuracies. These challenges and limitations can pose major obstacles to implementing precision therapy. To better target complex diseases, replicating and reconstructing human organs have become key areas of scientific development. While the concept of "organoid" was introduced in the 1980s, it wasn't until 2009 that Hans Clevers' research team in the Netherlands achieved a milestone by cultivating $Lgr5^{+}$ enteric stem cells into three-dimensional (3D) structures, featuring crypts and villous epithelia, now recognized as small intestinal organoids. This pivotal achievement ushered in a new chapter in organoid research. Organoids represent three-dimensional multicellular cultures that closely resemble the structural, physiological, and pathological characteristics of organs [3]. They exhibit structural and functional properties similar to those of tissues and organs *in vivo* [4], making them effective models for studying three-dimensional cell culture systems [5]. Organoids grown from stem cells mimic complex cellular interactions and spatial organization

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https://doi.org/10.1016/j.mtbio.2024.101438
Received 17 October 2024; Received in revised form 10 December 2024; Accepted 30 December 2024
Available online 31 December 2024

patterns, produce physiological responses similar to those of *in vivo* tissues, and closely resemble their source tissues (Fig. 1A) [6], Organoids have been developed as models for various tissues, including the retina, skin, small intestine, and kidney. These models closely simulate the internal environments of the respective organs, overcoming some limitations of traditional disease models. For drug screening [7], Bruti et al. developed organoid models of hepatocellular carcinoma, bile duct cancer, and cholangiocarcinoma, replicating the structure and expression characteristics of stem cell tumors treatments [8], and cancer biobank screening, allowing for rapid and efficient identification of drug candidates [9].

Although the tissues of these organs can, to a certain extent, reflect human diseases, they are reaching their limits in modeling complex illnesses, at a time when the need for precision medicine is growing

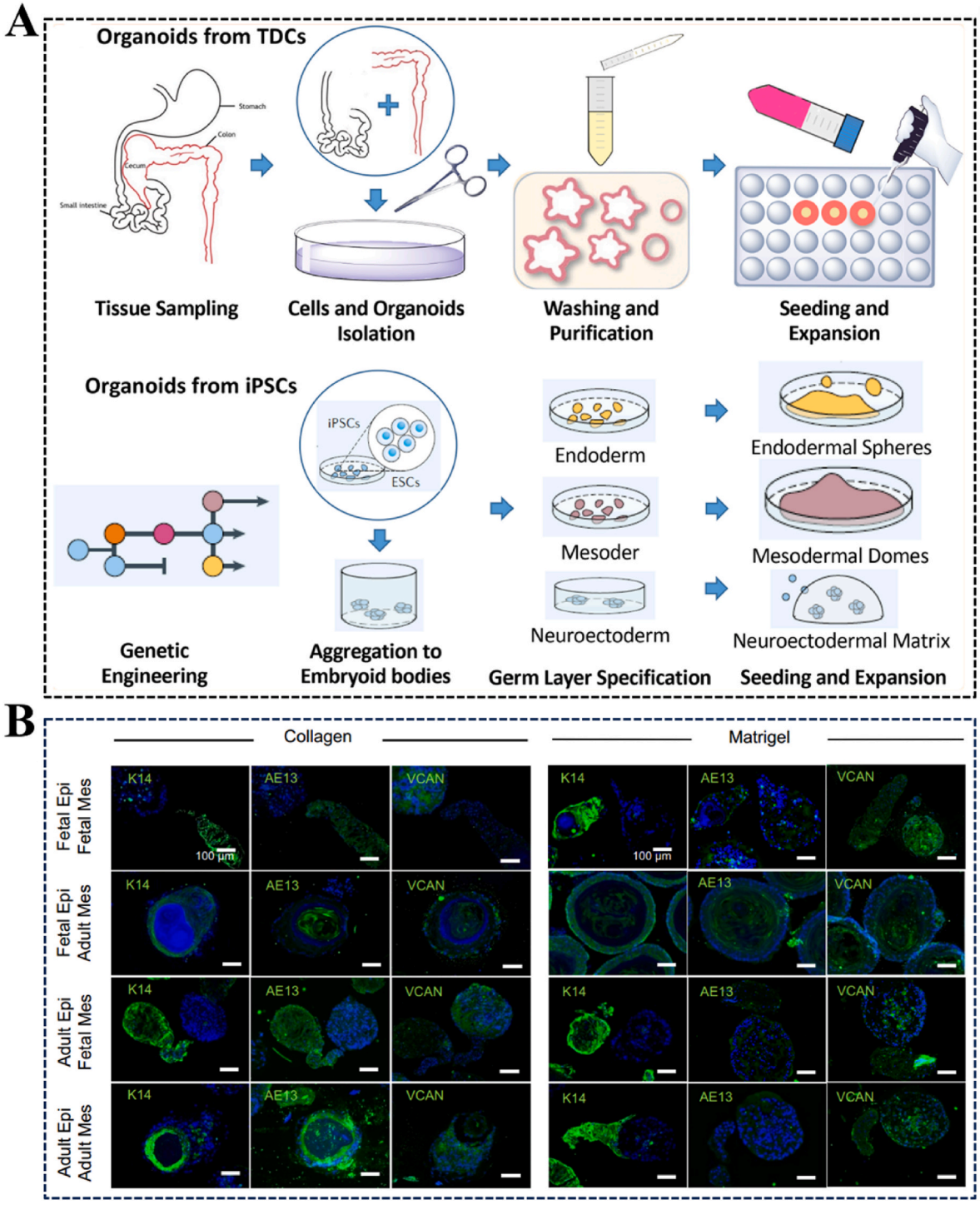

Fig. 1. Organoid Generation and Hair Follicle Histology (A) Schematic diagram of an organoid generation procedure that can be generated by TDC or iPSC. This diagram is reproduced with minor modifications from Ref. [65], Copyright © 2022 Nat Rev Methods Primers. published by Springer Nature. (**B**) Hair follicles were subjected to histological examination, which involved sectioning and staining with antibodies that were fluorescently labelled. Specifically, the antibodies targeted K14, AE13, and versican to visualize these proteins within the follicloids. This diagram is reproduced with minor modifications from Ref. [64], Copyright © 2023 Sci Rep. published by Nature Portfolio.

continually [10]. Biomaterials need to be applied to build organoids to enhance the accuracy of disease modeling and drug screening. Biomaterials can optimize drug delivery and uptake by modulating organoid biochemical properties such as adhesion and growth factor expression. For example, Kupffer cells (KCs) play an important function in drug associated hepatic injury; therefore, co-cultures of liver cells and KCs offer a highly robust cellular model [11]. Similarly, hyaluronic acid (HA) can better mimic the microenvironment generated by vascularized breast-like tumors, which contain MCF-7 cells and human fibroblasts [12], leading to the successful construction of breast-like organoids [13]. This type of organ model simulates realistic tumor behavior and should be used to develop efficient personalized chemotherapy regimens [14]. It helps to understand the occurrence and progression of diseases because it provides valuable information for designing therapeutic strategies [15]. For example, proteomic analyses of matrix gel samples have shown substantial protein heterogeneity within and between samples [16]. Furthermore, the early formation of organoid cells in the mouse intestine, after concomitant application of fibrin hydrogel and 10 % matrix gel, has been reported to be comparable to the formation of 100 % matrix gel, suggesting that only part of the signaling indicators induced by matrix gels are required for the initial formation of organoid cells [17,18]. For example, gelatin methacrylate (GelMA) is a modification of gelatin that primarily contains gelatin moieties and a small amount of a methacrylate moiety, and it can be cross-linked via photopolymerization [19]. GelMA, owing to its instantaneous cross-linking ability [20], tunable mechanical properties, and biocompatibility, has been widely used to create structured vascular constructs [21]. For example, the high-affinity structural protein collagen type I [22] is often used as a simple three-dimensional scaffold for culturing various cells, as well as for supporting cell aggregation spheres and organoids [23]. Multiple investigations into intestinal organoid cultures have demonstrated that hydrogels composed of type I collagen enhance the viability and expansion of these organoids [24]. In summary, organoid technologies grounded in biomaterials offer novel and potent means for modeling diseases and screening drugs, thereby accelerating the development of precision therapies.

2. Organoid origins

2.1. Tissue-derived organoids

Tissue biopsy-derived organoids represent autonomous extensions and expansions of non-engineered, organ-specific cell types isolated from patient tissues, whereas organism-origin-derived analogs model the epithelial cell ecological niches in that particular organ [25,26]. Consequently, tissue-derived organ models can only mimic the organization of the native organ. Most tissue-like organ models consist solely of epithelium; therefore, they provide an excellent system for studying the regulation of cell fate in a histological manner. Notably, two other cell types—neurons and fibroblasts—can be added to organoid cultures composed of epithelial cells [27,28]. These are used to study the interactions among cell compartments [29], leading to the formation of complex co-culture systems [30]. While the utilization of pluripotent stem cell (PSC)-derived biologic tissues faces challenges due to chromosomal properties and reliability concerns, tissue-specific stem cell-derived biologic tissues have also garnered attention, albeit to a lesser extent. Some analysts suggest that genetic stability is relatively high [31], at a rate comparable to the expected rate of mutation accumulation in the body [32]. Nevertheless, the ability of cells to reproduce and differentiate changes over time. Human tissues are generally divided into two categories based on their regenerative capacity. While it is possible to derive tissue-like organs from the superficial epithelial cells of most ectodermal and endodermal tissues, obtaining such structures from organs of mesodermal origin (such as the heart and blood) and from neural cells remains challenging. Investigating these non-epithelial mesodermal and ectodermal tissues *in vitro* requires targeted differentiation programs that mimic the signal transduction pathways active in the developing embryo [33].

By far, the most well-characterized tissue-based organ systems are those derived from the adult duodenal epithelium. Embedding single intestinal epithelial stem cells within matrices enriched with epidermal growth factor (EGF), bone morphogenetic protein inhibitors (Noggin), and Wnt pathway activators (Rspondin1) facilitated the efficient generation of organoid tissues from mouse samples, mimicking the stem cell microenvironments observed both *in vivo* and *in vitro* [34].

2.2. Organoids derived from pluripotent stem cells

Pluripotent stem cells (PSCs), specifically embryonic stem cells (ESCs) derived from early embryos, or somatic cells reprogrammed to a pluripotent state (termed induced pluripotent stem cells, iPSCs), can recapitulate the transitional cellular phenotypes observed during early embryonic development [35,36]. Organoid tissues derived from various types of hematopoietic stem cells do not replicate all functions of natural tissues but do retain fetal-like properties [37]. In some cases, transplantation into animal models promotes further maturation or extending the culture period [38–42]. enhances maturation. Some culture methods yield visible, self-organized structures within 2–3 weeks, whereas more complex structures, such as cortical organoids [43], exhibit sustained cellular complexity and may require several months to mature [44]. Similar to tissue-derived organoids, some hematopoietic stem cell-derived organ tissues (e.g., those derived from intestinal hematopoietic stem cells) possess an inherent capacity for self-renewal and continuous proliferation, mirroring the behavior of natural tissues [37]. In contrast, some tissue-derived organoid models (e.g., kidney) lack the ability to proliferate. This is reflected in the *in vivo* behavior of these organoids; for instance, early kidney organoids contain stem cell populations responsible for forming functional units [45,46].

Additionally, living tissues generated from hematopoietic stem cells provide a versatile tool for studying human developmental mechanisms and mutations associated with congenital defects from new perspectives. These models help elucidate how specific cell types contribute to tissue development and how gradients of growth factors, cytokines, and morphogenetic factors influence cell behavior during organogenesis. The ability to study morphogenesis *in vitro*, using patient-derived hematopoietic stem cells or by introducing mutations in alleles associated with congenital disorders, has facilitated research into diseases such as microcephaly [47], autism spectrum disorders [48], cystic nephropathy [49], ciliopathy [50], glomerulonephropathy [51], and congenital heart anomalies [52,53].

Models employing organoid tissues generated from hematopoietic stem cells have been instrumental in studying microbial interactions, encompassing viral infections like Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [54] and Zika virus [55], alongside bacterial infections such as *Clostridium difficile* [56] and Salmonella species [57]. Additionally, models of injury, such as cryotrauma and anthracycline-associated cardiotoxicity, have been developed. Collectively, these innovative models of diseases and injuries possess the capacity to transform the landscape of therapeutic development for both congenital conditions and infectious diseases [58].

3. Biomaterial hydrogels for organoid construction

Organoid development requires a three-dimensional microenvironment that supports cellular proliferation, adhesion, and differentiation. Hydrogels, frequently utilized as scaffolds in organoid cultures, exhibit mechanical and physical attributes conducive to supporting cellular activities [59,60]. In the realm of cell therapy, biomaterials are pivotal in maintaining cell viability [61], minimizing cell loss during administration, and enhancing the success rate of transplantations [62]. For instance, Kageyama et al. developed an *in vitro* model of hair follicloids by using Collagen I and Matrigel as extracellular matrices (ECMs). By

comparing the effects of these two substances on hair follicle growth and drug testing, it was demonstrated that both Matrigel and collagen I could simulate the hair follicle growth microenvironment *in vitro* and could be utilized for testing the effects of germinal drugs. Particularly, they discovered that hair follicle protrusion growth was significantly enhanced when minoxidil was present in the combination of adult epidermal cells/adult mesenchymal cells/Matrigel, suggesting that this model could be employed to evaluate the efficacy of germinal drugs [63] (Fig. 1B). Additionally, the authors also observed the formation of follicle-like structures in hair follicle cells of androgenetic alopecia (AGA) patients, although with a shorter growth length, indicating that this model might have potential applications in studying alopecia disorders and developing new treatments [64]. Consequently, further exploration into biomaterials that are compatible with organoid cultures, along with their potential uses, is vital for optimizing efficacy. When designing biomaterials for organoid purposes, it is imperative to assess how their properties affect the biological functionalities of the organoids.

The physiological cues provided by hydrogel surface morphological properties, encompassing factors like pore dimensions and fiber diameter, play a crucial role in influencing cell plasticity and differentiation processes [66]. Cell adhesion ligands, either present naturally in biomaterials or intentionally introduced, bind to cells, resulting in cytoskeletal changes and reorganization of the extracellular matrix (ECM) [67]. Furthermore, the aggregation of superficial sensory receptors, induced by cell adhesion ligands, alters the regulation of gene expression within organoid tissues. The mechanistic properties of biological materials are also critical factors influencing cell behavior in cultures of organoids; in particular, matrix stiffness can be detected at adhesion sites that regulate stem cell commitment and fate [68]. Stiffness can be adjusted according to molecular weight, polymer density, and crosslink density [69]. For example, ECM proteins in native biological materials are generally broken down by the action of cell proteases, whereas the degradation of artificial biological materials can be modulated by the degradation of proteases, photo purification, or the hydrolytic degradation of cross-linking agents [70]. Degradation of biomaterials due to matrix loss can stimulate cell proliferation or enhance intercellular interactions [67]. In addition, degradation products (HA fragments and lactic acid) can influence cell behavior [71]. Recently, researchers have started investigating the use of exogenous stimuli (especially light), as a form of spatiotemporal monitoring, to control cell migration and regulate cell fate [68]. Thus, spatial patterns of matrix decay or temporally controlled deletions from cell adhesion to the ligand may be used to provide information about substrate remodeling as well as the dynamics that govern symmetry-breaking events in organisms [72].

3.1. Polysaccharides

3.1.1. Hyaluronic acid

Hyaluronic acid (HA) belongs to the glycosaminoglycan family of intracellular polysaccharides and is widely distributed in vertebrate tissues and bodily fluids. It serves as a protective gastrointestinal membrane against certain bacteria. In the ECM near the cell surface, HA is non-covalently bound to cell surface receptor proteins, which in turn bind to proteoglycans, maintaining the osmolarity and physiological properties of the microenvironment of the cell. HA influences the distribution, trafficking, and interactions of proteins at the cell surface and plays a role in regulating homeostasis in signaling pathways critical for multiplication, trafficking, migration, differentiation, tissue repair, disease progression, and drug screening [73]. Its good biocompatibility, biodegradability, excellent water retention [74], unique viscoelasticity, and ability to be chemically modified through hydroxyl and carboxyl groups [75,76] make it an attractive option for organoid construction [77,78]. For example, Zhao et al. designed a dual network hydrogel (HAMA-SA-DMA-c(RGDfC), HADR) made of hyaluronic acid methacrylate (HAMA) and sodium alginate (SA) for the construction of liver cancer organoids. By varying the amount of HAMA and SA in the gel to control the cross-linking density, we aligned the mechanical properties of the bionic ECM with those of the liver under physiological conditions (1.3 kPa) [79]. They developed HepG2 to obtain liver cancer-based organoid 2 cells transformed into HADR hydrogels by inoculation with HepG and examined the effects of HADR hydrogels on tumor growth and drug therapy by *in vitro* and *in vivo* DOX efficacy tests (Fig. 2A). These results provide important insights for liver cancer organoid construction and drug detection applications [80].

3.1.2. Sodium alginate

Sodium alginate is derived from brown algae (e.g., kelp or sargassum) and is a source of iodine and mannuronic acid. It consists of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues linked through (1 → 4) glycosidic bonds. Sodium alginate solutions exhibit high viscosity and possess a polyanionic nature due to the abundance of COO- groups, which contribute to their adhesive properties in aqueous environments. These properties make sodium alginate an ideal drug carrier for treating mucous membrane tissues [81]. Sodium alginate demonstrates significant pH-sensitivity and rapidly forms gels under gentle conditions, thereby safeguarding the activity of sensitive drugs, proteins, cellular components, and enzymes from inactivation [82]. Alginate microcapsules have been used to create disease models that simulate dynamic interactions among tumor cells and their microenvironment [83]. For instance, Chooi et al. explored the use of alginate hydrogel as a matrix to build an organoid model of the spinal cord containing mature motor neurons and neuroflora, using TDP43 pathology as a proof-of-concept to simulate spinal cord disease and to provide an excellent model for evaluating drug candidates, demonstrating the feasibility of this model in disease modeling [84].

3.1.3. Chitosan

Derived from chitin, the second most abundant renewable natural resource after cellulose, chitosan is a cationic polysaccharide that exists as a linear copolymer. It contains reactive amino (-NH2) and hydroxyl (-OH) groups and requires acetic or citric acid for solubilization. Chitosan exhibits superior mechanical strength and is highly amenable to chemical modifications. The presence of reactive functional groups enables these polysaccharides to interact with various biomolecules. Additionally, chitosan can form soft gels and cross-link with other polymers [85,86]. Structurally similar to glycosaminoglycans—an important component of the tumor ECM—chitosan serves as an effective alternative for three-dimensional cultured cancer cells [87]. The interaction between the amine groups of chitosan and cellulose alginate (CA) forms porous scaffolds with enhanced chemical resistance, mechanical strength, and shape retention. These three-dimensional cellulose alginate scaffolds provide a cost-effective and feasible *in vitro* model for studying clinically relevant tumor-immune system interactions [88]. For instance, inhibiting the activation of cancer-associated fibroblasts (CAFs) within the tumor microenvironment (TME) of breast cancer cells can suppress T-cell function in the stromal compartment of mammary tumors [89,90]. Furthermore, existing T-cell therapies for breast cancer may benefit from combinatorial gene therapies designed to augment T-cell infiltration and rejuvenation within the tumor microenvironment (TME), thereby enhancing their therapeutic efficacy [91].

3.2. Proteins

3.2.1. Collagen

By dry weight, collagen constitutes roughly 25 % of the body's total protein content. Among the diverse collagen types, type I collagen stands out as the most abundant and is extensively utilized in tissue engineering applications, owing to its straightforward extraction process and extensive versatility [92,93]. Type IV collagen serves as a versatile scaffold with a wide range of applications, yet comparing studies can be difficult due to significant differences in the hydrogel preparation

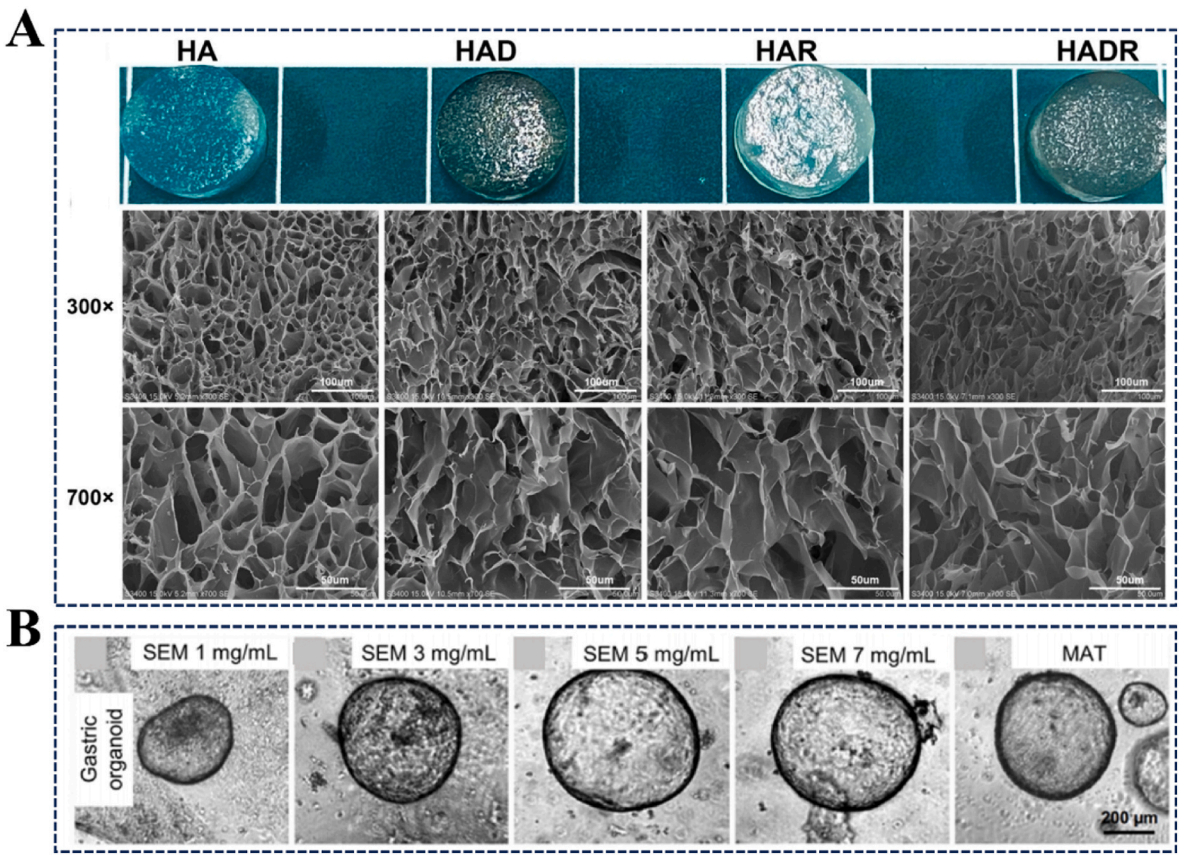

Fig. 2. Histological Staining and 3D Cell Culture Techniques (A) Optical appearance and microstructure of HA, HAD, HAR, and HADR hydrogels, respectively (scale bar: 100 μm and 50 μm). This figure is reproduced with minor modifications from Ref. [80], Copyright © 2024 Int J Biol Macromol. Published by ELSEVIER **(B)** Brightfield images of gastric organoids grown in decellularized stomach derived ECM (SEM) hydrogels and Matrigel (MAT) at day 5 [104], Copyright ©2024 J Biomed Sci. published by BioMed Central.

methodologies adopted by various researchers. The properties of the scaffold material are pivotal in shaping cellular behavior. Nonetheless, a significant limitation in utilizing collagen hydrogels as scaffolds for tissue engineering lies in their variability and susceptibility to various manufacturing factors, such as collagen sourcing and gel pH, leading to a vast design landscape. The scientific community has acknowledged the importance of quantitative characterization of collagen hydrogels as a fundamental step for conducting quantitative research, optimizing tissue constructs, and performing comparative evaluations [94,95]. For example, Hirayama et al. established iPSC-derived collagen α5(IV)-expressing renal organoids and demonstrated that renal organoids derived from COL4A5 mutation-corrected iPSC restored collagen α 5(IV) protein expression, demonstrating the potential of the chemical chaperone, 4-phenylbutyric acid, to correct the GBM abnormality in renal organoids displaying a mild AS phenotype. This iPSC-derived renal organoid model will be useful for drug discovery in AS [84]. Collagen is biocompatible due to its composition and biological properties, allowing it to interact harmoniously with the cellular environment, facilitating tissue repair and new tissue formation. Studies have shown that recombinant human collagen nanofibers are hemocompatible and non-cytotoxic. *In vitro* experiments on cell-scaffold composite cultures have demonstrated that the scaffold material can enhance fibroblast adhesion, proliferation, and cytocompatibility. Moreover, *in vivo* experiments have shown that this material is associated with a low inflammatory response and promotes wound healing, making it suitable for studying disease models.

3.2.2. Mineral Gelatine

Gelatin is produced via the partial hydrolysis of collagen, resulting in the formation of helical structures composed of three intertwined polypeptide chains. During the hydrolysis process, collagen molecular helices are denatured and decomposed into α- (single polypeptide chains), β- (dimers of α-chains), and γ-components (trimers of α-chains), along with molecular chain fragments that are either intermediate in size between the α-components or larger than the γ-components [96]. Consequently, gelatin exhibits a polydisperse molecular weight distribution influenced by different processing conditions, which impacts its physical and chemical properties [97]. Gelatin hydrogels are frequently combined with various support materials, including chitosan, polyvinyl alcohols, alginates, carbon nanotubes, and HAs. These hybrid materials have unique physical and chemical properties, such as antimicrobial activity, biodegradability, and biocompatibility, making attractive in nanomedicine. They are applied in drug screening and in the construction of organoid disease models [98].

3.3. Combination of natural materials

Various configurations of natural materials are used to produce organoids. For instance, combinations of HA and other molecules, such as collagen, gelatin, chitosan, and lamellipodial adhesion proteins, hold considerable value in regenerative medicine [99]. Sokol et al. developed a hydrogel scaffold containing HA, collagen, laminin, and fibronectin to mimic the ECM complex of breast tissue. The use of these hydrogel scaffolds also facilitates breast tissue treatment following surgery or injury [100]. This elastomeric matrix dynamically regulated the concentration, rigidity, and stress-relaxation properties of integrin ligands, thereby enhancing the refinement of cell culture environments. Seeking an alternative to Matrigel, Broguiere and colleagues devised a

fibronectin-based hydrogel, incorporating laminin-111—a key extracellular matrix (ECM) constituent of Matrigel [17]. Matrigel is a material secreted from Engelbreth-Holm-Swarm mouse sarcoma cells and is enriched with extracellular matrix (ECM) proteins. In an early report on organoid cultures, Sato and colleagues cultured mouse intestinal $Lgr5^{+}$ stem cells in high concentrations of Matrigel supplemented with the growth factors WNT, Noggin, R-spondin, and EGF [84].These fibronectin hydrogels emerged as versatile scaffolds supporting the growth of diverse epithelial-mimicking organs. A recent study demonstrated that incorporating developing kidney tissue sections into a fibronectin-gelatin composite hydrogel layer on microfluidic perfusion chips promotes the maturation and vascularization of kidney tissue [101,102]. Organoids grown in this composite hydrogel exhibited increased vascular marker expression compared to those in other non-adhesive ECM materials.

3.4. Synthetic materials

3.4.1. dECM

As the field has evolved, the traditional use of animal or tumor-derived extracellular matrix (ECM) as scaffolds has become increasingly inadequate. This shift has led to an interest in developing synthetic scaffolds off. dECM consists of biomaterials derived from human or animal organs or tissues that are obtained by applying decellularization techniques that remove immunogenic cellular components. In 2018 Lin and his team demonstrated that decellularized porcine neural matrix supports Schwann cell proliferation and peripheral nerve regeneration as it retains primary ECM components and nanofiber structure. This finding prompted further research into the repair of nerve defects with decellularized peripheral nerve matrix hydrogels [103]. In 2019, Giobbe et al. demonstrated that hydrogels from the mucosa/submucosa of decellularized porcine small intestine promoted the formation and growth of endoderm-derived organoids, including those from the stomach, liver, pancreas, and small intestine [104](Fig. 2B). This study demonstrated the potential of these materials as effective biomaterials for constructing disease organoid models, thereby enhancing our understanding of disease pathology and potentially offering novel therapeutic approaches [105].

3.4.2. Co-Assembled supramolecular hydrogelators

Although studies have progressed in the differentiation of renal precursor cells from human iPSCs using soluble biochemical factors, this process relies on a series of protein cascade reactions linking the extracellular matrix to the nucleus. During kidney development, mechanosignaling is critical for the differentiation of renal precursor cells, the maturation of kidney structure, and the formation of function [106,107]. However, most current cultures for renal organoids rely on naturally sourced or synthetic hydrogel matrices, which, while providing certain biochemical and mechanical cues, often lack the ability to precisely regulate cell behavior [108–111]. In addition, uncertainty about the biochemical composition of natural source materials may increase the inter-batch variability of renal organoids, affecting the reproducibility of experiments and the reliability of results [112,113]. Sprang et al. proposed a novel strategy of self-assembly of low molecular weight monomers and bivalent monomers to form supramolecular hydrogels (supramolecular hydrogels) as a means to construct a mechano-responsive nano-environment with cell-adhesion properties for encapsulating and culturing renal organoids. This environment not only provides a new tool to complement traditional soluble biochemical factors, but also induces biological responses during renal development by modulating the mechanical microenvironment of renal organoids, especially promoting glomerulogenesis, which is of great scientific value and application to improve the maturation and function of renal organoids [114]. It not only fills the gap in the understanding of the influence of the mechanical environment on kidney-like organs in existing research, but also provides new ideas and methods for the treatment of kidney diseases and regenerative medicine. By precisely regulating the microenvironment of kidney-like organs, scientists are expected to better simulate the process of kidney development and provide a more reliable experimental model for the study of the mechanism of kidney diseases and the development of new therapies. Meanwhile, the application of this supramolecular hydrogel technology is also expected to be expanded to other types of tissues and organs, bringing new technological innovations to the field of tissue engineering and regenerative medicine.

4. Organoid-based engineering technology

4.1. 3D culture

The 3D culture system employs a suspension approach to prevent cells from having direct contact with the plastic petri dish, whether through the utilization of stand technology or not [115]. A scaffold is a biological or synthetic hydrogel that mimics natural HCM. Log Gel, a proprietary blend of diverse proteins secreted by mouse Engelbrachium Holm-Swarm (EHS) granuloma cells, is the prevalent type used. These proteins consist mainly of adhesion proteins including collagen, actin, myosin, laminin, and heparan sulphate proteoglycans, which mimic the extracellular environment to ensure structural support of the cell and ECM signaling.

Current *in vitro* animal and two-dimensional (2D) models have limitations that hinder the understanding of biological structure and complexity and the development of effective therapies. Recently, with *in vitro* modeling based on 3D biomaterials, a considerably more robust biomimetic replacement than that of previous models has achieved significant results in understanding biological models, disease models, and screening drugs and drug compositions for individualized medicine [116]. For example, Tomar [117] employed polyhydroxystreptanates synthesized by microorganisms to create 3D porous scaffolds through particle solubilization, showcasing their potential as effective 3D biomaterials for supporting cancer models *in vitro*. The generation and utilization of one of these *in vitro* models is a promising biomimetic alternative to traditional cell culture, in particular, contributing to the development of personalized cancer therapies [118].

In the field of 3D cell culture, geometric guidance is a pivotal technique that can be divided into two main categories: uniform arrays and biomimetic structures. Uniform arrays encompass superficial patterns, microwells, and microcarriers, which are essential for the high-throughput production of consistent organoids, thereby enhancing the efficiency of organoid systems [119,120]. A notable example is the work of Liu et al., who developed an all-in-water droplet microfluidic platform for the creation of hybrid hydrogel capsules made from alginate and chitosan. This method enabled the large-scale generation of functional and uniform islet organoids derived from human induced pluripotent stem cells (iPSCs) [121]. These organoids were found to have high levels of expression for pancreatic hormone-specific genes and proteins, as well as the ability to secrete insulin in response to glucose stimulation, thus validating the effectiveness of these microcarriers in establishing robust organoid models.

4.2. 3D print technology

Three-dimensional printing technology has been applied to control cell assembly by depositing single or multiple cell types with different support matrices [122]. Bioprinting, a type of 3D printing, is often utilized to fabricate scaffolds with intricate structures that emulate natural organs to model diseases, and has potential applications in clinical transplantation [123]. Unlike traditional tissue engineering methods, 3D bioimprinting facilitates the development of customized models of organs or diseases for clinical applications. For example, patients with urological diseases often have different phenotypes, particularly urological cancers; therefore, the development of customized

monocarboxylate transporters (MCTs) is crucial for more precise *in vitro* drug screening than that of previous models [124,125].

Three-dimensional bioprinting is categorized into two broad groups: cell-containing bioprinting and cell-free bioprinting. Cell-containing bioprinting allows precise placement of various types of cells in different locations to create biological constructs that mimic as closely as possible the structure and arrangement of cells in natural organs (Fig. 3A). For example, HA-based bioprinter 3D cellular scaffolds can be used to mimic the biological and mechanistic properties of localized environments in the human brain as well as to construct and study polymorphic glioma types. These scaffolds can provide a favorable environment for drug screening [126]. In contrast, cell-free biomaterials facilitate more versatile material selection and complex structural design, in addition to increasing the strength, as the cells can be transplanted following printing. In addition, cell survivability during printing is negligible. Wang et al. combined 3D printing technology and freeze casting to manufacture microporous scaffolds that successfully supported the growth of skin cancer cells. This approach is best suited to the study of breast cancer models, as it allows us to simultaneously control cell accumulation and manipulate cell distribution and composition in an organism with a specific morphology at the 3D microscopic scale [124].

4.3. Microfluidic technology

Microfluidics is a fluid handling technology that enables a high

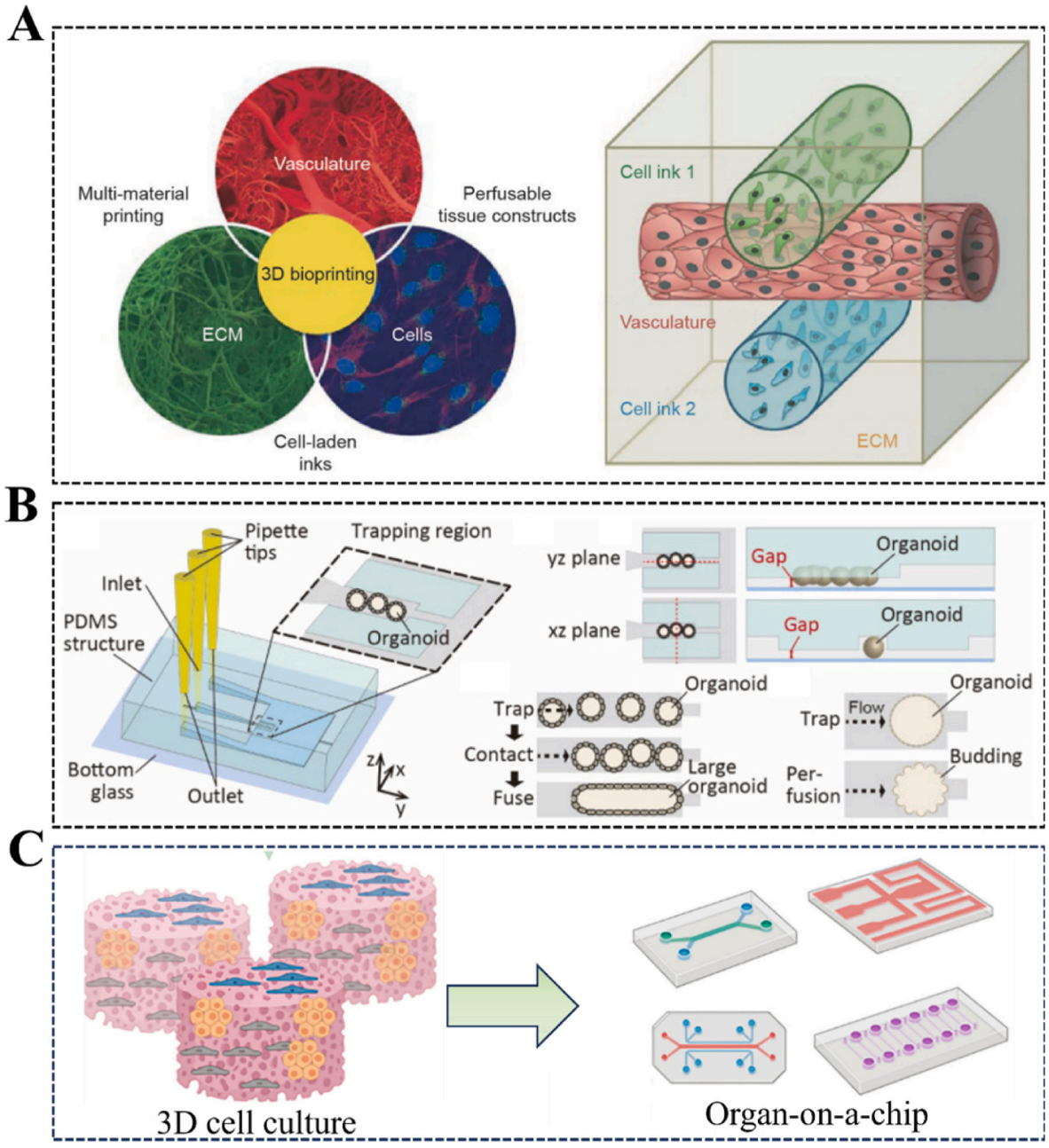

Fig. 3. Bioprinting and Organ-on-a-Chip Technologies (A) Three-dimensional bioprinting [129],Copyright © 2018 Journal of Biomedical Science, published by Elsevier. **(B)** Conceptual diagram of organoid manipulation using the proposed microfluidic device. The figure is reproduced with minor modifications from Ref. [130], copyright © Micromachines (Basel). Published by MDPI **(C)** The organ-on-a-chip platform facilitates controlled cell cultivation within a microstructured, organotypic environment based on 3D culture techniques. This figure is reproduced with minor modifications from Ref. [131], Copyright © 2021 Trends Pharmacol Sci. Published by Elsevier Ltd.

degree of control over fluid flow. In a microfluidic system, at least one component has an inner size of <1 mm. It is a powerful technology with applications in areas such as fluid dynamics, synthesis and assay chemicals, biotechnology and pharmaceuticals, drug toxicity assessment, delivery system design and research, single-cell analysis, and regenerative medicine [127]. Microfluidics enables a high level of fluid flow control as well as the study and use of fluid properties that are not characteristic of macroscopic systems. As the scale of the system decreases, the fluid forces change from gravity to surface tension. In addition, as the Reynolds number increases, the inertial and viscous forces acting on the fluid change at the micrometer scale [1] (Fig. 3B).

In the realm of biomedicine, microfluidics is extensively applied in creating *in vitro* disease models and organ microarrays, offering realistic representations of the *in vivo* environment and enhancing the comprehension of intricate physiological and pathological mechanisms. For example, this technology can accurately simulate immune responses, tissue dynamic homeostasis, disease spread, and drug effect evaluation, thereby providing an efficient platform for drug discovery and toxicity testing.

Organoid microarrays, as a fusion innovation of microfluidic technology and organoid culture technology, represent the cutting-edge direction of biomedical engineering. Although organoids can organize themselves and project the basic organelle structure and function, culture systems are often unable to regulate a finely tuned microenvironment. The emergence of organoid chips has solved this problem by integrating microfluidic systems that precisely regulate the cell growth microenvironment (including nutrient supply, oxygen level, and drug exposure) and also monitor and intervene in the development and functional performance of organoids in real-time. The Shirure et al. study on organoid microarrays for breast cancer is a prime example of how the TME can be mimicked by constructing organoid models containing microvascular networks, which can then be used to explore the biology of tumors and optimize therapeutic strategies [128] (Fig. 3C).

5. Uses of biomaterial-assisted organoid technology: Building disease models and drug screening

Biomaterials, serving as scaffolds for organoid technology, not only offer a physical and chemical environment resembling the extracellular matrix (ECM) *in vivo* but also play a vital role in preserving the structural integrity and function of organoids [132,133]. The physicochemical properties of these biomaterials have a significant impact on cell behavior, such as cell adhesion, proliferation, and differentiation, thereby mimicking the *in vivo* microenvironment and being of critical importance for organoid significant applications in the construction of disease models and drug screening [134,135]. They can provide more precise disease state models and meticulously evaluate the efficacy and safety of drugs [136]. By utilizing patient-derived cells, like induced pluripotent stem cells (iPSCs), and specific biomaterials, personalized organoid models can be established for studying individual responses to drugs and disease development [137]. With advancements in biomaterials science, it becomes feasible to design biomaterials that are more responsive to physiological needs, enhancing the complexity and utility of organoid models [15]. By optimizing biomaterials, we can further enhance the potential of organoid technology in disease research and drug development, thereby promoting the advancement of personalized medicine and precision medicine [138] (Table 1).

5.1. Intestinal organoid

The Intestin is a key site for the survival of symbiotic organisms of the intestinal microbiota, which subsequently play a role in intestinal homeostasis through interactions with intestinal lymphoid tissue and the host immune system. Contemporary research has indicated that the gut microbiota and its metabolites, such as short-chain fatty acids, play a pivotal role in sustaining gut health, modulating the immune system, and promoting gut development [151]. However, the knowledge about gut microbes interacting with human gut cells is limited to genetic or macro-genomic analyses owing to the inability to culture these microbes with live epithelial cells for more than a day, as performed in traditional culture models or more complex gut organoid cultures. Ongoing research endeavors are focused on creating *in vitro* or *in vivo* laboratory models of the human gut to investigate intestinal pathophysiology, both in the absence and presence of viable microorganisms.

The prevalent *in vitro* model utilized for studying intestinal barrier function and drug absorption employs human intestinal epithelial cell lines grown on ECM-coated porous membranes within culture inserts. Despite their widespread adoption in the pharmaceutical sector, these two-dimensional culture systems are unable to the three-dimensional physiological characteristics of intestinal cells and tissues. Specifically, they fail to mimic essential intestinal functions, such as mucus secretion, villus development, and cytochrome P-450-based drug metabolism Moreover, these models are inadequate for sustaining long-term symbiotic cultures with commensal microorganisms due to the rapid overgrowth and colonization of human cell cultures by bacteria within a day. While isolated gut organoid models, such as pouches or perfusion chambers, have been devised for drug screening purposes, their limited lifespan (typically less than 8 h) hampers their effectiveness in studying normal gut pathophysiology, developing disease models, or conducting clinically pertinent host-microbiome interaction studies. However, the advent of three-dimensional gut organoid cultures derived from endogenous enterocytes or pluripotent stem cells has revolutionized the

Table 1
A brief summary of biomaterial-assisted organoid technology.

Organoid	Cells Used	Biomaterial	Property	Application	Advantage	Limitation
Intestinal Organoid	$Lgr5^+$ Intestinal Stem Cell, Enterocyte [3]	Matrigel	Rich in ECM proteins, supports stem cell niche [139]	Model intestinal crypts and villi [108]	Mimics *in vivo* tissue environment closely [68]	Batch-to-batch variability [140]
Liver Organoid	Hepatocyte, Cholangiocyte	Collagen Type IV [84]	Provides 3D scaffold, supports cell aggregation	Hepatocyte and liver tissue culture	Facilitates tissue repair and new tissue formation	Variability in hydrogel preparation methods
Skin Organoid	Keratinocyte, Fibroblast [141]	Gelatin Methacrylate (GelMA) [98]	Photocrosslinkable, tunable mechanical properties	Structured vascular constructs [142]	Instantaneous crosslinking ability [143]	Requires photopolymerization
Brain Organoid	Neural Stem Cell, Neuronal Progenitor Cell [15]	Matrigel	High viscosity, non-inflammatory, non-immunogenic [144]	Brain organoid models [144]	Benefits in creating high viscosity solutions for organoid culture [145]	Mechanical strength may be limited [146]
Tumor Organoid	Cancer Stem Cell, Tumor Cell [7]	Sodium Alginate [83]	PH-sensitive, forms gels under mild conditions	Simulate tumor-stromal interactions	Protects sensitive drugs, proteins from inactivation [147]	Rapid degradation may affect long-term cultures
Retinal Organoid	Photoreceptor Precursor, Retinal Pigment Epithelium [148]	Polyethylene Glycol (PEG) [149]	Biocompatible, tunable mechanical properties [149]	Ophthalmological applications [150]	Precise control over scaffold structure	Bio-inertness, inadequate antimicrobial properties

field by preserving the stem cell niche and facilitating the *in vitro* differentiation of diverse intestinal epithelial cell subpopulations [152,153] (Fig. 4A). In the intestinal organoid model, a three-dimensional extracellular matrix (ECM) gel is employed as the scaffold. This 3D ECM gel has been shown to promote embryonic crypt morphogenesis and intestinal organogenesis when cultured in a medium supplemented with Wnt, R-spondin, Noggin, and other growth factors. The composition of this 3D ECM gel closely resembles that of natural intestinal ECM in terms of its chemical makeup, nanofiber architecture, crypt structure, stability, and mechanical properties; it also effectively simulates the mechanical characteristics of intestinal tissue. Notably, when utilized as a scaffold exhibiting mechanical properties akin to those of intestinal tissue—specifically elasticity and viscoelasticity—the 3D ECM gel demonstrates optimal biocompatibility along with superior cell proliferation and differentiation capabilities [139]. This makes the resulting intestinal epithelial model highly representative of its corresponding native tissue. Furthermore, studies indicate that hydrogels derived from cellular tissues exhibit physiological and mechanical properties comparable to commercially available gels such as Matrigel, thereby supporting the culture of intestinal organoids.

In conclusion, it can be asserted that the 3D ECM gel used in the intestinal organoid model shares numerous similarities with natural intestinal ECM across various dimensions. This resemblance facilitates the simulation and investigation of both physiological and pathological processes within the intestine *in vitro* [153]. For each patient's intestinal tissue biopsy, organoids can be propagated, cryopreserved, and rejuvenated for multiple applications, thereby facilitating the establishment of biobanks [154,155] and multi-screening systems for the validation of novel drug candidates and the development of personalized therapies [156]. Nevertheless, organoids do possess limitations, notably the absence of supportive cell types such as vascular endothelial cells and immune cells, which are crucial for drug screening, translocation studies, pharmacokinetic (PK) assessments, and disease modeling. Furthermore, they cannot replicate the fluid flow or mechanical strain of intestinal peristalsis, which is critical for maintaining intestinal function and health.

Intestinal microarray platforms provide good experimental control through multiple connected microfluidic channels. More recently, complex two-channel microfluidic gut phantoms were created in which human gut epithelial cells, capillary endothelial cells, human immunocytes, and eventual microscopic microbial symbionts are able to grow, coexist, and interact with each other, recreating *in vitro* physiological fluid flow and peristaltic-like mechanical strain [157]. "Intestinal microarray" refers to a recently released model of the human intestine containing Caco-2 cells [158,159] (Fig. 4B). Gut microarrays are made of flexible and breathable silicone polymers (polydimethylsiloxane, PDMS). High-resolution images of this crystalline material can be obtained using phase contrast, differential interference contrast, or confocal immunofluorescence microscopy. Intestinal microarrays can mimic periodic mechanical stress similar to that undergone by gut tissues during peristalsis, thus, more accurately modeling the dynamic microenvironment of the human gut. This approach allows for a more accurate modeling of intestinal function than that of the *in vitro* models described earlier. This model also includes pathogenic bacteria, such as invasive *Escherichia coli*, as well as members of the normal microbiota. As a result, it allows researchers to study the interactions between these microorganisms and the human intestinal epithelium, shedding light on gut homeostasis and the development of bowel diseases.

A native human intestinal microarray microfluidic model was developed by combining organ-like and organ-on-a-chip approaches. Human intestinal stem cells were isolated from enzymatically digested duodenal biopsy tissues and seeded onto an ECM-coated porous film within a dual-channel ECM PDMS microfluidic device. Primary intestinal microvascular pericytes were placed in parallel channels on the opposite sides of the film [108]. Like the Caco-2 cell-lined microenvironment, intestinal epithelial cells in this system undergo organogenesis and multilayered differentiation under fluid flow and peristaltic stress. Transcriptome analyses indicate that the mechanically activated intestinal microvilli in these models closely replicate the proliferation and host defense mechanisms observed in the human duodenum.

On drug screening, Pocock and colleagues conducted a study on the oral absorption of the chemotherapeutic agent SN-38 (7-ethyl-10-hydroxycamptothecin) using an intestine-on-chip model, which enhances the traditional Caco-2 Transwell method by more accurately replicating the biological barrier functions [160]. They differentiated an epithelial cell monolayer with external mechanical stimulation to achieve a 3D undulating structure that emulates the expression of microvilli. The research then focused on the permeability of SN38 when modified with fatty acid esters of varying chain lengths and positions, revealing that lipophilic prodrugs could potentially address the challenges of low oral bioavailability. This model is also applicable to the study of nanoformulations and biological entities.

In another study, Kultong et al. examined the transport of both high- and low-permeability pharmaceutical compounds across the intestinal barrier using a dynamic gut-on-chip model [161]. The compounds tested included antipyrine, ketoprofen, digoxin, and amoxicillin, with concentrations ranging from 500 μM to 250 μM for a duration of 24 h on a differentiated monolayer of human colorectal adenocarcinoma cells (Caco-2). The researchers compared the apparent permeability (Papp) values of these compounds and found that for antipyrine and ketoprofen, the Papp values decreased under dynamic flow conditions compared to static conditions in transwell systems. This could be attributed to the chip design, the material of the diffusion membrane, and the presence of laminar flow. In contrast, for amoxicillin, a compound with low permeability, the Papp values were consistent under both dynamic and static conditions. Kultong et al. concluded that their gut-on-chip model was suitable for studying drug transport when compared to the static transwell model [162].

The intestinal DNA chip has become a valuable tool for understanding gut functions, including metabolism, nutrition, cancer development, disease modeling, and drug absorption. It has demonstrated efficacy in pinpointing targets for disease modeling and drug discovery endeavors. Variations in genetic sequences among drug transporters, metabolic enzymes, and therapeutic targets have been implicated in human pharmacodynamics, dosing requirements, and toxicity profiles. Organoid models of the gut exhibit versatility in applications, ranging from the investigation of specific pathological processes, including inflammation, infection, and nutrient uptake, to the tailored development of pharmaceuticals for individual diseases and patient populations [163].

5.2. Brain organoid

The nervous ecosystem originates from neuroectoderm, from which the neural plate is initially formed, followed by a process of metamorphosis, fusion, and morphogenesis into the auditory tubules. Neurons usually arise from neural stem blood cells located in the vicinity of the ventricles. These cells migrate outward to form layered structures in specific regions, such as the medulla oblongata, retina, and cerebral cortex [15] (Fig. 5A).

Extensive research has been conducted on the potential application of brain organoids in modeling neurodevelopmental disorders [144]. Brain organoids have been successfully used to recapitulate disease phenotypes associated with structural malformations evident at the early stages of embryo development. The pathogenesis of these disorders is usually ascribed to disturbances in the regulation of progenitor cells, which include prematurity of differentiation, decreased multiplication, and cell cycle disorders. Matrigel, a matrix derived from murine tumor tissue, is abundant in extracellular matrix (ECM) proteins such as laminin, collagen, and various growth factors. This composition allows it to effectively mimic the diverse biological functions of natural ECM and plays a crucial role in organoid culture [164]. Studies have

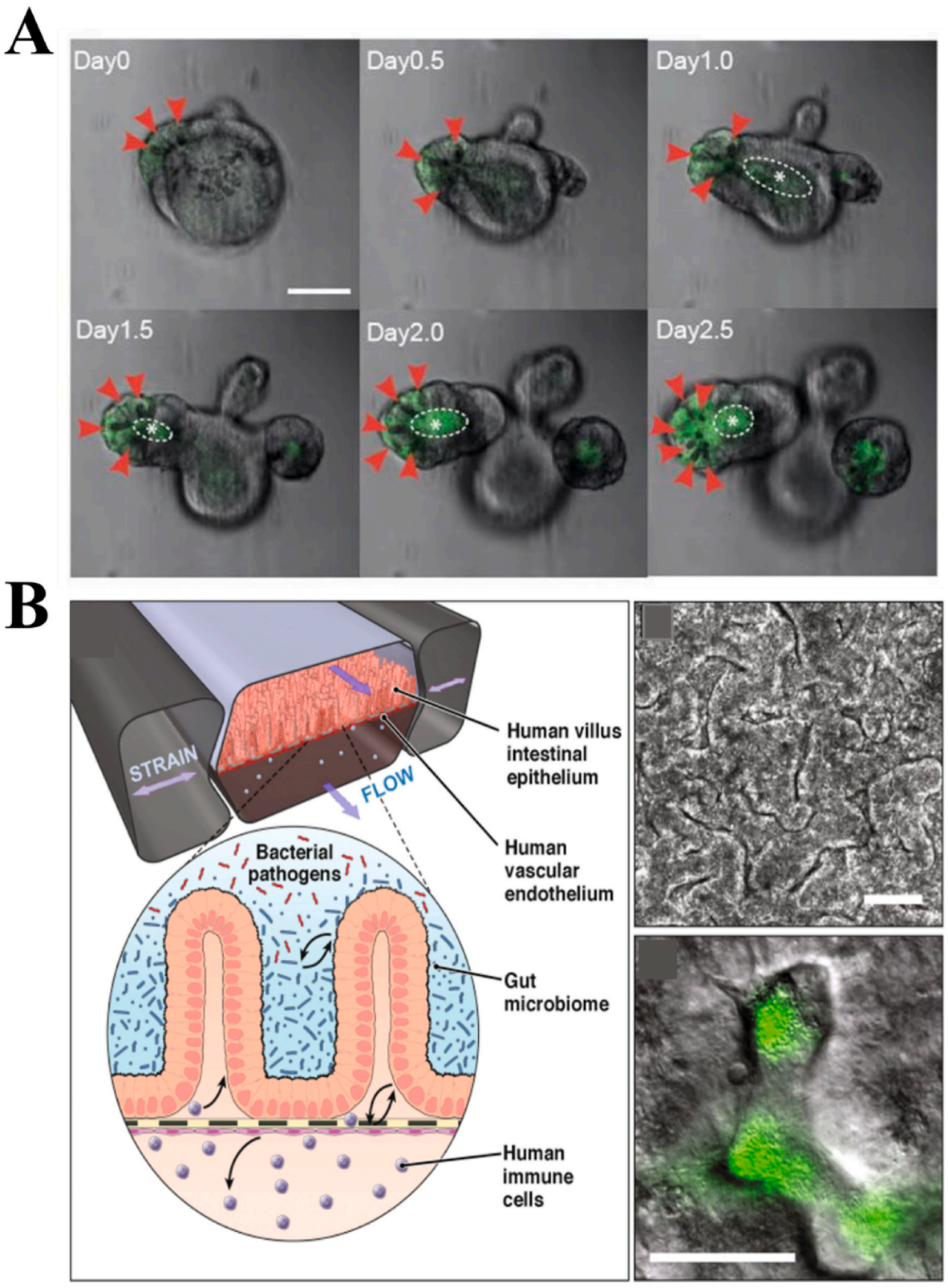

Fig. 4. Advancements in Gut Organoid Technology and Intestinal Ecology (A) Time course of crypt-like organ growth. Differential interference contrast images show granule-containing Pan cells (red arrows) at the ectodermal site of neocrypt formation. Lgr5-GFP (green) stem cells expand at the base of the crypt close to the Pan cells. Zoom bars: 50 μm. this figure is reproduced with minor modifications from Ref. [153], Copyright © 2011 Nature. published by Nature Publishing Group. **(B)** An *in vivo* intestinal microarray in which human villous epithelium and vascular endothelium are arranged on opposite sides of a pliable porous surface in response to fluid flow and peristaltic-like stimuli. This figure is reproduced with minor changes from Ref. [140], copyright ©2018 Cell Mol Gastroenterol Hepatol. By Elsevier.

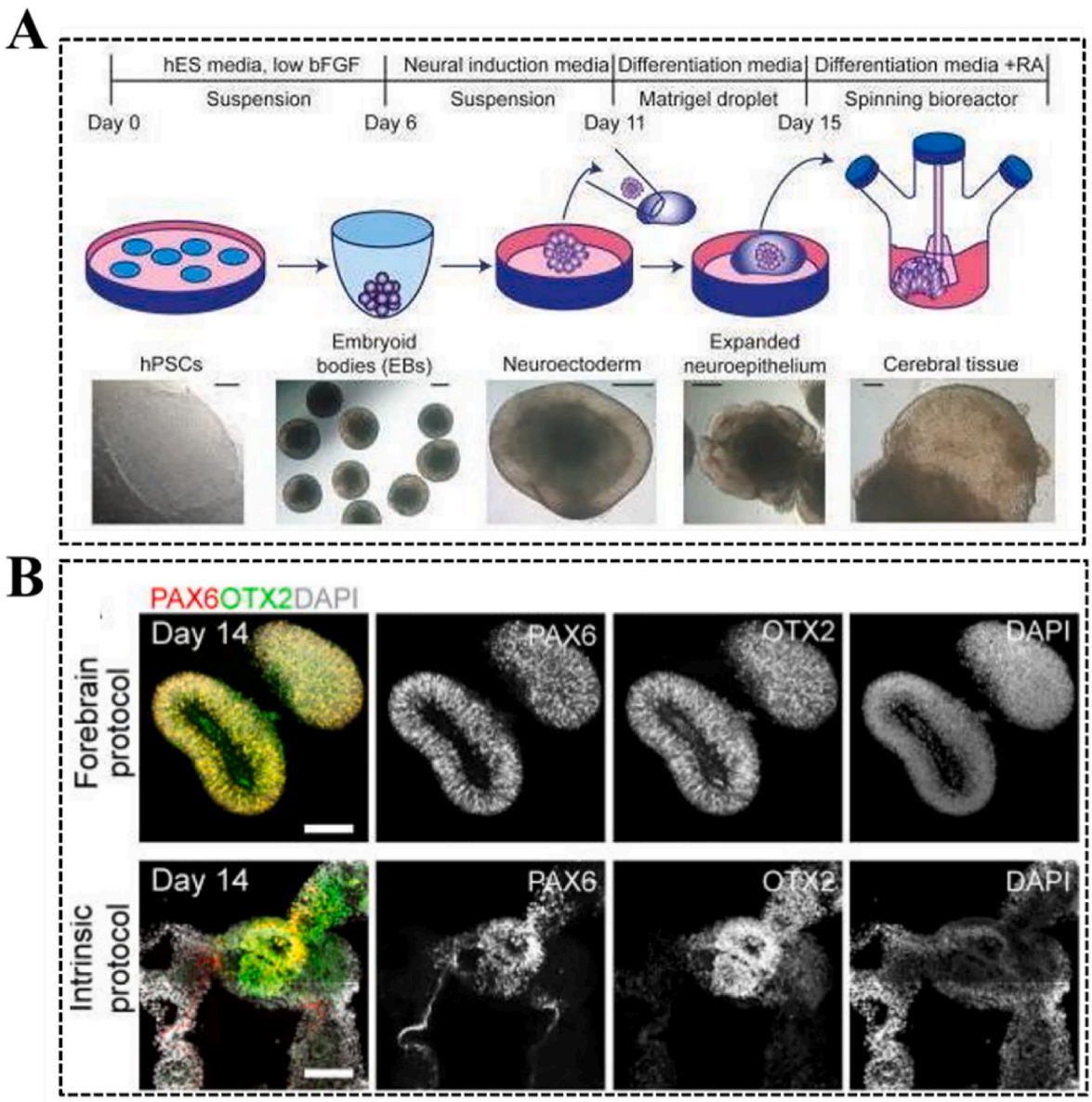

Fig. 5. Brain Organoid Culture System and Zika Virus Impact on Neural Stem Cells (A) Brain-like organ culture system with example images of each stage. This figure has been slightly altered and is reproduced from Ref. [165]. Copyright © 2013 Nature. Published by Nature Publishing Group. **(B)** Zika virus infects neural stem cells and causes microcephaly. Figure slightly adapted from Ref. [172], Copyright © 2016 Cell. by Elsevier Publishing.

demonstrated that induced multipotent stem cells from patients with microcephaly possess mitosis-associated mutagenesis, and organ tissues derived from iPSCs showed that dysregulation of the cell division plane leads to early neural progenitor cell (NPC) failure and the formation of smaller organ tissues [145,165] (Fig. 5B). Deficiency of the tumor suppressor gene in human pluripotent stem cells (hPSCs), PTEN, leads to delayed over-proliferation of NPCs and altered neurogenesis in organ tissues, resulting in the formation of abnormally large organ tissues resembling megalencephaly [166]. Beyond genetic conditions, brain organ tissues can model neuropathogenic infections affecting brain development. For example, the Zika virus has a propensity to infect NPCs, resulting in the inhibition of their proliferation and induction of cell death. Consequently, this leads to a notable decrease in the size of the organoid tissue, as reported in studies [167–169]. Furthermore, cerebral cortex organoid tissues infected with the virus displayed characteristics of congenital Zika syndrome, including neuronal layer atrophy, adherens junction disruption, and ventricular membrane dilatation. These observations offer direct evidence of a causal relationship between embryonic exposure to the Zika virus and the development of neurological disorders [170–172]. Ha Nam Nguyen points out that the deficiency of testing platforms capable of accurately predicting the performance of drugs in humans has resulted in an extremely low success rate during the discovery process. Traditional two-dimensional (2D) cell culture models are inaccurate, while three-dimensional (3D) brain organoids can imitate the structure, composition, and physiological characteristics of the human brain, offering an alternative system that might break through key aspects of drug testing and toxicological evaluation. Ha Nam Nguyen stated that brain organoids can be utilized for drug testing at any stage of differentiation, including fixed and frozen sections for immunohistochemical work, or fixed and stained in multiwell plates for high-content analysis, demonstrating the potential and efficacy of using ipSC-derived brain organoids in drug screening and toxicological evaluation. This approach provides a platform that more closely resembles human physiological conditions and is anticipated to enhance the accuracy and success rate of drug screening [146]. Consequently, organoids have been utilized as a

platform to validate the results of screening antiviral drug candidate compounds [173–175].

5.3. Tumor organoid

The tissue of a tumor organ can be used to predict a patient's ability to be sensitive to a substance, providing valuable insights into precision medicine treatments (Fig. 6A). Sahs et al. conducted a comparative study of organoid and patient responses to tamoxifen using breast cancer organoids undergoing standard clinical therapy. The study revealed that the medication's *in vivo* reaction within organ tissues aligned with the corresponding patients' *in vitro* drug response, hinting at the prospective application of organ tissues in forecasting patient pharmacological responses [176]. In this study, the extracellular matrix (ECM) scaffold utilized by Sahs et al. is Matrigel, a commercially available substrate frequently employed in *in vitro* cell culture. This material exhibits similarities to natural ECM as it encompasses various growth factors and matrix proteins that replicate the *in vivo* environment, thereby providing essential support for organoid growth and maintenance [177]. Additionally, a comparison was conducted between the oncologic drug therapy response observed in organoids and that of matched patients in a clinical setting. The organoids exhibited a sensitivity of 100 %, specificity of 93 %, positive predictive value of 88 %, and a negative predictive value of 100 % in predicting patient responses to targeted therapies and chemotherapeutics. These results validate the capacity of organoids to precisely anticipate drug responses, enhancing the precision in diagnostics and therapy. For example, research by van de Wetering et al. [147] demonstrated that organoids harboring the BRAF V600E mutation displayed varied drug sensitivities, even within tissues from the same patient. This underscores the importance of considering tumor heterogeneity during drug sensitivity screening. Similarly, Sachs et al. showed that HER2-overexpressing breast cancer organoids were responsive to HER2-targeting drugs, while organoids with high levels of BRCA1/2 expression were sensitive to ADP ribose polymerase inhibitors, in contrast to those with low BRCA1/2 expression, which exhibited resistance. These findings highlight the potential of using gene expression profiles in organoids as an essential basis for drug sensitivity screening. Furthermore, Broutier et al. [176] employed hepatocellular carcinoma organoids to screen 29 anti-tumor compounds, including both clinically approved drugs and those in development. They observed that hepatocellular carcinoma organoids with the CTNNB1 mutation were resistant to LGK974, an insecticide, whereas Wnt pathway-dependent hepatocellular carcinoma organoids were sensitive to it. Additionally, wild-type KRAS organoids responded to the EGF receptor inhibitor AZD8931, while KRAS mutant organoids were resistant to the same drug (Fig. 6B).

A class of organic chip platforms was described by Skardal et al. Within this system, multiple cancer cell-forming organoids are individually and independently encapsulated in Matrigel, whereas fibroblasts are cultured in alginate gel in other chambers, with fluids circulating between specific chambers, which better mimics the TME. This combination of organoid microarrays and microfluidic technology allows bulk culture of organoids and high-throughput drug sensitivity testing, providing a good platform for individualized TME simulation and drug screening.

Compared to traditional 2D cell lines and immunodeficient mouse models, organ tissues offer the potential to unveil fresh and innovative perspectives on tumor immune response therapies [178]. In recent years, tumor immunotherapy has been widely used. Although some progress has been made, the overall efficacy is low and only effective in some patients. In addition, there is still a strong need for immunotherapy to meet the standards of precision medicine. Jacob et al. achieved successful co-culturing of glioblastoma organoids with CAR-T cells specifically designed to target the cell expression of epidermal growth factor receptor variant III (EGFRvIII), through the advancement of tumor-immune co-culture organoid systems. By assessing T cell multiplication as well as tumor cell mortality in the presence of EGFRvIII, the researchers validated the utility of organoids in facilitating rapid endogenous target testing and immunotherapy. In addition, the team utilized organoids to study the efficacy of an anti-programmed degenerative cell death proteins-1 (PD-1) therapy. Neal et al. [178] established 20 tumor-immune organoids and tested the efficacy of the curative PD-1-suppressing anti-body nabulizumab. The results showed that nabulizumab significantly induced gamma interferon (IFNG),

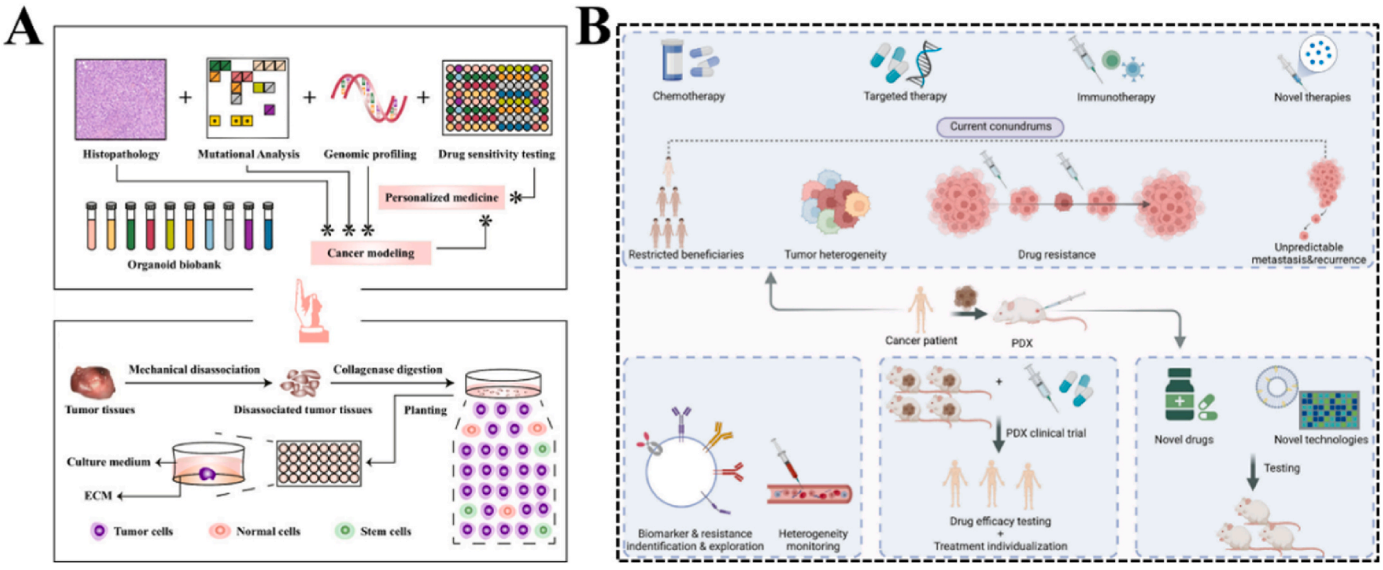

Fig. 6. PDX Production, PDO Applications, and Tumor Tissue Analysis (A) PDX Production method steps and PDO applications. Tumour-like tissues containing cancer cells, fibroblasts, myofibroblasts or stem cells are mechanically and chemically dissociated into very small fragments, cell membranes or single cells and cultured under appropriate three-dimensional conditions in a gel system containing ECM components. This figure is reproduced with minor modifications from Ref. [180], copyright Cell. Published by Cell. **(B)** PDX in the new era of cancer treatment. This figure shows the current conundrums of cancer treatment including restricted beneficiaries, tumor heterogeneity, drug resistance as well as tumor metastasis and recurrence, and shows the versatile functions of PDX in developing therapeutics against cancer [181]. This figure is reproduced with minor modifications from reference Copyright ©2023 Signal Transduct Target Ther. by Springer Nature.

perforin 1 (PRF1), and granzyme B in $CD3^+$ lymphocytes infiltrating carcinoid organs, demonstrating functional suppression of immune checkpoints *in vitro*. The finding showed that the PD1 blocking antibody, nabulizumab, effectively inhibited IFNG, PRF1, and granzyme B in tumor-bearing organs. The findings align with those observed in personalized anti-PD-1 clinical trials.

Patient-derived organ tissue can also be used to follow the evolution of drug resistance before and after tumor treatment. Vlachogiannis et al. [176] produced organ tissues using liver metastases from patients with rectal cancer before and after treatment with regorafenib; a mouse model of transplanted tumors was created from this organ and the mice were treated with regorafenib. Immunohistochemical staining of mouse tumors for CD31 showed that the microvascular system was more significantly reduced by regorafenib treatment in the organoid mouse model than that without regorafenib treatment, whereas the microvascular system in the regorafenib-treated organoid mouse model was resistant to regorafenib and did not respond to subsequent regorafenib treatment. The progressive development of regorafenib resistance seen in patients corresponds with these observations, underscoring the crucial role of organ tissues in predicting the evolution of tumoral resistance.

In applying organoids to precision medicine, it is crucial to accurately identify drugs with notable efficacy on tumors through drug screening and establish organoids from the patient's Para cancerous or normal tissues. This approach allows for drug testing to avoid additional damage to normal tissues. Dst et al. [178] recommend culturing hepatocyte-like organs for the detection of hepatotoxicity and to prevent drug-induced liver damage, thereby protecting the patient's health. Drug-induced nephrotoxicity represents a notable cause of treatment failure in hospitalized patients. Morizane et al. [179] made a major breakthrough in nephrotoxicity studies by using organ tissues to detect cisplatin toxicity to the proximal and distal renal tubules of the kidneys. In addition, iPSCs-derived cardiac organ tissues have been used to study cardiotoxicity. These organ tissues have provided valuable insights for studying the toxicity of anticancer drugs in individualized therapy.

5.4. Skin organoid

Skin-like organ tissues are basic *in vitro* cultures that preserve essential cytoarchitectural characteristics, intercellular interrelationships, and ECM. Despite originating from distinct embryonic layers—the ectoderm for the human epidermis and a different layer for the dermis—both skin tissues necessitate the interplay between epithelial (epidermal) and mesenchymal (dermal) cells for the normal development of the skin and the formation of skin appendages [182–184] (Fig. 7A). Type IV glue was used originally as an ECM bracket. Type IV collagen, a type of collagen found primarily in the basement membrane, bears some similarity to natural ECMs in that it provides the structural support needed for cell attachment and migration, and is able to mimic some of the biological properties found in natural ECMs [185]. By using type IV collagen, the researchers were able to successfully differentiate keratinocytes and fibroblasts and induce the stratification of skin organoids.

In 1975, Rheinwatd et al. were the first to develop a self-tissuing squamous epithelial pro-generation strategy by sequentially co-culturing primary human keratinocytes with irradiated primary mouse fiber cells, a breaking point that paved the way for the cultivation of self-tissuing skin tissues *in vitro*. The introduction of fibroblast rearing in 1989 ensured stable deposition and expanded keratinogen-forming cells. Following this, successive ESCs as well as iPSCs became powerful and effective *in vitro* tools for studying dermal organogenesis. The development of 3D self-organizing stratified surface epidermal equals (SESDEs) derived either from the ESCs in literature or iPSCs in the late 2000s and 2010s, which was an important milestone in the field of dermal organogenesis. In 2020, Lee et al. [186] documented a nearly completed *in vitro* self-organizing skin system derived from iPSCs, which has a complete *in vitro* self-organizing dermal system that can evolve into hierarchical dermal organoids containing multiple accessory structures such as hair follicles. Meanwhile, the generation of organoids with either lipid glands of sebaceous or sweat organs stemming from preprogrammed epithelial progenitor cells suggests that the accessory organs have been successfully integrated into mature skin systems [187, 188].

For nearly two decades, *in vitro* models have served as a crucial research tool in the field of dermatopathology. Initially, these *in vitro* systems for modeling the superficial dermal layer comprised solely of a segmented epidermis. More complex full-thickness skin models were created by seeding keratin-forming cells on collagen or fibronectin matrix scaffolds containing fibroblasts. In addition, the ability of fibroblasts to self-separate ECM *in vitro* was utilized to generate a 3D skin cast composed entirely of body components. In contrast to traditional full-thickness skin models, stem cell culture techniques are capable of generating skin-like organs that organize themselves and differentiate directionally according to cell type, mirroring the developmental processes observed *in vivo*. These models can generate accessory organs of the skin like the hair follicles and sebaceous glands, which is unmatched by the conventional skin models. Most of the models available for *in vitro* skin studies are based on 2D and 3D cultured skin cell models, which still differ considerably in terms of interlayer interactions and actual physiological states. However, cutaneous-like organs also face some limitations, such as unstandardized growth cycles and consistency problems (Table 2).

Skin organoids offer therapeutic options with clinical potential for skin grafting and serve as valuable models for discovering new treatments in regenerative medicine and gene therapies. These organoids closely mimic the composition and architecture of native skin tissue, while also being convenient to manipulate and store through cryopreservation [200]. Notably, more advanced types of biotechnological approaches, including multi-physiological families or organoids and organoid platforms on a chip, are available. Some of these models offer performance comparable to that of animal [201,202]. FOXC1 overexpression induces epidermal cells to express functional proteins resembling those of sweat glands, which facilitate wound healing and sweat gland regeneration [203]. Skin organ tissues have been employed to investigate the development progression, and drug responsiveness of various skin tumors, including basal cell carcinoma, squamous cell carcinoma, melanoma, and Merkel cell carcinoma [204] (Fig. 7B). Furthermore, patient-derived or genetically corrected human induced pluripotent stem cells (hiPSCs) offer promising avenues for treating inherited skin disorders. Specifically, genetically autologous epidermal cells (GAECs) could provide a sustained therapeutic option for herpetic skin conditions. Promising results have emerged from CRISPR/Cas9-based genome editing technology in correcting genetic skin disorders such as epidermolysis bullosa [143,205–207]. In addition, hiPSCs are also an ideal source for generating skin organ tissues. Their cultivability in Petri dishes broadens their application scope, enabling research into human skin development, disease modeling, pharmacological testing, skin barrier biology, and the advancement of cell and gene therapies, as well as toxicological assessments [143]. hiPSC-derived skin organoids can be swiftly produced from existing cellular spheres or aggregates, rendering them ideal for high-throughput screening and drug efficacy testing. By employing a human induced pluripotent stem cell (hiPSC)-derived skin organoids model to study Mpox virus (MPXV) infection and drug treatment, Li et al. demonstrated that hiPSC-derived skin organoids are vulnerable to MPXV infection. Moreover, the capacity to support viral replication and the production of infectious viral particles established human skin organoids as a potent experimental model for studying MPXV infection, mapping virus-host interactions, and testing therapeutic drugs, providing a significant tool for comprehending the pathophysiology of MPXV infection, virus-host interactions, and the development of new therapeutic approaches [208]. In summary, skin organoids provide a versatile platform for drug

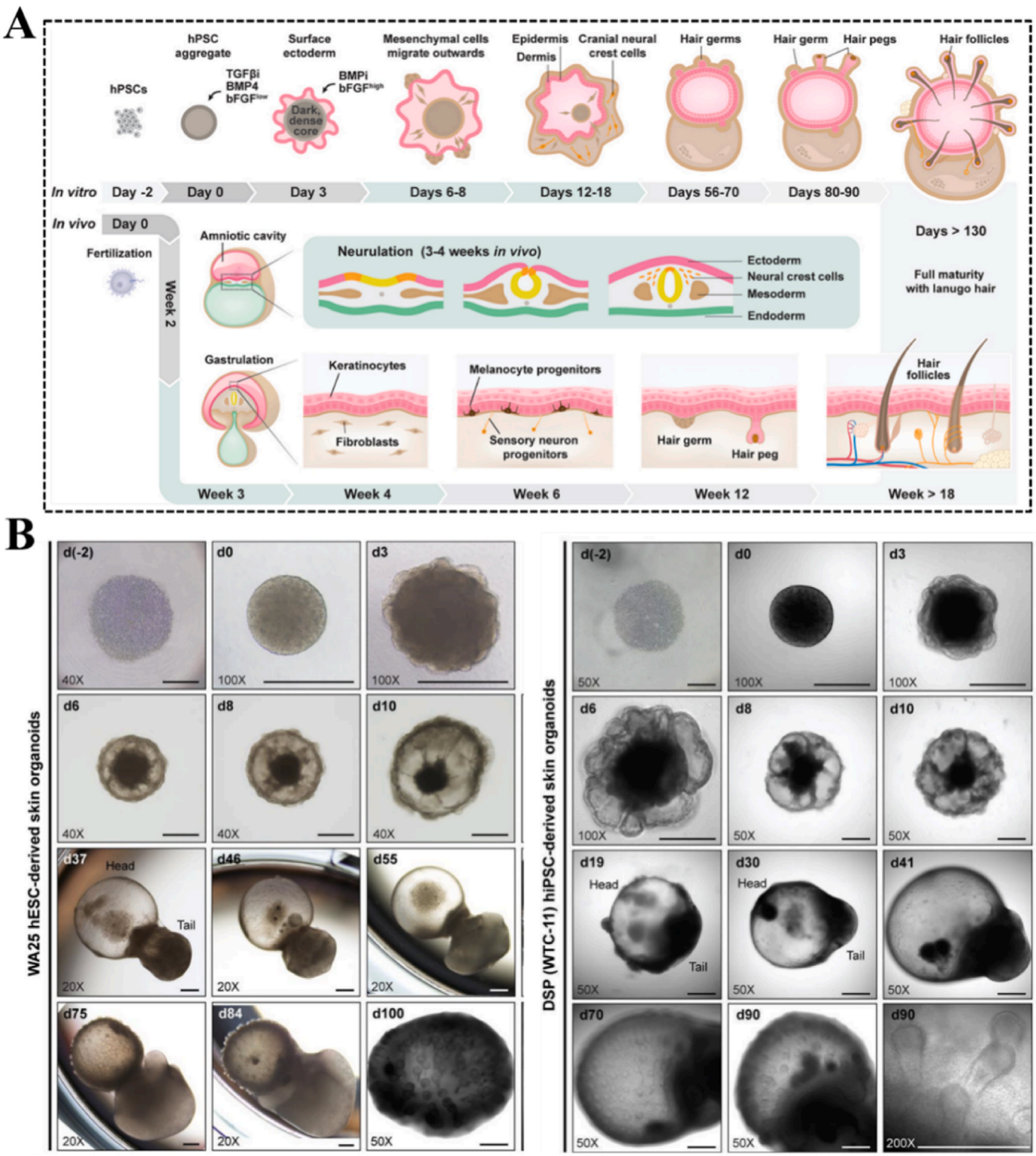

Fig. 7. Methods for skin organoid preparation and culturing (A) The figure discloses a method and application for preparing an organoid. Specifically, the method comprises culturing at least one organoid derived from a patient during a period from day 3 to day 8 to form clusters of organoids comprising a plurality of organoids. These organoid clusters are then further cultured during a period from day 9 to day 13 to form organoids having a diameter greater than 1 mm. The Figure is reproduced with minor adaptations from Ref. [209] with permission, Copyright ©2023 Nat Protoc. Published by Nature Publishing Group. **(B)** The present figure provides a method of preparing a class organ, characterised in that it comprises: culturing at least one class organ derived from a patient in a skin class organ medium of W25, W35 and/or W45 (W25, day 25; W35, day 35; W45, day 45); and culturing said class organ in a mixture of an inducer of differentiation (IDC), said IDC being selected from W20, W30, W40, W50, W60 and W70 of skin organoid medium (W20, day 20; W30, day 30; W40, day 40; W50, day 50; W60, day 60; W70, day 70). The Figure is reproduced with minor adaptations from Ref. [209] with permission, Copyright ©2023 Nat Protoc. Published by Springer Nature.

Table 2
Advantages and weaknesses in various skin cell models.

	2D skin cell model	3D skin cell model	3D skin organoid
Advantage	Simple and easy to use method; short experimental period [189]; high reproducibility; lower cost; easier to control growth conditions	Multiple cell co-culture [190]; mimics *in vivo* intercellular information exchange [191]; three-dimensional growth; high stability; high drug sensitivity [192]	Self-organizing differentiation *in vitro* [193]; observation of cellular responses and cellular homeostasis; intercellular signaling; proximity to *in vivo* physiological conditions [194]; greater stress capacity; visual simulation of drug effects [195]
Weakness	Single culture type; heterogeneous physiological environment [190]; complex cellular environment [196]; large differences from *in vivo* physiology, not yet representative [191]	Cultivation conditions are strict and cumbersome [197]; high requirements for manipulation techniques; there remains a significant disparity between the interlayer interactions and the actual physiological state [198]	No harmonized testing standards yet [197] varying experimental growth cycles [194]; poor consistency of finished products [199] with variations between batches of matrix gel [193]

screening, which can be used to investigate the antiviral efficacy, safety, and mechanism of action of drugs, and to optimize treatment regimens.

5.5. Retinal organoid

Several retinal diseases in humans, such as retinitis pigmentosa and age-associated macular degeneration result in irreversible degeneration and destruction of the retina [210–212]. The retina has a high degree of regenerative capacity; therefore, it can regenerate. Amphibians and lower evolved vertebrates (e.g., zebrafish) have a high capacity for retinal regeneration. In contrast, bird retinas have very limited regenerative capacity, and mammalian retinas, once damaged, are virtually incapable of regeneration [213]. Despite extensive insights gained from studies in mice and other model organisms, the human retina exhibits distinct structural and cellular differences compared to these models (Fig. 8A). Human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) can effectively recapitulate human retinal development *in vitro*, offering personalized treatment potential based on individual genetic profiles. These cells are valuable for drug screening, gene therapy, and cell transplantation applications [148].

Human retinal organoids (ROs) have been utilized for investigating retinal development and diseases [214]. A pivotal study in 2006, conducted by Tagahashi and Yamanaka, demonstrated the reprogramming of mouse somatic cells into a pluripotent state through the introduction of a defined set of four transcription factors. Later that year, Lamba et al. directed pluripotent ESCs towards a retinal fate by supplementing them with factors such as Noggin, DKK1, and IGF-1. Beyond their application in studying retinal development, these light-sensitive precursor cells show promise for medical applications, particularly in retinal cell transplantation [215]. Until now, over 20 patient-derived retinal organoid (RO) disease models have been established, offering numerous advantages and accelerating the progress of personalized medical treatments.

In the culture of retinal organoids, common ECM scaffolds include natural materials and synthetic polymers. Natural materials such as amniotic membrane, acellular cornea, fibroin and collagen are widely used due to their good biocompatibility and bioactivity. Synthetic polymers such as polylactic acid (PLA), polylactic acid-glycolic acid (PLGA), and polycaprolactone (PCL) have attracted attention due to their adjustable mechanical properties and degradation rates. ECM scaffolds not only provide a tridimensional environment for cells to grow, but also simulate the physical and chemical properties of extracellular matrix *in vivo*, thereby promoting cell adhesion, proliferation, differentiation and migration. These stents play an important role in mimicking the complexity and functionality of natural ECMs, providing an important support structure for the culture and transplantation of retinal organoids [149].

Despite the considerable potential of ROs, their application in drug development and therapy is hindered by several key challenges. First, the growth process is labor- and time-intensive, making large-scale production of ROs both expensive and resource-demanding. Secondly, during prolonged culture of organ tissues, the inner cellular layer, notably the ganglion cell layer, often undergoes degradation. This deterioration may stem from inadequate nutrition and insufficient connections to the optic nerve center. Thirdly, ROs are devoid of extraretinal structures vital for the *in vitro* functionality and viability of the neural retina, including retinal ganglion cells (RGCs), which progressively diminish over extended culture durations. This decline could be due to the absence of a vascular reentrant system during RO development, resulting in intracellular hypoxia and nutrient insufficiency (Fig. 8B). Finally, a significant challenge lies in the heterogeneity among cellular sources and the derived organ tissues. Due to the variability of ROs, establishing stable models for disease studies and developing consistent criteria for drug efficacy assessment in high-throughput screening is difficult [150]. Therefore, further research on ROs is essential to address these challenges.

5.6. Liver organoid

The liver, a crucial organ positioned in the upper right abdominal region of vertebrates, serves essential roles in various biological processes, including metabolism and detoxification, and possesses remarkable regenerative abilities. Hepatocytes, derived from endothelial precursors, are the primary functional cells in the liver. Liver organoid models, which are three-dimensional structures mimicking liver tissue, are cultured *in vitro* and composed of hepatocytes and other associated cell types. These organoids recapitulate the fundamental structure and function of the liver, rendering them invaluable for liver-focused research and applications. Typically, liver organoids are generated using hematopoietic stem cells, such as induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs), or primary hepatocytes. Under defined culture conditions, these cells can spontaneously organize to form liver-mimicking structures, encompassing hepatocytes, cholangiocytes, and endothelial cells of the vascular system. (Fig. 9A). In the culture of liver organoids, ECM (Extracellular matrix) scaffolds include natural materials and synthetic polymers. In particular, the advantages of nanofiber scaffolds in simulating the natural characteristics of ECM are mentioned. These nanofiber scaffolds can be used alone or in combination with growth factors and seed cells to restore liver function in animals with liver damage. In addition, studies have been conducted to combine human acellular extracellular matrix (dECM) with electrospun polycaprolactone (PCL) fibers for the construction of liver microenvironments. The hybrid scaffold utilizes human liver dECM, which contains human-specific proteins that can be used as a scaffold material to work synergically with biological and topographical cues in electrospun materials. The morphology, mechanical properties, hydrophilicity, and stability of these scaffolds were analyzed and validated using HepG2 and primary mouse liver cells, showing that these modified scaffolds can maintain cell growth and affect cell attachment, proliferation, and liver-related gene expression. These stents play an important role in mimicking the complexity and functionality of natural ECMs, providing an important support structure for the culture and transplantation of liver organoids [218,219].

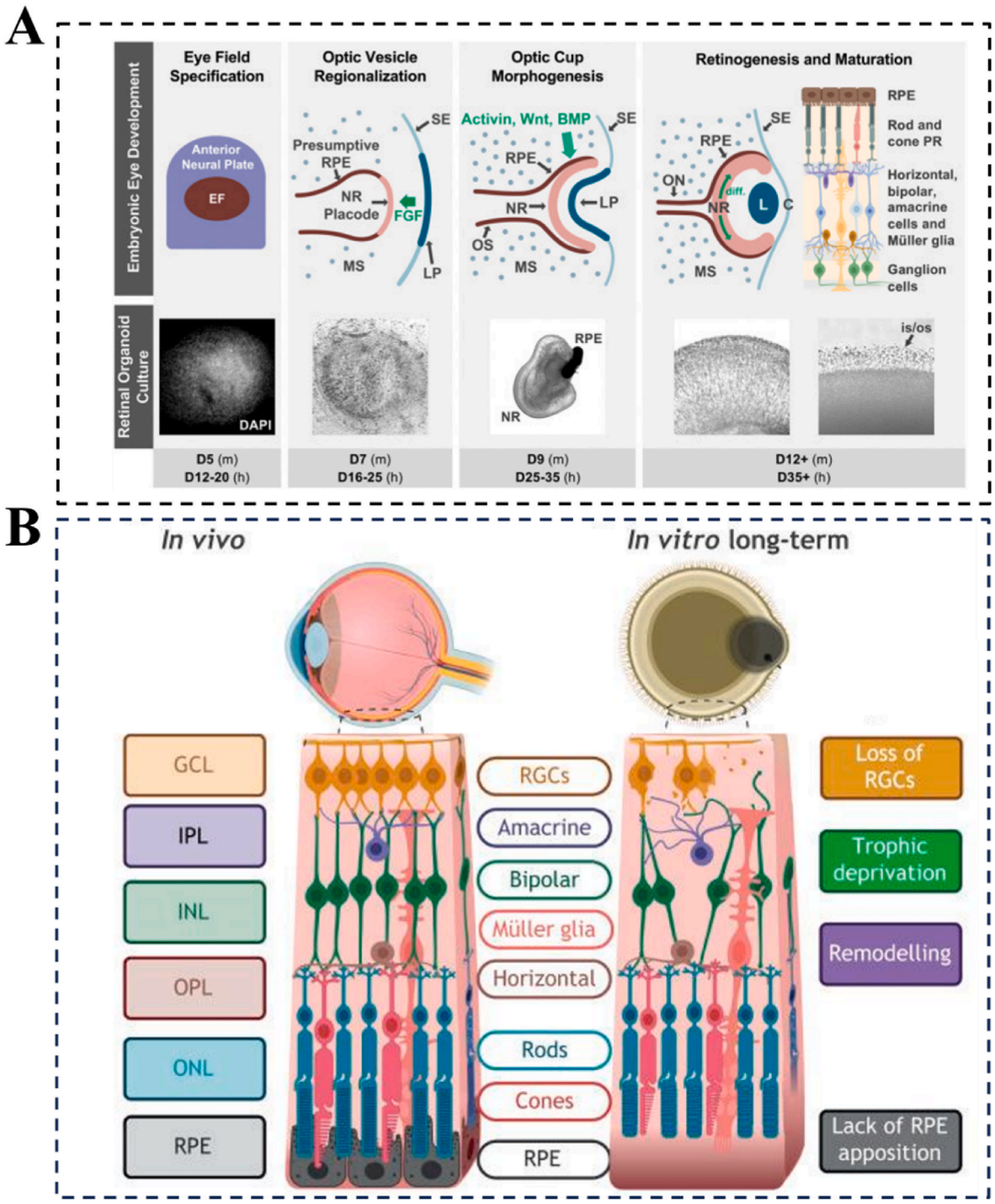

Fig. 8. Retinal Organoid Culture and Layer Simulation (A) This figure provides a retinal organoid culture mould inserted for retinal development *in vivo*. The upper row shows some features of retinal development and some key signal transduction interactions. Photographs capturing both fluorescence (API) and field intensity in the same row illustrate the morphology of retinal organoid tissue at each respective developmental stage. The final column presents the timing of each developmental phase in both mouse (m) and human (h) retinal organoid cultures. This figure is reproduced with minor modifications from Ref. [216]. Copyright © 2021 Front Cell Neurosci. **(B)** Simulation of retinal layers *in vitro*. This figure is reproduced with minor modifications from Ref. [217] with permission, Copyright ©20 Development. published by The Biologist, Inc.

In 2001, Michalopoulos and colleagues isolated hepatocytes from mice and developed a three-dimensional culture system derived from liver tissue. A decade later, in 2011, Sekiya and Suzuki reprogrammed mouse embryonic fibroblasts into hepatocyte-like cells using the factors Hnf4α and a member of the Foxa family (Foxa1, Foxa2, or Foxa3). Subsequent research continued to employ Hnf4α and Foxa3 for generating hepatocyte-like cells. Huang and team demonstrated the direct conversion of fibroblasts into functional hepatocyte-like cells through the overexpression of Gata4, Hnf1α, and Foxa3. In 2013, Huch and colleagues created liver-mimicking organoid tissues and reported the emergence of $Lgr5^{+}$ cells in mice post-liver injury. They discovered that, when treated with the Wnt agonist RSPO1 *in vitro*, even individual cells could differentiate into hepatocytes and assemble into functional hepatocyte-like organoid tissues. To delve deeper into organogenesis,

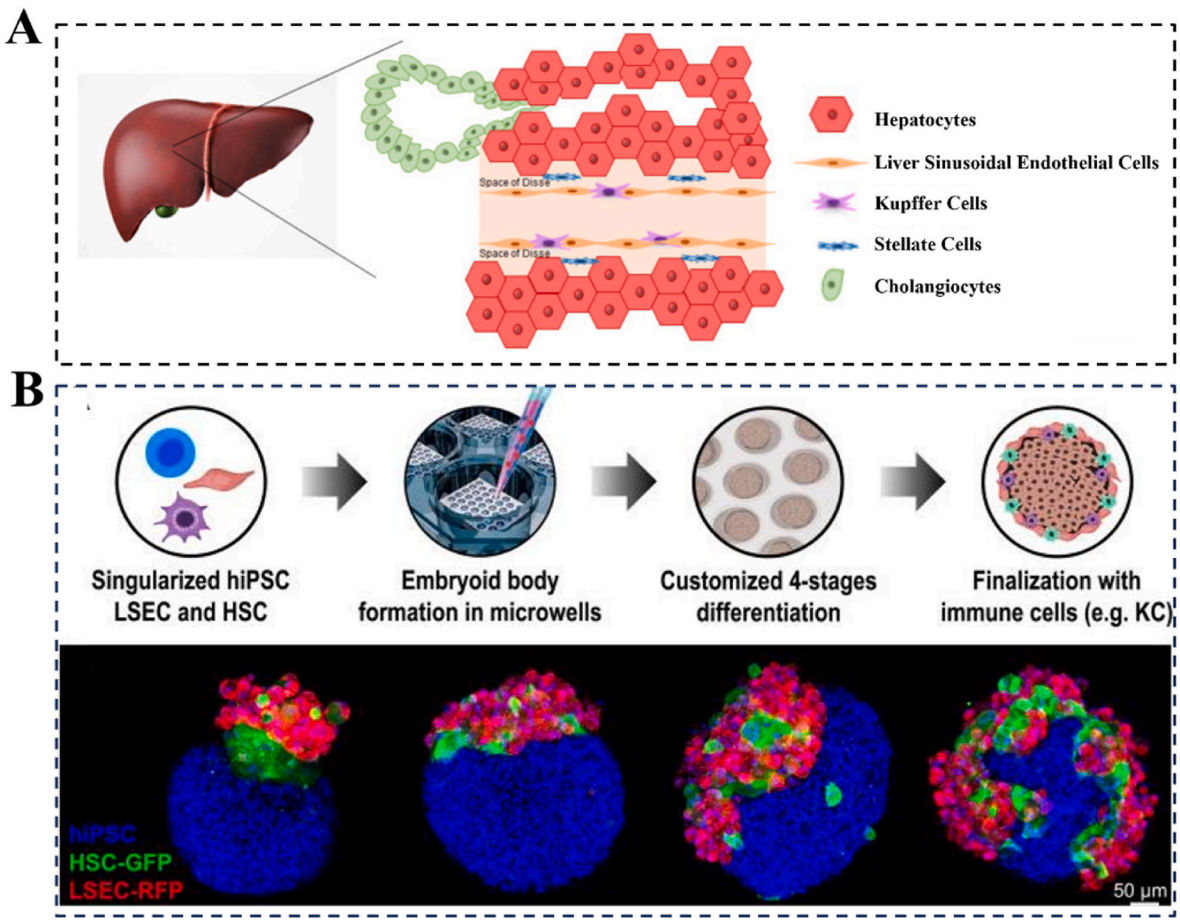

Fig. 9. Liver Anatomy and Hybrid Live Organoid Model (A) Diagram of the anatomy of the liver. Localised hepatic endothelial cells (LSEC) surrounding the hepatic Sinusoid. The Disse space, which harbors stellate cells, separates hepatocytes from the inner cortical layer. The hepatic macrophages, known as Kupffer cells, maintain close proximity to liver sinusoidal endothelial cells (LSECs), facing the bloodstream. Miliary cells coat the internal spaces within the biliary tree. The Figure is reproduced with minor adaptations from Ref. [9] with permission, Copyright ©2020 Int J Mol Sci. Published by MDPI. **(B)** Scheme of the different steps involved in obtaining a hybrid multicellular liver organoid model using our agarose micromoulding technique. Image of immunofluorescence of the progression of differentiated multicellular liver organoids. Differentiated human induced pluripotent stem cells (hiPSC) labelled with nuclear staining DAPI; human stellate cells (HSC) labelled with GFP; and hepatic sinusoidal endothelial cells (LSEC) labelled with RFP. scale bar 50 μm [220]. with permission, Copyright ©2021 Nature Communications. Published by Nature.

they induced primary human cholangiocytes to form three-dimensional liver-like structures, emphasizing the roles of cyclic adenosine monophosphate and TGF-β inhibitors in sustained culture conditions.

To generalize the regenerative processes in the liver following acute injury, Hu and colleagues generated liver buds within the posterior foregut during the initial stages of organogenesis. Takebe and team co-cultured endodermal cells derived from hepatocellular carcinoma with human induced pluripotent stem cells-derived hepatocytes (hiPSC-HEs), human umbilical vein endothelial cells (HUVECs), and mesenchymal stem cells, mimicking liver bud formation and restoring hepatic function in mice post-transplantation. This approach successfully differentiated hiPSCs into liver buds, addressing the limitation of cell availability (Fig. 9B). Hu and colleagues further developed a method to generate mouse and human hepatocyte-like organoid tissues capable of sustaining long-term proliferative responses to injury. Similarly, Peng and team expanded mouse hepatocyte-like organoids, focusing on the inflammatory cytokine tumor necrosis factor-α (TNF-α), which is induced by injury and promotes hepatocyte proliferation. While bile secreted by these organoid tissues is collected by bile ducts, replicating these anatomical structures has posed significant challenges [5].

For drug screening, Broutier et al. verified the screening outcomes through organoid formation efficiency experiments employing a Primary liver cancer (PLC)-derived organoid culture model. The sensitivity of specific agents (such as taselisib, gemcitabine, AZD8931, SCH772984, and dasatinib) to different organ classes was affirmed. We further examined the *in vivo* efficacy of SCH772984 in the NSG mouse model and discovered that the drug significantly suppressed the growth of CC-1 organoid xenografts and decreased the tumor volume. By using Western blot analysis and histological analysis, the authors confirmed that SCH772984 inhibited ERK phosphorylation and induced tumor cell apoptosis both *in vitro* and *in vivo*. It is demonstrated that this model can be utilized to predict patient-specific drug responses, providing a new resource for the development of personalized medicine approaches [176].

5.7. Kidney Organoid

The human body's renal glomerulus stands out as a highly intricate and functionally pivotal component. It comprises approximately one million functional units known as glomeruli, which are essential for filtering blood. Each glomerulus is made up of various specialized cell types connected to a complex network of convoluted tubules that empty into the collecting ducts [221]. The number of glomeruli, which is established during kidney formation at birth, can fluctuate according to age and health conditions. Renal diseases are associated with irreversible glomerular loss [5]. Hence, the development of novel therapeutic

strategies, in conjunction with pharmacological treatments, is urgently required [222] (Fig. 10A).

Scientists have been investigating renal organ tissues since the 1990s, making significant progress in moving from two-dimensional to three-dimensional structures. For instance, Ding and colleagues achieved the successful creation of three-dimensional renal organ tissues both *in vitro* and *in vivo*, utilizing fragments derived from human kidneys. Cells were isolated from donor kidneys and plated onto suspension droplet cultures. These cellular clusters were then nurtured in a kidney-specific medium enriched with solubilized human kidney extracellular matrix (K-ECM). The resultant multicellular 3D tissues encompassed diverse kidney cell types, indicating the potential application of this model in drug screening and disease modeling endeavors.

During the COVID-19 pandemic in 2020, Mondeil and colleagues evaluated the effectiveness of human recombinant soluble angiotensin-converting enzyme 2 (hrsACE2) in combating SARS-CoV-2 infection in renal tissues. They differentiated human embryonic stem cells (hESCs) into three-dimensional renal organoids [223]. containing proximal tubules (LTL/SCL3A1/SCL27A2/SCL5A12) and podocytes which featured proximal tubules (marked by LTL/SCL3A1/SCL27A2/SCL5A12) and podocytes (marked by PODXL/NPHS1/NPHS2), both expressing ACE2, the primary receptor for SARS-CoV-2. The expression profile of hrsACE2 in these renal tissues closely mirrored that of normal renal tissues [224]. Notably, SARS-CoV-2 was capable of replicating and directly infecting these kidney organ tissues. The research team demonstrated that hrsACE2 significantly impeded the initial attachment of SARS-CoV-2 to cells during early stages of infection. Therefore, kidney organ tissues serve as a crucial model for studying SARS-CoV-2 infection [101,225] (Fig. 10B).

The integration of microfluidic devices and micromachining with renal organoids represents a key technological advancement in the development of renal organoid systems. For instance, Homan et al. [101] demonstrated that culturing organoids in microfluidic devices resulted in larger renal organoids compared to those cultured under

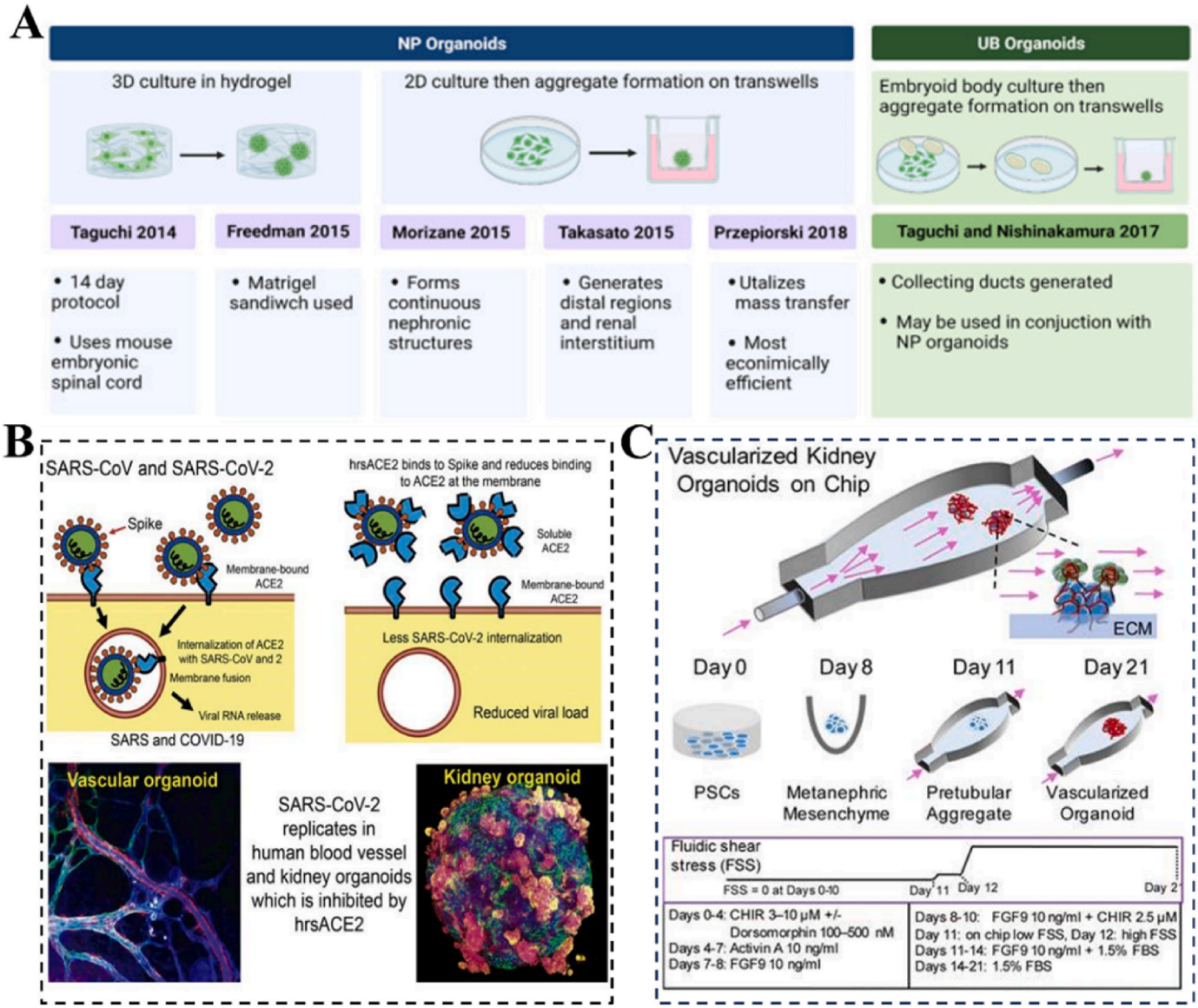

Fig. 10. Organoid Formation and Viral Infection Mitigation (A) The organism formation protocol depicted in this figure, which has undergone slight modifications, is adapted from Ref. [238], copyright Micromachines (Basel), published by MDPI (Multidisciplinary Digital Publishing Institute). **(B)** A clinical-grade version of recombinant human ACE2 has been shown to diminish SARS-CoV-2 infection in cellular and various human organoid models. This figure is reproduced with minor modifications from Ref. [224], Copyright ©20 Cell. published by Cell Press. **(C)** Developing kidne organs cultured *in vitro* at high fluid flow rates exhibit enhanced angiogenesis during nephrogenesis. Developing renal organoid tissues were placed on engineered extracellular matrix (ECM) in a perfusable millifluidic chip with controlled fluidic shear stress (FSS) applied. This figure is reproduced with minor changes from Ref. [239], Copyright © 2018 Cell. by Cell Press.

static conditions [226]. Additionally, microarrays replicating renal tubular uptake *in vitro* have been developed [227]. Combining these technological advances with the generation of organoids enriched with podocytes could lead to large-scale physiological kidney models for drug screening [228,229] (Fig. 10C).

The kidneys play an essential role in eliminating numerous drugs and metabolites through urine, filtering waste products, and maintaining the proper fluid and electrolyte balance. Emerging technologies that combine engineered three-dimensional (3D) *in vitro* cell culture models, such as organoids and microphysiological system (MPS) culture platforms, have been developed to replicate the function of nephronium, thereby enhancing the efficacy, safety, and toxicity assessment for new drugs and environmental exposures [230]. Microphysiological systems (MPS) that incorporate kidney tubular epithelial cells are instrumental in assessing the distribution and toxicity of pharmaceuticals and environmental toxins. These systems have been deployed to evaluate kidney-specific injury biomarkers and to study transport and metabolic functions within the kidney [231,232]. MPS have also been utilized to assess the efficacy of experimental therapeutics. In 2018, Weber et al. detailed the application of a human kidney MPS for the safety evaluation of new chemical entities, defining toxicological pathways. They observed increases in biomarkers such as kidney injury molecule-1 (KIM-1), urinary protein, and miRNA following exposure to polymyxin B using a PTEC MPS [233]. Chapron et al. utilized this PTEC MPS to clarify the role of renal megalin in vitamin D homeostasis [234].

Advancements in bioengineering have enabled the development of MPS that support the co-culture of various cell types, moving beyond single-cell cultures. Lin et al. described a 3D vascularized proximal tubule MPS (VP-MPS) that illustrated active reabsorption of albumin and glucose, highlighting the interaction between tubular epithelial and vascular endothelial cells in renal disease [232]. Chapron et al. also constructed a dual-channel MPS, co-culturing human PTECs with human umbilical vein endothelial cells to emulate the vascularized kidney proximal tubule, including renal vessel and tubule structures. A characteristic of many dual-channel VP-MPS is the presence of an "interstitial" matrix, which allows for solute movement between the vascular endothelial and tubular epithelial channels through extravasation and diffusion. The co-culture system established by Chapron et al. showed expression of endothelial CD-31 and tight junction protein ZO-1, indicating the formation of intact cellular barriers, as well as Na^+/K^+ ATPase and organic anion transporter (OAT) 1, localized to the basolateral cell aspect. This study also verified active tubular secretion of the anionic drug substrate, p-aminohippuric acid [235].

Beyond predicting clinical dosing parameters, kidney MPS can investigate nephrotoxicity pathways. Imaoka et al. employed a PTEC MPS to explore the mechanisms of Ochratoxin A (OTA)-induced kidney injury. In their study, PTEC MPS were exposed to clinically relevant concentrations of OTA. A notable reduction in OTA-induced toxicity was observed with the administration of ABT (1-aminobenzotriazole), a broad inhibitor of P450; conversely, OTA-induced toxicity was aggravated by NBDHEX (6-(7-Nitro-2,1,3-benzoxadiazol-4-ylthio) hexanol), an inhibitor of glutathione S-transferase enzymes. These findings confirm the PTEC MPS system's capacity to detoxify or bioactivate OTA. Furthermore, VP-MPS confirmed that basolateral OTA uptake was primarily mediated by OAT 1/3 transporters [236]. Yin et al. developed a PDMS-based platform interlayering PTECs and peritubular capillary endothelial cells, capable of generating concentration gradients and monitoring membrane permeability, offering potential as a model for evaluating drug nephrotoxicity [237].

The creation of renal organoids marks significant progress in the *in vitro* modeling of kidney diseases. Renal organoids enable individualized studies and drug screening for inherited kidney diseases using human-derived platforms. These models offer new opportunities to identify pathways in disease pathogenesis and to develop drugs for future precision medicine strategies.

5.8. Bone organoid

Highly mineralized bones serve as crucial scaffolds that offer mechanical stability to soft organs and tissues, thereby playing an indispensable role in sustaining vital mineral homeostasis. The global aging demographic and escalating obesity levels have significantly influenced orthopedic conditions like osteoporosis (OP) and osteoarthritis (OA), profoundly affecting the mobility of millions across the globe. The prevalence of bone and joint disorders escalates notably with advancing age [240]. Thus, imposing a substantial economic burden. Despite decades of research, much remains unknown about these diseases.

Bone and cartilage organoid tissues are self-organizing and self-renewing microtissues that replicate bone and cartilage structure and function under both normal and disease conditions. The bone, a vital living organ, provides structural support to the body while maintaining immune cells, hematopoietic cells, and regulating calcium and phosphorus metabolism. Mesenchymal stem cells and induced pluripotent stem cells (iPSCs) are the most frequently utilized cell sources for generating bone or cartilage organoid tissues (Fig. 11A). Various methodologies and protocols exist for differentiating these cells into chondrocytes, adipocytes, and osteoblasts. It is anticipated that endothelial cells, osteoblasts, and other immune components can be specialized from these iPSCs.

Modeling organoid diseases is essential for basic research. Biocompatible hydrogels, known for their high-water content, have been widely used to develop organoid disease models. For example, Dr. Mouney, a prominent scholar in biomaterials from the Harvard Corporation, presented an enhanced hydrogel characterized by a rapid relaxation rate, which resulted in improvements in its initial elastic modulus, degradation profile, and cell-adhesive ligand concentration [241] (Fig. 11B). The 3D culture system reduces the gap between cells and physiological tissues in the culture dish and improves drug screening and toxicity prediction. The application of various biocompatible materials, such as hydrogels, has accelerated research in this area. For instance, HA hydrogels are used for chondrocyte induction and culture [242]. Hydrogels supplemented with hydroxyapatite can effectively mimic the TME [243], and hydroxyapatite scaffolds embedded in GelMA hydrogels have been applied in cartilage-bone-vessel tri-phase culture systems [244].

In vitro construction of human bone-like organ tissues allows for precise replication of pathological environments, aiding in the understanding of disease mechanisms. Imbalances in bone remodeling can lead to diseases such as OP, osteochondrosis, arthritis, and tumors. OP, characterized by bone resorption exceeding bone formation, leads to decreased bone density. Traditionally, OP models are created using animals, which is time-consuming and costly. Constructing bone organ tissues that resemble osteoporotic (OP) bone could significantly reduce study time and costs [226]. For example, the addition of equal proportions of RANKL and MCSF could mimic the microenvironment of OP and enhance osteoclast activity. These tissues exhibit lower mineral deposition (as demonstrated by micro-computed tomography analysis) and higher anti-tartrate phosphatase (TRAP) activity (as shown by TRAP staining analysis) compared to healthy bone. This methodology introduces an innovative approach to modeling osteoporosis (OP). Osteomyelitis, a sophisticated inflammatory bone condition resulting from microbial infections, causes bone infection and subsequent destruction [245]. Commonly employed animal models for studying osteomyelitis involve either intravenous administration or direct inoculation of Staphylococcus aureus into the bone marrow space, or the utilization of implants impregnated with S. aureus. Nevertheless, these techniques frequently fall short in accurately mimicking clinical scenarios and may cause premature demise of the animals due to excessive bacterial proliferation [246]. By simulating the osteomyelitis microenvironment, osteomyelitis-like organ tissues can be constructed to mimic clinical causative factors while avoiding model death. This provides a novel approach to developing osteomyelitis models that are closer to clinical

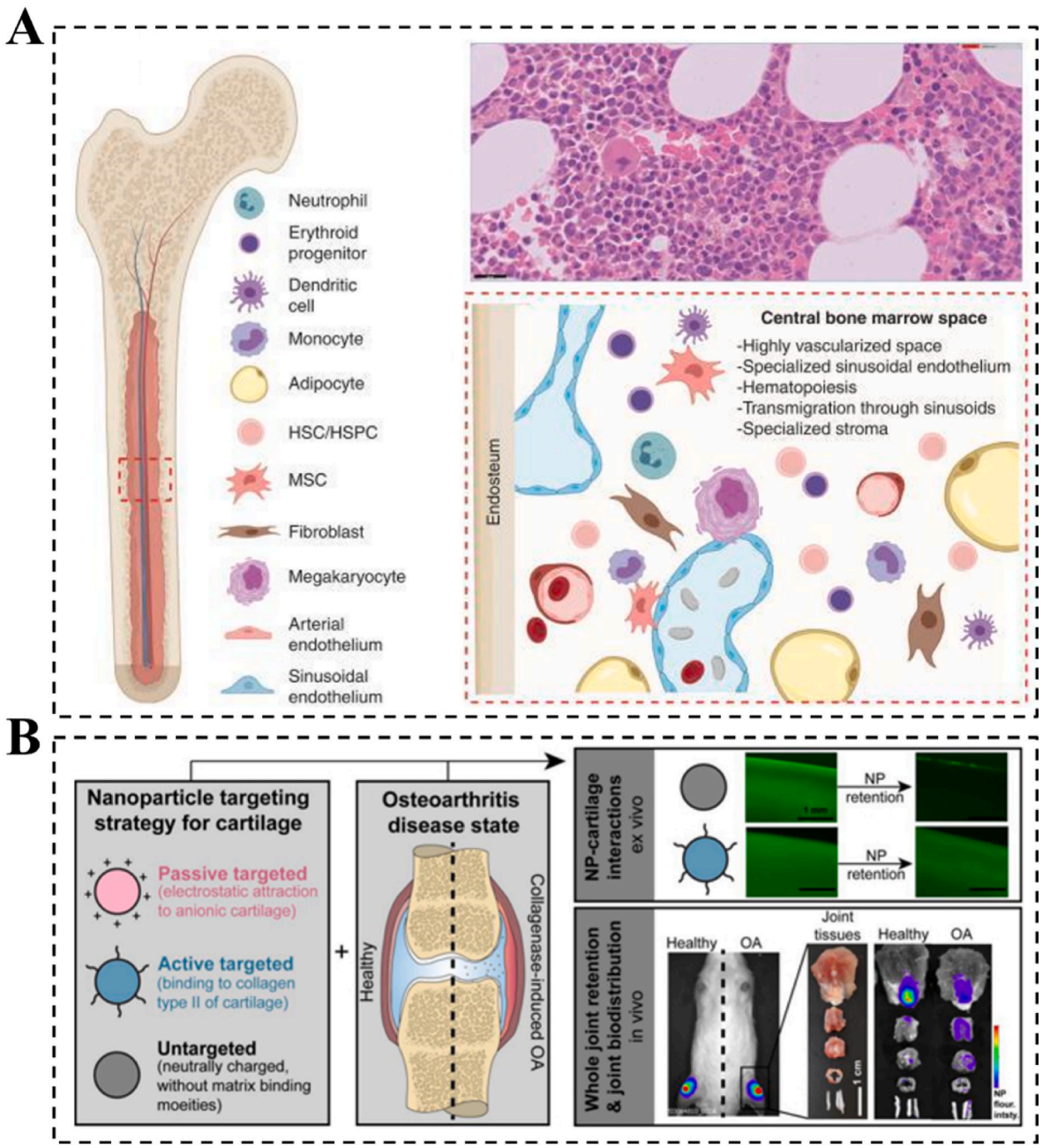

Fig. 11. MSC Isolation and Hydrogel Strategies for Cartilage Repair (A) MSCs are easily detached from bone marrow and adipose tissue, however, as part of the microvascular system, all tissues contain MSC-like cells. This figure is reproduced with minor changes from Ref. [250], Copyright © 2019 NPJ Regen Med. by Nature Publishing Group. **(B)** Hydrogel strategies for targeting articular cartilage. The biodistribution patterns of diverse targeted (either passive or active) hydrogel particles are examined in both healthy and osteoarthritic joint tissues. This figure is reproduced with minor modifications from Ref. [251], Copyright ©20 Acta Biomater. published by Elsevier BV.

practice.

Medications intended for the treatment of bone disorders, encompassing anti-resorptive agents, angiogenic therapies, bone anabolic agents, and anti-inflammatory substances, undergo rigorous *in vitro* and *in vivo* evaluations prior to gaining clinical approval [247]. However, many drugs are discontinued during phase I trials due to lengthy development times and organ toxicity. Translating the results of cell and animal experiments to clinical settings remains challenging. Constructing bone-like organ tissues that closely resemble the human skeleton can shorten drug trial cycles and more accurately predict drug toxicity [248]. The authors initially obtained cells from human bone and cartilage tissues through enzymatic digestion and subsequently suspended these cells in Matrigel to form organoids that imitate the cellular environment and extracellular matrix organization present in natural tissues. Next, they employed specific media, such as cartilage organoid medium (COM) and bone organoid medium (BBOM), to support the growth of mesenchymal stem cells (MSCS) and endothelial cells for long-term *in vitro* culture. These organoids are capable of responding to differentiation stimuli and mimicking inflammatory diseases, such as osteoarthritis, *in vitro*. Moreover, the A2AR agonist CGS21680 was able to influence certain gene expression in organoids, suggesting that it might have a regulatory effect on bone tissue development and inflammatory responses. Therefore, these organoids can be utilized not only as a platform for studying bone tissue development and disease modeling, but also for drug screening, providing novel approaches for drug development and discovery [249].

6. Limitations of biomaterial-assisted organoid technologies

Although organoid technology has achieved remarkable progress in simulating certain structures and functions of organs, there are still substantial challenges in fully replicating the intricate physiological environment and pathological processes within the human body [252]. For instance, organoids might lack complete vasculature, innervation, and immune-cell interactions that are crucial for maintaining organ functionality [253]. Additionally, organoids might gradually lose their original functional and structural characteristics during long-term cultivation, such as the degeneration of the retinal ganglion cell layer in neural retinal organoids, which could have implications for their long-term application and the reliability of research outcomes [254].

The cell sources of organoids are diverse, encompassing adult stem cells and induced pluripotent stem cells (iPSCs), leading to genetic background and functional heterogeneity of organoids [255]. This heterogeneity may influence the accuracy of disease modeling and the consistency of drug screening results. Furthermore, there are variations in organoid culture techniques and methods employed in different studies, giving rise to issues regarding the comparability and reproducibility of results and further restricting the wide application of organoid technology [256]. Despite the potential of organoids in *in vitro* models, their translation into clinical applications remains challenging. This includes ensuring the long-term stability of organoids, integrating organoid technology with existing clinical practices, and addressing ethical and legal concerns [257]. The application of organoids in drug screening and toxicity testing requires consideration of drug metabolism, distribution, excretion, and toxic effects, and these processes might differ from the *in vivo* situation in in vitro models and necessitate further studies for optimization and validation.

In conclusion, although biomaterial-assisted organoid technology holds significant potential for disease modeling and drug screening, the limitations and bottlenecks described above still need to be overcome to facilitate widespread clinical and research applications [258]. Future research should focus on enhancing organoid functionality, stability, and reproducibility, as well as developing standardized and cost-effective approaches to advance the development and application of organoid technology [259].

7. Multifaceted repair of organoids

Organisms possess a unique reparative capacity to maintain the fundamental functions and characteristics of their native tissues [260]. Biliary epithelial cells, for example, are a clinically significant system. From cholangiocytes (bile duct epithelial cells), it is possible to derive organ tissue cells suitable for regenerative medicine applications [261,262]. The biliary system, which facilitates the transportation of bile from the liver to the duodenum, constitutes a significant proportion of liver transplants, accounting for 70 % of pediatric cases and one-third of adult cases [263]. To address this, Fotios Sampaziotis and colleagues have devised an innovative cellular implantation model capable of perfusing the human liver *in vivo*. The results demonstrated its potential for treating bile-related liver conditions. The use of ambient perfusion demonstrated successful restoration of human intrahepatic ducts after undergoing a transplantation procedure resembling extrahepatic organ replacement. This finding indicates that cholangiocyte-derived organoid tissues hold potential for repairing human biliary epithelial cells [264].

The rapid development of organoid technology provides a powerful platform for studying human disease mechanisms. In bile duct surgery, the scarcity of donor tissue is considered a major limitation in repairing biliary diseases [265]. In this regard, two studies by Sampaziotis et al. demonstrated how bile ducts could be regenerated using cholangiocyte-like organ tissues by combining human and mouse tissues with an innovatively developed *in vitro* perfusion model. Initially, they showed that human cholangiocyte-like organ tissues embedded in polyglycolic acid scaffolds could promote gallbladder incision healing and replace part of the common bile duct in mice [261]. These mice survived for over a month, maintained normal liver function, and the engineered epithelial cells self-renewed and maintained an open bile duct lumen. In subsequent studies, intraductal infusion of organ tissue from gallbladder bile duct cells successfully treated induced bile duct lesions [264]. Building on these successes, Sampaziotis et al. used an isolated organ perfusion model to treat humans. In this study, Sampaziotis et al. transplanted labelled cholangiocytes were transplanted into the conduit of a liver in a room-temperature perfusion circuit transplanted from a deceased donor suffering from ischemic conduit injury [264].

The development of organ tissues offers a renewable resource for tissue replacement and repair strategies. For instance, bone-like organ tissues can be used for autologous transplantation by amplifying homologous genetic tissues. Gabriela and colleagues described the creation of tissue-like organoids engineered to self-assemble into substantial tissues for repairing severely damaged long bones in mice. These engineered tissues exhibited morphological similarities to native tibiae [266]. Furthermore, Tam and team reported that their developed cartilage-mimicking organoid tissue facilitated scaffold-independent healing of severely defective long bones [267]. Additionally, bone-related growth factors and activators sourced from bone-mimetic organ tissues hold potential as bioactive agents to promote bone regeneration. Trubiani et al. demonstrated, for instance, that culturing stem cells on cortical cancellous bone scaffolds enhanced osteogenic activity and expedited bone restoration [268]. Hence, bone growth activators produced by bone-associated cells and bone-mimetic organ tissues can serve as bioactive components in stimulating bone regeneration processes.

8. Opportunities and challenges encountered by the institute of organoid technology with summary and future prospects

Organoids offer significant potential for drug screening and toxicity assessment by mimicking the metabolic and detoxification functions of organs, enabling the evaluation of drug metabolism, toxic effects, and interactions. They also provide a platform for modeling diseases and studying mechanisms, pathological processes, and therapeutic strategies through gene editing or induced lesions. These advancements open new avenues for regenerative medicine. Organoids can act as seed cells for cell transplantation or tissue engineering products. By gene editing or transfecting organoids, researchers can study specific genes in the organ can be studied, furnishing insights into the biological processes of organs. Furthermore, organ tissues cultured from patient-derived iPSCs can be utilized in personalized medicine, predicting drug efficacy and virulence, thereby enhancing treatment precision and safety. However, it is important to recognize that organoid research is still in the developmental stage, with certain limitations and challenges, such as achieving full functional mimicry, scaling up processes, and clinical translation. With ongoing technological advancements and further research, organoids are expected to bring major breakthroughs in organ-related research and applications.

CRediT authorship contribution statement

Yunyuan Shao: Writing – original draft. **Juncheng Wang:** Writing – review & editing. **Anqi Jin:** Investigation. **Shicui Jiang:** Visualization. **Lanjie Lei:** Formal analysis, Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Liangle Liu:** Data curation, Conceptualization, Funding acquisition, Project administration, Supervision, Visualization.

Ethics approval and consent to participate

There are no human and animal subjects in this review and informed consent is not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported by the Funds of the Natural Science Foundation of Hangzhou (2024SZRYBH180001), the Medical Science and Technology Plan Project of Zhejiang Province (2022KY354) and Rui'an Science and Technology project of China (MS2022017).

Data availability

No data was used for the research described in the article.

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