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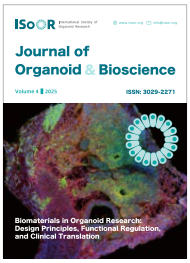

Review

Biomaterials in Organoid Research: Design Principles, Functional Regulation, and Clinical Translation

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Abstract

Organoids, as three-dimensional (3D) in vitro models derived from stem cells, have revolutionized biomedical research by recapitulating the physiological architecture and functional characteristics of native organs. However, the full potential of organoids in disease modeling, drug discovery, and regenerative medicine remains constrained by inherent challenges in reproducibility, functional maturation, and structural complexity—limitations predominantly attributed to the inadequacy of conventional culture microenvironments. Biomaterials have emerged as indispensable tools to address these bottlenecks, providing tunable platforms that deliver instructive biophysical and biochemical cues to modulate cell fate determination, enhance tissue-level functionality, and improve experimental reproducibility. This comprehensive review systematically elucidates the pivotal role of biomaterials in advancing organoid research, with a focus on their design rationale, mechanisms of functional regulation, and translational pathways toward clinical application. We delve into the diverse repertoire of natural and synthetic biomaterials, advanced biofabrication strategies (e.g., 3D bioprinting and microfluidics), and how engineered matrices precisely tailor mechanical stiffness, biochemical composition, and electrical microenvironments to guide organoid development and functional maturation. Furthermore, we highlight the broad spectrum of clinical applications, ranging from modeling complex pathologies such as cancer and neurological disorders to enabling high-throughput drug screening and advancing regenerative therapeutic strategies. Finally, we discuss current challenges, including standardization of culture protocols, vascularization of organoids, and immune integration, and outline future perspectives for biomaterial-enhanced organoids to realize their transformative potential in precision medicine and beyond.

Keywords

Organoids, Biomaterials, Extracellular Matrix, 3D Bioprinting, Microfluidics, Functional Regulation, Disease Modeling, Drug Screening, Regenerative Medicine, Clinical Translation.

Introduction

The advent of organoid technology has maked a significant shift in biomedical research, offering unprecedented opportunities to study embryo development, simulate complex diseases, and expedite drug discovery within a physiologically relevant three-dimensional (3D) context[1,2]. Organoids are self-organizing, miniaturized organotypic constructs derived from pluripotent stem cells (PSCs) or adult stem cells (ASCs), endowed with the capacity to recapitulate the intricate cellular heterogeneity, tissue architecture, and functional phenotypes of their in vivo counterparts[3,4]. Distinct from conventional two-dimensional (2D) cell culture, organoids recapitulate tissue complexity with superior fidelity, enabling in-depth interrogation of intercellular crosstalk, developmental trajectories, and pathophysiology[5,6]. Nevertheless, inherent limitations—including batch-to-batch variability, constrained scalability, and incomplete functional maturation—persist in organoids cultured in traditional undefined matrices (e.g., Matrigel), posing substantial barriers to their widespread adoption and clinical translation[1,7].

Biomaterials stand at the forefront of addressing these bottlenecks, functioning as critical scaffolds and instructive microenvironments that guide organoid morphogenesis, augment functional maturation, and enhance experimental reproducibility[3,8]. By mimicking the native extracellular matrix (ECM), biomaterials confer essential structural support, biochemical cues, and mechanical signals—all of which are pivotal for cell survival, proliferation, lineage commitment, and self-organization into complex tissue architecture[8,9]. The precise engineering of biomaterial properties, encompassing stiffness, porosity, biodegradability, and the presentation of specific growth factors or adhesion ligands, empowers researchers to construct highly controlled and tunable niches that direct organoid development in a manner closely recapitulating in vivo physiological conditions[3,10]. This rational engineering strategy is indispensable for overcoming the drawbacks of traditional undefined matrices and advancing organoid technology toward robust, standardized platforms for diverse biomedical applications[1,2].

This review aims to provide a comprehensive overview of the pivotal role of biomaterials in organoid research, which comes down to three aspects: design principles, functional regulation, and clinical translation. On top of the agenda, the fundamental design considerations for biomaterials are explored, including the selection of natural and synthetic polymers, and the implementation of advanced biofabrication techniques (e.g., 3D bioprinting and microfluidics) to fabricate sophisticated organoid microenvironments. Subsequently, the mechanisms by which biomaterial properties are investigated—such as mechanical stiffness, biochemical signaling, and electrical cues—functionally regulate organoid differentiation, maturation, and structural complexity. Finally, we discuss the diverse clinical applications of biomaterial-enhanced organoids in disease modeling, drug discovery, and regenerative medicine, while addressing the prevailing challenges and future opportunities for their successful translation into clinical practice. In this review, the transformative potential of integrating biomaterials science with organoid technology is emphasized to unlock new frontiers in understanding human biology and developing next-generation therapeutics.

1. Biomaterial Design Principles for Organoid Engineering

The successful establishment of organoids hinges critically on the rational design and strategic selection of biomaterials capable of recapitulating the complex physicochemical and biological cues of the native extracellular matrix (ECM) as complete as possible[3,8]. The ECM is a dynamic, bioactive network of proteins, carbohydrates, and signaling molecules that confers structural integrity, mediates cell adhesion, and orchestrates spatiotemporal cell signaling—thereby profoundly regulating cell behavior, tissue morphogenesis, and physiological homeostasis[8]. Biomaterials, whether of natural origin or synthetic derivation, are meticulously engineered to mimic these multifaceted ECM functions, offering tunable platforms that regulate organoid morphogenesis, lineage specification, and functional maturation. The physicochemical properties of the biomaterial, alongside its fabrication strategy, are paramount in dictating the resulting organoid's architectural complexity, cellular heterogeneity, and functional fidelity to native tissue.

1.1 *Mimicking the Extracellular Matrix: Natural and Synthetic Polymers*

The foundation of biomaterial design for organoids lies in replicating the native ECM, which is a complex and dynamic network of proteins, proteoglycans, and other molecules that provides structural support and biochemical signals to cells[8]. This biomimicry is achieved through the judicious selection and engineering of various polymers, broadly categorized into natural and synthetic types, each offering distinct advantages and limitations (Fig.1).

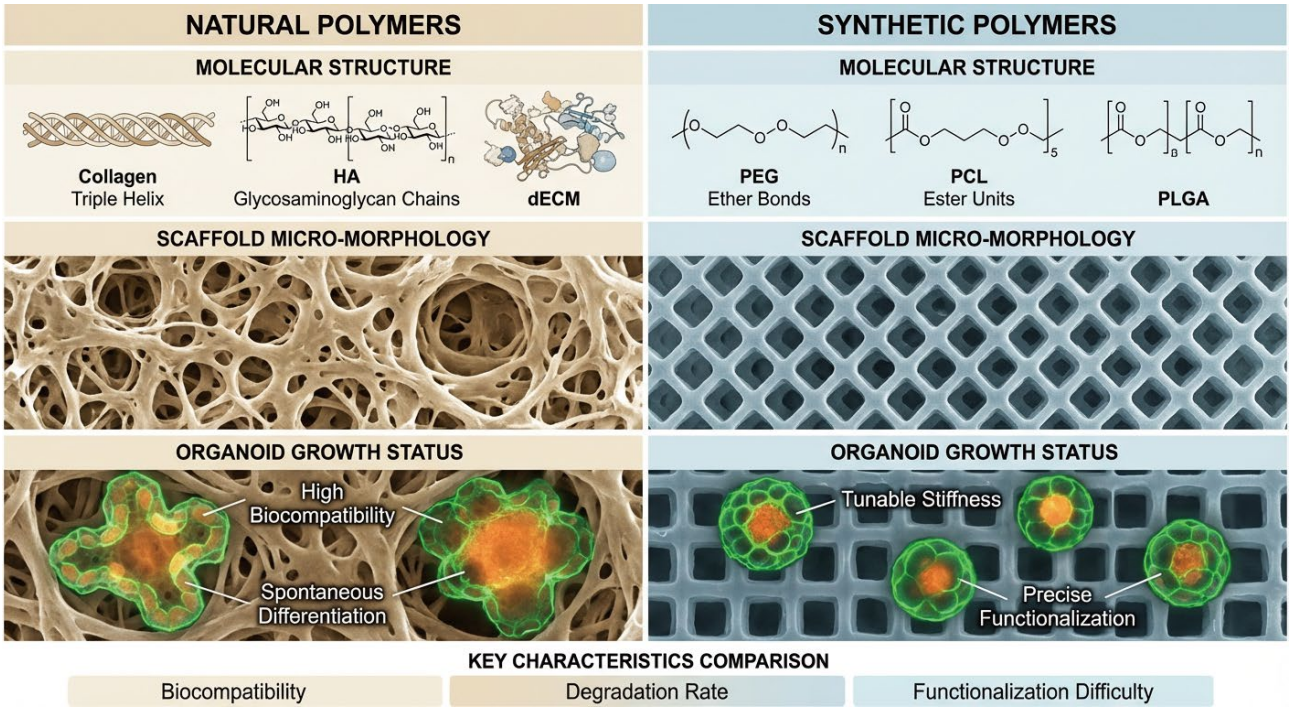


Figure 1. Comparison of natural and synthetic polymer-based organoid scaffolds.

1.1.1 Natural Polymers

Natural polymers are highly favored in organoid research due to their inherent biocompatibility, biodegradability, and the presence of native cell-binding motifs that promote cell adhesion and signaling[9,11]. These materials often derive directly from biological tissues or are components of the ECM, making them intrinsically suitable for creating biomimetic microenvironments.

Collagen and Gelatin: Collagen, the most abundant protein in the ECM, is a cornerstone biomaterial for tissue engineering and organoid culture due to its excellent biocompatibility, biodegradability, and ability to form hydrogels that support cell growth and differentiation[9,12]. It provides structural support and facilitates cell adhesion, crucial for the self-organization processes observed in organoids. Gelatin, a denatured form of collagen, retains many of collagen's beneficial properties, including biocompatibility and cell adhesion sites, while offering greater versatility in terms of processing and modification[13]. Gelatin-based biomaterials, particularly gelatin methacryloyl (GelMA) and gelatin thiolated (GelSH) hydrogels, have been successfully employed as 3D *ex vivo* drug testing for patient-derived breast cancer organoids, demonstrating their ability to support cell growth and organoid formation while allowing for tunable biophysical properties[14]. These materials can be engineered to promote hemostasis, antibacterial properties, and cell regeneration, making them valuable for various regenerative applications[13]. The use of collagen-based biomaterials (CBBs) is particularly crucial in organoid technology for reproductive medicine, where they simulate physiological activities in vivo, despite challenges in developing critical tissue models[15]. Fibrin, another natural protein, is also gaining traction, with detailed overviews highlighting its use in skin, bone, and nervous tissues, providing insights for future clinical treatments[16].

Hyaluronic Acid (HA): Hyaluronic acid is a glycosaminoglycan naturally found in the ECM, known for its high water retention capacity, viscoelasticity, and role in cell proliferation and migration[11]. Its non-sulfated nature and ability to interact with cell surface receptors make it an attractive component for hydrogels, often combined with other polymers to fine-tune mechanical properties and introduce specific biological cues.

Decellularized Extracellular Matrix (dECM): Decellularized extracellular matrix (dECM) biomaterials represent a highly biomimetic approach, as they are derived directly from native tissues via the selective removal of cellular components while retaining the intricate architectural topology and bioactive biochemical composition of the original tissues[17,18]. The preservation of native matrix biomolecules endows dECM with a rich repertoire of instructive biophysical and biochemical cues, which can markedly enhance organoid lineage specification, functional maturation, and phenotypic fidelity[17]. In regenerative medicine, dECM biomaterials have demonstrated substantial potential by facilitating in situ tissue repair through paracrine and chemotactic effects, paving the way for growth factor-free and cell-free tissue engineering paradigms[18]. They are particularly invaluable for organoid and engineered organ culture, owing to their capacity to preserve essential biomolecules and bioactive epitopes—thereby establishing a physiologically relevant niche that supports cell proliferation, angiogenesis, and modulation of immune responses[11,17].

Chitosan and Silk Fibroin: Chitosan, a chitin-derived biopolymer, is recognized for its biocompatibility, low toxicity, and antimicrobial activity, making it suitable for tissue regeneration and drug delivery applications[19]. It can be formulated into various forms like nanoparticles, scaffolds, and hydrogels to stimulate regeneration in diverse tissues. Silk

fibroin (SF)-based hydrogels, with their ECM-like structure and biocompatibility, are ideal for constructing cartilage organoids, particularly for osteoarthritis treatment, and can be iteratively optimized through AI calculations[20].

1.1.2 Synthetic Polymers

Synthetic polymers confer unparalleled spatiotemporal control over their intrinsic physicochemical properties, encompassing mechanical stiffness, degradation kinetics, and porous architecture—all of which can be precisely tailored to match the tissue-specific requirements of target organoids[1,11]. In contrast to natural polymers (e.g., collagen, Matrigel) and decellularized extracellular matrix (dECM), synthetic materials typically lack inherent bioactive recognition motifs (e.g., RGD peptides, LN511E8)—a characteristic that may initially appear as the limitation[1]. However, this inherent "bioinertness" allows for site-specific and dose-controlled functionalization with exogenous bioactive molecules, such as cell-adhesive peptides, growth factors, or signaling ligands, to orchestrate cell behavior (e.g., proliferation, lineage commitment, intercellular crosstalk) in a highly tunable and reproducible manner.

Poly(ε-caprolactone) (PCL), Poly(lactic acid) (PLA), Poly(glycolic acid) (PGA), and Poly(lactic-co-glycolic acid) (PLGA): These biodegradable polyesters have been extensively utilized in tissue engineering, attributed to their superior mechanical properties and tailorable degradation kinetics[11]. Notably, they can be fabricated into diverse configurations, including three-dimensional (3D) scaffolds and microfibers, which serve to provide structural support and a biomimetic microenvironment for organoid development and maturation. Importantly, the degradation byproducts of these polyesters are generally non-cytotoxic and biocompatible, thereby rendering them well-suited for long-term *in vitro* organoid culture and potential in *vivo* translational applications.

Poly(ethylene glycol) (PEG): PEG is a highly hydrophilic, biocompatible polymer extensively employed for the fabrication of hydrogels tailored to organoid culture systems. Owing to its inherent inertness, PEG enables precise and site-specific functionalization with cell-adhesive ligands (e.g., RGD) or bioactive growth factors, thereby allowing researchers to spatially and temporally define specific biochemical cues within the organoid niche[1]. Notably, PEG-based hydrogels, combined with gelatin methacryloyl (GelMA), have been demonstrated to robustly support cell proliferation, differentiation, and subsequent organoid morphogenesis in breast cancer models. This combinatorial platform offers a highly scalable 3D microenvironment, rendering it a valuable tool for high-throughput drug screening and preclinical efficacy evaluation[14].

Bioorthogonally Cross-Linked Hydrogels: A significant advancement in synthetic polymer design lies in bioorthogonally cross-linked hydrogels, which permit independent modulation of material properties (e.g., stiffness, porosity) and cell encapsulation efficiency without perturbing intrinsic biological processes[21]. For instance, hydrogels fabricated from gelatin precursors functionalized with tetrazine (Tz) or norbornene (Nb) moieties can be precisely tailored by adjusting gelatin concentration and the stoichiometric ratio of Tz/Nb reactive groups. This well-defined and highly tunable 3D platform has been demonstrated to support the proliferation kinetics, differentiation, and morphogenesis of tooth germs in vitro, thereby establishing a robust experimental system for tooth organoid engineering and developmental modeling[21]. Notably, this bioorthogonal cross-linking strategy underscores the unique capacity of synthetic materials to construct a spatiotemporally controlled 3D matrix—an essential prerequisite for recapitulating the intricate signaling cascades and morphogenetic events inherent to complex organ development.

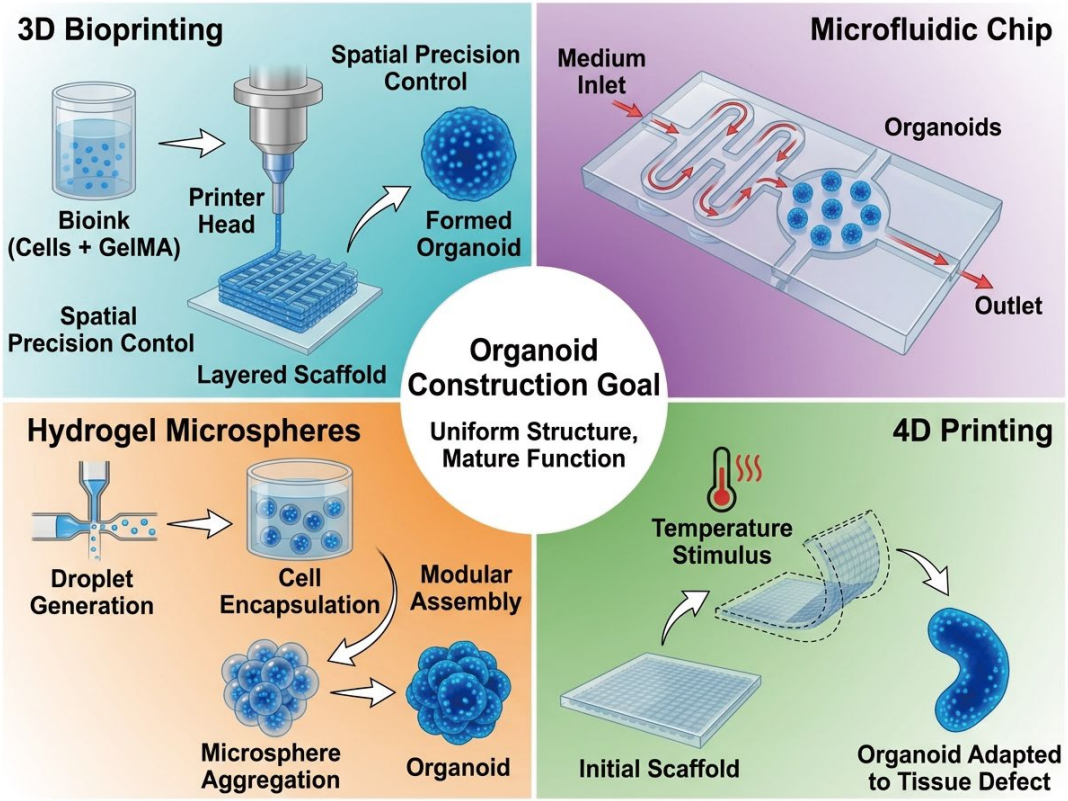


Figure 2. Integrated flowchart of advanced organoid fabrication techniques.

1.2 *Advanced Fabrication Techniques*

Beyond rational material choice, the fabrication methodologies employed to construct biomaterial scaffolds and engineer biomimetic microenvironments are pivotal for achieving the desired structural complexity, spatiotemporal control over biochemical cues, and functional integration within organoid systems. Advanced manufacturing techniques, such as hydrogel microsphere engineering, three-dimensional (3D) bioprinting, and microfluidic-based niche engineering, confer unprecedented capabilities to fabricate highly organized, physiologically relevant organoid models that recapitulate key structural and functional features of native tissues (Fig.2).

1.2.1 Engineered Hydrogel Microspheres

Hydrogel microspheres have emerged as ideal modular platforms for engineering spheroids and organoids, primarily due to their capacity to faithfully mimic the native extracellular matrix (ECM) niche in a highly controllable and scalable manner[10]. These microspherical constructs offer distinct advantages, including precise modulation of size, morphology, and internal biochemical composition—features that directly regulate cell-matrix and cell-cell interactions, as well as the subsequent architectural maturation of the resulting organoids. Notably, the rational engineering of hydrogel microspheres enables the spatiotemporal incorporation of specific functional motifs (e.g., cell-adhesive ligands, degradable linkers) and bioactive molecules (e.g., growth factors, cytokines), thereby empowering researchers to precisely guide cell proliferation, differentiation, and tissue assembly, while promoting the formation of more complex, functionally competent organoid models[10]. This versatile approach is particularly valuable for translational applications in regenerative medicine and disease modeling, where the accurate recapitulation of native tissue architecture and physiological functions is paramount for preclinical validation and therapeutic development.

1.2.2 3D Bioprinting and Bioinks

Three-dimensional (3D) bioprinting represents a transformative technology in organoid engineering, enabling the precise deposition of cells and biomaterial-based bioinks into predefined 3D architectures[22-24]. This additive manufacturing approach effectively addresses several limitations of traditional organoid culture systems, including inherent variability in size and morphology, as well as the inability to construct complex multi-cellular structures with spatiotemporal control[23,25].

3D bioprinting confers a suite of pivotal advantages that substantially advance organoid engineering, starting with its capacity to support the formulation of bioinks with high cellular densities—enabling the mimicry of the physiological cellularity inherent to native tissues[22]. Complementing this, it empowers the fabrication of intricate 3D geometries and multi-layered tissue constructs, which are indispensable for recapitulating the structural complexity and hierarchical organization of native organs[22,26]. Beyond structural control, 3D bioprinting facilitates standardized and automated organoid production workflows, a feature that significantly enhances experimental reproducibility and scalability—two foundational prerequisites for translating organoid technologies into clinical applications and enabling high-throughput drug screening platforms[22,25,27]. Additionally, its inherent ability to precisely modulate the biochemical composition and mechanical properties of bioinks allows for the creation of tunable microenvironments that actively mediate cell proliferation, differentiation, and tissue maturation processes, thereby promoting the development of functionally competent organoid models[24,28].

Underpinning the success of 3D bioprinting for organoid engineering is the development of suitable bioinks, which typically comprise a biomaterial matrix (e.g., hydrogels such as gelatin methacryloyl (GelMA), alginate, hyaluronic acid, and collagen) integrated with viable cells[24,28]. These biomaterials must satisfy specific performance criteria, including biocompatibility, printability (characterized by appropriate viscosity and shear-thinning behavior), and post-printing mechanical stability[29]. Recent advancements in bioink design have focused on incorporating both stromal and cancer cells to construct more physiologically relevant 3D bioprinted cancer models, which faithfully recapitulate the complex tumor microenvironment (TME)[28]. For instance, 3D bioprinting has been successfully applied to generate models of lung, prostate, skin, brain, and colon cancers, providing unique insights into cancer biology and therapeutic response mechanisms[28].

Beyond bioink development, 3D bioprinting exhibits versatile integration with organoid systems, either by directly printing organoids or by fabricating supportive scaffolds that promote organoid growth and vascularization. For example, hydrogel-in-hydrogel live bioprinting enables the dynamic fabrication of instructive cues within organ-like cultures, which can guide neural axon directionality, regulate cell migration in cancer organoids, and enhance cell polarity in liver organoids, while also facilitating small intestinal organoid morphogenesis and lung tip bifurcation—underscoring its potential to direct complex developmental processes[30]. Additionally, the combination of 3D bioprinting with self-organizing cardiac organoids aims to generate functional cardiac tissues, where bioprinting provides critical spatial control and mechanical support for cardiac self-organization[31]. Furthermore, the integration of "organ building blocks" (OBBs)—including spheroids, organoids, and assembloids—with 3D bioprinting offers a promising strategy for accelerating the production of large-scale tissue constructs with cell densities approaching those of native tissues, although significant challenges persist in the assembly of these OBBs and the fabrication of functional vascular networks to sustain tissue viability[32].

1.2.3 Microfluidics and Organ-on-a-Chip Integration

Microfluidic systems, often integrated into "organ-on-a-chip" (OOC) platforms, provide dynamic and precisely controlled microenvironments that substantially enhance the physiological relevance and functional maturity of organoids[33,34]. These systems enable meticulous regulation of fluid flow, nutrient transport, waste clearance, and the application of physiological mechanical stimuli—all critical factors for sustaining long-term organoid culture and promoting their functional maturation[35,36].

A pivotal strength of microfluidic technology lies in its suite of distinct advantages for organoid research. Foremost, it can recapitulate the extrinsic physiological characteristics of native organs, such as hemodynamic flow and biomechanical forces, which are typically absent in conventional static organoid cultures[33]. Furthermore, the dynamic culture conditions fostered by microfluidics not only promote organoid proliferation and structural maturation but also enhance their functional specialization, including de novo vascularization and the establishment of functional intercellular or tissue-level connections[35,36]. Additionally, microfluidic platforms can be engineered for automated, real-time, and whole-course monitoring of organoid responses to pharmaceutical compounds, thereby improving data reproducibility and accuracy compared to traditional end-point detection methods[37]. Last but not least, "organoids-on-a-chip" (OoCs) enable the integration of multiple organoid types to model inter-organ crosstalk, providing a more holistic and physiologically relevant representation of systemic physiology and disease progression [33,34].

In terms of translational applications, microfluidic platforms have been successfully developed to facilitate the formation of functional endothelial networks around various 3D cell aggregates, including mesenchymal spheroids, pancreatic islet spheroids, and blood vessel organoids, supporting long-term culture (up to 30 days) with viable intravascular perfusion[35]. This enhanced vascularization is pivotal for advancing next-generation, high-complexity in vitro models for developmental biology research, clinical diagnostics, and preclinical drug development[38]. For instance, "mini-colon" models have been constructed by integrating organoid culture with OOC technology, offering a precise experimental platform to systematically investigate human gut physiology and pathology while serving as a reliable preclinical tool for drug safety evaluation [36]. Similarly, kidney organoids generated using microfluidic bioprinters have demonstrated robust functional activity and specific responsiveness to nephrotoxic agents, underscoring the potential of this technology for advancing kidney disease therapeutics and preclinical drug screening[39]. Notably, the fusion of organoid culture with microfluidic chips in OoCs holds particular promise for personalized precision medicine, as it enables the optimization of therapeutic strategies, the development of patient-specific disease models, and the design of individualized treatment regimens based on patient-derived organoids [40].

1.2.4 4D Printing

Four-dimensional (4D) printing, an emerging technology in tissue engineering and regenerative medicine, incorporates time as the fourth dimension, enabling the fabrication of shape-transforming biomimetic constructs. This dynamic functionality is achieved through stimuli-responsive mechanisms such as shape-memory behavior and differential swelling, with shape-memory effects typically realized using polymers like poly(lactic acid) (PLA) and poly(glycolic acid-co-d,l-lactide) (PGDA), while differential swelling is facilitated by hydrophilic biomaterials including alginate,

hyaluronan, and gelatin[41]. Although direct applications of 4D printing to organoid formation remain in their nascent stages, this technology holds immense potential for engineering dynamic, spatiotemporally responsive scaffolds that can undergo programmed evolution over time—providing tailored, time-dependent mechanical or structural cues to guide organoid maturation or recapitulate the sequential morphogenetic events inherent to native organ development. To fully unlock its potential in organoid engineering, future research endeavors will focus on integrating multiple stimuli-responsive modalities and leveraging computational modeling-assisted design strategies, thereby further enhancing the precision and versatility of 4D-printed constructs for guiding complex organoid development.

1.2.5 Self-Assembly and Organ Building Blocks

Beyond direct biofabrication, biomaterials act as indispensable regulatory scaffolds to mediate the spontaneous self-assembly of cells into organoids or larger "organ building blocks" (OBBs)[32]. This strategy capitalizes on the intrinsic spatiotemporal self-organization capacity of stem cells—an evolutionarily conserved property that drives the formation of hierarchically complex multicellular structures when cells are encapsulated within a biomimetic microenvironment recapitulating the biophysical rigidity, biochemical ligand presentation, and mechanical cues of native tissues. OBBs, encompassing spheroids, organoids, and assembloids, serve as modular functional units for advanced biofabrication; this modular paradigm enables the construction of macroscale tissue constructs with elevated cell seeding densities, intricate multicellular network organization, and enhanced physiological fidelity—characteristics that closely approximate the structural complexity and functional phenotypes of native organs[32]. Notably, when synergistically integrated with bioprinting technologies, this approach provides a viable solution to address long-standing bottlenecks in organoid scaling, including inadequate vascular infiltration, heterogeneous dimensional distribution, and compromised structural integrity.

2. Functional Regulation of Organoid Development and Maturation

The development and functional maturation of organoids are not exclusively governed by their intrinsic genetic programs but are profoundly modulated by extrinsic cues from the surrounding microenvironment—with biomaterials serving as key mediators of such regulatory signals[3]. Biomaterials function as active regulators that guide cell fate determination, facilitate tissue-scale spatiotemporal organization, and enhance the physiological fidelity of organoids by precisely tailoring mechanical, biochemical, electrical, and topographical cues. This section focuses on how the engineered properties of biomaterials are exploited to achieve precise spatiotemporal control over organoid development and functional maturation.

2.1 *Mechanical Cues: Stiffness, Topography, and Mechanotransduction*

The mechanical properties of the extracellular matrix (ECM), encompassing stiffness and topographical features, serve as pivotal regulators of cellular behavior, orchestrating processes such as proliferation, lineage specification, migration, and tissue-level organization[42,43]. Biomaterials provide a powerful means to precisely tune these mechanical cues within organoid cultures, thereby directing their development and maturation.

Matrix stiffness, a well-characterized mechanical cue, is a key determinant of stem cell fate. For instance, engineered biomimetic matrices have uncovered stiffness-mediated chemoresistance in patient-derived pancreatic cancer organoids, underscoring the

critical role of the mechanical microenvironment in disease pathophysiology and therapeutic responsiveness[42]. The ability to fine-tune matrix stiffness enables researchers to recapitulate the heterogeneous mechanical properties of distinct native tissues or pathological microenvironments—such as the pathological stiffening associated with fibrosis or tumor stroma[42,43]. Hydrogels, with their inherently tunable mechanical characteristics, are particularly well-suited for this application, as their elastic modulus can be precisely modulated by adjusting polymer concentration, crosslinking density, or chemical functionalization (e.g., conjugation of bioactive ligands)[10,21]. Studies investigating organoid growth dynamics within 3D matrices spanning a range of mechanical stiffness (e.g., 0.5–8 kPa) have demonstrated that while matrix stiffness can indeed influence organoid size and morphological homogeneity, its regulatory effects may be attenuated at lower stiffness ranges, suggesting complex context-dependent crosstalk between mechanical cues and intrinsic cellular signaling pathways[44].

Beyond static matrix stiffness, mechano-responsive biomaterials—engineered to dynamically adapt their physical or biochemical properties in response to external mechanical stimuli (e.g., shear stress, compressive force, or cell-generated traction forces)—play a critical role in regulating stem cell fate during physiological processes such as embryogenesis and tissue regeneration. By integrating tunable stiffness, nanotopographical features, and stimulus-responsive functional moieties, these biomaterials precisely regulate stem cell proliferation and lineage-specific differentiation, rendering them indispensable for organoid culture and organ-on-a-chip platforms across diverse tissue engineering applications, including neurological, musculoskeletal, and endocrine tissues[45]. Specifically, in bone organoid engineering, mechano-responsive biomaterials are indispensable for recapitulating the native bone microenvironment, given that mechanical loading serves as a central regulator of bone development, remodeling, and repair. Through their stimulus-responsive mechanisms (e.g., dynamic stiffness modulation, on-demand release of osteogenic growth factors), these biomaterials effectively promote osteogenic differentiation and bone regeneration, holding substantial translational potential for advanced bone repair strategies[46].

At the cutting edge of mechanical cue engineering, advanced strategies employ co-assembled supramolecular hydrogelators that form transient, dynamic networks for the encapsulation of kidney organoids. This mechanoresponsive nanoenvironment enhances glomerulogenesis by permeating the organoid interior, triggering biological responses that extend beyond the organoid-hydrogel interface. Notably, this approach complements soluble biochemical factors in precisely tuning lineage commitment and refining organoid functional maturation, exemplifying the sophisticated spatiotemporal control over organoid development that can be achieved through rationally engineered mechanical cues[47]. Collectively, these advancements highlight the integral role of biomaterial-mediated mechanical regulation in advancing organoid technology toward more physiologically relevant and translationally viable models.

2.2 *Biochemical Signaling: Growth Factors, Extracellular Vesicles, and Bioactive Molecules*

Biomaterials act as multifunctional and tunable platforms for presenting biochemical signals that are indispensable for orchestrating cell fate determination, promoting lineage-specific differentiation, and facilitating the functional maturation of organoids. These bioactive cues encompass growth factors, extracellular vesicles (EVs), ECM-mimicking peptides, and various bioactive molecules, which collectively recapitulate the complex signaling milieu of the native extracellular matrix (ECM) to

guide organoid development.

Notably, the rational incorporation of specific growth factors and bioactive substances into biomaterial scaffolds is a well-established strategy to potentiate the regenerative potential of organoid systems. For instance, in endometrial regeneration, the integration of mesenchymal stem cells (MSCs), extracellular vesicles, and pro-regenerative growth factors into bioengineered ECM-based scaffolds has been shown to significantly enhance tissue repair and functional recovery[11]. Similarly, for bone/cartilage organoids, the selection of appropriate cells, matrix gels, and cytokines is crucial for successful construction and application[48]. Biomaterials can be precisely engineered to encapsulate these bioactive factors and achieve spatiotemporally controlled, sustained release, ensuring their bioavailability throughout the dynamic process of organoid development. This controlled delivery paradigm is critical for guiding complex developmental programs and promoting the formation of mature, functionally competent tissues. For example, oxygen-releasing biomaterials have been utilized to fabricate oxygenated 3D scaffolds for induced pluripotent stem cell (iPSC)-derived pancreatic lineage differentiation, resulting in islet organoids with upregulated islet signature genes, optimized pancreatic cell type composition, and enhanced glucose-responsive insulin secretion[40]. This exemplifies how biomaterials can precisely regulate even environmental biochemical cues (e.g., oxygen tension) to drive organoid functional maturation.

Furthermore, organoid-derived extracellular vesicles (OEVs)—biocompatible nanoscale vesicles that shuttle bioactive cargoes (e.g., proteins, miRNAs, lipids) and retain stem cell-like bioactivity—have emerged as promising therapeutic agents[49]. Both organoids and OEVs are being actively explored for disease treatment strategies, with OEVs exhibiting inherent advantages such as high production yield, potentiated bioactivity, and reduced immunogenicity compared to whole cells[49]. Biomaterials play a synergistic role in optimizing OEV production, purification, and targeted delivery, thereby further augmenting their therapeutic efficacy in organoid-based regenerative medicine.

In addition to full-length ECM proteins and growth factors, ECM-mimicking peptides can be covalently conjugated to synthetic biomaterials to present specific cell-adhesive ligands (e.g., RGD, IKVAV) or signaling epitopes, enabling precise modulation of cell-matrix interactions and directed cell behavior in a chemically defined manner[8]. For example, bioorthogonally cross-linked hydrogels functionalized with modified gelatin precursors have been engineered to tune mechanical properties and bioactive ligand presentation, supporting the proliferative kinetics and morphogenetic progression of tooth germs—demonstrating the utility of defined, tunable biomaterial platforms for organoid engineering[21]. The capacity to functionalize biomaterials with varying levels of complexity, from structural support to precise signal transduction, underscores their immense potential in advancing tissue engineering and regenerative medicine[8].

Beyond these biological cues, biomaterials and advanced encapsulation technologies have enabled a novel translational application: preserving the viability, stability, and bioactivity of probiotics within organoid cultures or other biomedical contexts[50]. This highlights the versatility of biomaterials in delivering not only soluble growth factors but also live bioactive agents, facilitating their site-targeted delivery and controlled release while enhancing their in vitro or in vivo stability.

Importantly, inorganic biomaterials such as silicate-based formulations have also exhibited considerable potential in regulating organoid homeostasis and functional integrity. For instance, engineered bone marrow organoids (BMOs)

incorporating calcium silicate nanowires (CSNWs) and magnesium silicate nanospheres (MSNs) have been shown to form well-formed endothelial networks, enhance mesenchymal stem cell (MSC) self-renewal, and exert favorable regulatory effects on hematopoietic stem cell (HSC) expansion and differentiation. Co-culture experiments utilizing these silicate-functionalized BMOs have further demonstrated improved chondrocyte, MSC, and Schwann cell bioactivity, with silicate biomaterials activating osteogenic and angiogenic signaling pathways. In in vivo studies, these engineered BMOs effectively promoted osteochondral defect regeneration, highlighting the potent biochemical signaling capabilities of specific inorganic biomaterials in modulating organoid function and translational efficacy[51].

2.3 *Electrical and Other Physical Stimuli: Electroactive Biomaterials and Optogenetics*

Beyond mechanical and biochemical cues, other physical stimuli—particularly electrical signals—are increasingly recognized for their profound regulatory effects on cellular behavior, tissue morphogenesis, and regenerative processes. Biomaterials can be rationally engineered to either respond to endogenous bioelectric signals or exogenously generate targeted electrical stimuli, introducing an additional dimension of spatiotemporal regulation over organoid development and function.

Endogenous bioelectricity plays a pivotal role in maintaining tissue electrophysiological homeostasis and driving regeneration, with well-characterized effects in bone and cartilage repair[52,53]. Electrical stimulation (ES) has been shown to enhance extracellular matrix (ECM) biosynthesis, accelerate tissue regeneration, and modulate lineage-specific differentiation. Electroactive biomaterials are designed to recapitulate these physiological electrical microenvironments, often integrating multimodal regulatory cues—electrical, biochemical, and mechanical—to synergistically promote tissue repair and functional restoration[52]. These advanced materials can be engineered as self-powered systems, leveraging triboelectric nanogenerators, piezoelectric materials, or photovoltaic cells to sustainably create an electrophysiological niche conducive to osteogenic differentiation and bone regeneration[53]. Notably, piezoelectric biomaterials—which transduce mechanical stress into localized electrical potentials—further underscore the intrinsic crosstalk between bioelectricity and tissue remodeling, offering promising avenues for the development of clinically translatable, personalized biomaterials[54]. Moreover, stimuli-responsive biomaterials that react to external cues (e.g., electricity, light, ultrasound, magnetism) have been shown to modulate key cellular signaling pathways, solidifying their role as cornerstone tools in advanced biomedical engineering and organoid technology[55].

Given the unique electrophysiological properties of neural tissues, the integration of advanced electronic systems and light-responsive technologies has emerged as a transformative approach for neural organoid research. For neural organoids, the ability to precisely record and manipulate electrical activity is critical for deciphering developmental trajectories, functional maturation, and disease-related pathophysiological changes. Flexible electronic platforms, such as kirigami electronics (KiriE), have been successfully integrated with cortical organoids to enable long-term chronic electrophysiological recording (extending up to 120 days) while preserving the organoids' structural integrity, morphological complexity, and cellular composition[56]. This technological breakthrough facilitates in-depth investigations into disease mechanisms and activity-dependent circuit assembly underlying nervous system development. Furthermore, optogenetic stimulation—coupled with neural organoids reciprocally connected via axon bundles—has been shown to induce short-term synaptic plasticity, providing

unprecedented insights into the formation and functionality of macroscopic neural circuits[57]. Collectively, these advancements highlight the indispensable role of integrating electroactive biomaterials, flexible electronics, and light-responsive systems to achieve precise spatiotemporal control and real-time monitoring of the electrophysiological microenvironment in organoids, particularly for neural tissue engineering and neurodevelopmental disorder modeling.

2.4 *Oxygenation and Microenvironment Control*

Oxygen tension serves as a pivotal microenvironmental cue that exerts a profound regulatory effect on cellular metabolism, proliferation, and lineage-specific differentiation—especially in the context of tissue morphogenesis and regenerative processes. Biomaterials can be rationally engineered to spatiotemporally modulate oxygen tension within organoid cultures, thereby synergistically optimizing organoid maturation and functional competency. Consistent with prior observations, oxygen-releasing biomaterials have been successfully employed to fabricate oxygenated 3D scaffolds for induced pluripotent stem cell (iPSC)-derived pancreatic lineage differentiation. This strategy not only preserved the mechanical integrity of the scaffold but also precisely elevated the local oxygen tension within the 3D culture microenvironment, resulting in islet-like organoids (ILOs) with upregulated expression of islet-specific marker genes and proteins, a more physiological cell subtype composition mimicking native pancreatic islets, and enhanced glucose-responsive insulin secretory capacity[40]. Such precise spatiotemporal regulation of the oxygen microenvironment is indispensable for recapitulating the physiological oxygen gradients of developing tissues, which is critical for generating organoids with enhanced maturity and physiological relevance—particularly for applications in diabetes pathophysiology research and translational therapeutic development.

2.5 *Surface Chemistry and Cell Adhesion*

The surface properties of biomaterials, encompassing their physicochemical characteristics and topographical features, serve as pivotal regulators orchestrating cell adhesion, migration, and lineage specification within organoid culture systems. Rational modification of these surface properties allows for precise modulation of cell-material interactions, which constitutes a fundamental prerequisite for guiding spatiotemporally controlled organoid development and functional maturation.

Notably, surface chemical modifications exert profound regulatory effects on organoid behavior and fate determination. For instance, hydrophilic surfaces—particularly those functionalized with amine (-NH_2) and hydroxyl (-OH) moieties—have been demonstrated to selectively facilitate the adhesion and lineage commitment of retinal organoids (ROs), while augmenting cellular migration and the differentiation of retinal ganglion cells (RGCs)[46]. In contrast, low-wettability surfaces, such as those modified with phenyl or methyl groups, restrict cellular attachment and impede subsequent developmental processes. These findings underscore the critical role of the biomaterial-cell interface in mediating 3D organoid morphogenesis, providing critical mechanistic insights for refining organoid-based delivery strategies and functional performance in regenerative medicine applications[46].

Beyond mediating direct cell-material adhesion, surface properties of biomaterials can actively modulate the host immune microenvironment—an indispensable factor for the long-term viability and functional integration of organoids, especially in translatable regenerative therapies. Immunomodulatory biomaterials are rationally engineered to tailor surface physicochemical properties, thereby mitigating foreign body reactions (FBR) and potentiating tissue regeneration[58]. By precisely regulating immune cell recruitment,

activation, and cytokine secretion, these materials can attenuate chronic inflammatory responses and promote tissue repair, which represents a pivotal prerequisite for the clinical translation of organoids—particularly when in vivo transplantation is envisioned. Furthermore, surface-functionalized formulations of blood-contacting biomaterials are being actively developed to inhibit thrombosis and promote hemostasis, which is critical for vascularized organoid systems and implantable biomedical devices[59]. These designs often involve super-lubricated, super-hydrophobic coatings, or drug-delivering coatings, highlighting the diverse strategies for surface engineering.

In the context of implantable biomaterial scaffolds or organoids subjected to long-term in vitro culture or in vivo transplantation, inhibiting bacterial biofilm formation is of paramount importance. Bacterial biofilm colonization on biomaterial surfaces can induce device-related infections (DRIs) and subsequent implant failure[60]. Current research endeavors are focused on augmenting the antibacterial efficacy of dental implants—an application with direct implications for organoid scaffolds—via surface topographical modification, functional coating strategies, and the development of intrinsically antibacterial biomaterials[61]. These antibacterial platforms can be further combined with bioactive molecules or metallic nanoparticles to synergistically enhance osteogenic potential and accelerate osseointegration, while maintaining a sterile microenvironment. Such principles are directly translatable to organoid culture systems, ensuring a sterile, bioactive niche conducive to organoid development, functional maintenance, and translational applicability.

3. Clinical Translation and Advanced Applications

The integration of biomaterials into organoid research is not merely an academic pursuit. It is inherently motivated by its substantial translational potential across a broad spectrum of biomedical applications. Biomaterial-functionalized organoids hold transformative potential to revolutionize disease modeling, expedite drug discovery and development, and pioneer innovative regenerative therapeutic strategies—thus providing more physiologically relevant, patient-tailored, and ethically compliant alternatives to conventional preclinical research models (e.g., 2D cell cultures and animal models). In this section, we elaborate on the multifaceted clinical applications of these advanced biomaterial-organoid complexes and delineate the critical bottlenecks that need to be addressed to facilitate their successful translational implementation.

3.1 *Disease Modeling*

Organoids, particularly when supported by intelligently designed biomaterials, provide unparalleled platforms for modeling human diseases, offering insights into pathogenesis, progression, and potential therapeutic interventions. Their ability to recapitulate tissue-specific complexity and patient-specific responses makes them invaluable tools.

3.1.1 Cancer Organoids

Cancer organoids, particularly patient-derived tumor organoids (PDTOs), have emerged as robust 3D in vitro models that faithfully recapitulate the phenotypic, genotypic, and functional characteristics of primary tumors, thereby overcoming the inherent limitations of traditional 2D cell cultures and preclinical animal models[4,5,62]. Biomaterials play an indispensable role in constructing these physiologically relevant models by mimicking the complex tumor microenvironment (TME)—a dynamic

niche encompassing heterogeneous cell populations (e.g., cancer-associated fibroblasts, immune cells, endothelial cells), soluble factors, and a structurally complex extracellular matrix (ECM)[28,63].

PDTOs offer an unparalleled ability to recapitulate intratumoral and intertumoral heterogeneity, providing a powerful tool to dissect the inherent complexity of tumors[64]. As a critical determinant of tumor progression, metastasis, and therapeutic responsiveness, the TME requires precise biomimetic reconstruction, and biomaterial scaffolds—often integrated with 3D bioprinting technologies—enable the spatial patterning of stromal cells, cancer cells, and ECM components in 3D constructs, generating customized models that closely mirror the in vivo TME architecture and signaling crosstalk[28,65]. This capability is pivotal for deciphering the molecular mechanisms underlying cancer progression and metastasis, as well as for developing personalized therapeutic strategies[63]. Advanced 3D tumor organoid models are rapidly evolving to recapitulate key immunological hallmarks of the TME, including immune cell infiltration, cytokine gradients, and immune checkpoint expression, opening up unprecedented avenues for organoid-based investigations of tumor immunity, immunotherapeutic drug development, and precision medicine[66]. For instance, the integration of artificial intelligence, multi-omics analysis, and organoid models has guided the rational design of bioactive biomaterials for enhanced tumor immunotherapy—specifically by eliciting pyroptosis, a gasdermin-mediated programmed cell death pathway that triggers robust inflammatory responses to convert "cold" (immunologically quiescent) tumors to "hot" (immunologically active) ones, thereby augmenting antitumor immune efficacy[67].

Cancer organoids have become indispensable tools for anticancer drug discovery and development, facilitating therapeutic target identification, anticancer compound validation, and the advancement of precision medicine[4,62,68]. Patient-derived organoids (PDOs) exhibit high fidelity to the histological and molecular features of parental tumors, enabling the identification of patient-specific effective treatments. In advanced pancreatic ductal adenocarcinoma (PDAC), for example, PDOs have enabled the validation of candidate drugs and identification of synergistic drug combinations, revealing that KRASG12D variant tumors exhibit enhanced sensitivity to anti-EGFR therapies in combination with chemotherapeutics; notably, patients receiving these matched treatments demonstrated significantly higher overall response rates and prolonged progression-free survival[69]. Biomaterial-enhanced platforms, such as bioprinted polyethylene glycol (PEG) and gelatin methacryloyl (GelMA) hydrogels, sustain the proliferation and organoid formation of breast cancer cells, providing a physiologically relevant niche for drug testing—studies using these platforms have demonstrated elevated IC50 values for chemotherapeutic agents (e.g., doxorubicin, EP31670, paclitaxel) in 3D hydrogel cultures compared to 2D monolayers, underscoring the superior physiological relevance of biomaterial-supported organoids for accurate drug efficacy assessment[14]. While challenges persist—including the complete recapitulation of intratumoral heterogeneity and the standardization of culture protocols and functional assays—technological advancements (e.g., microfluidic integration, AI-guided culture optimization) and stromal cell co-culture systems are actively addressing these limitations, propelling PDTOs into a new era of precision oncology[62,70]. Furthermore, a novel 3D hydrogel culture system has been developed to biomimic the lymph node microenvironment, supporting the survival and proliferation of chronic lymphocytic leukemia (CLL) cells and recapitulating disease-specific biological behaviors, which highlights the potential of biomaterials to recreate tissue-specific niches for modeling hematological malignancies[71].

3.1.2 Neurological Organoids

Neurological organoids, encompassing brain organoids, spinal cord organoids, and blood-brain barrier (BBB) models, have revolutionized neuroscience research by providing human-specific, physiologically relevant in vitro platforms to dissect neural development, disease pathogenesis, and drug responsiveness—effectively overcoming the species-specific limitations and translational gaps of traditional animal models[6,72].

Brain Organoids: Human brain organoids, derived from pluripotent stem cells, recapitulate human brain features, including neural cell types, synapses, and myelination, enabling detailed investigation of development, dysfunction, and neurological diseases[72,73]. Advances in directed stem cell differentiation protocols and synthetic biomaterial engineering have further enhanced the complexity and physiological fidelity of brain organoids, expanding their utility in studying preterm birth-associated brain dysfunction, viral neurotropism (e.g., Zika virus infection), neuroinflammation, and both neurodevelopmental (e.g., autism spectrum disorder) and neurodegenerative (e.g., Alzheimer's disease) conditions[73]. To address reproducibility challenges in the field, an international consortium of neuroscience researchers has proposed a standardized experimental framework for neural organoids, assembloids, and transplantation studies, aiming to unify experimental designs and data reporting[74]. Complementing PSC-derived brain organoids, human fetal brain tissues have been shown to self-organize into long-term expandable fetal brain organoids (FeBOs) in vitro, which phenocopy in vivo cellular heterogeneity and complex tissue architecture, offering a complementary platform for studying central nervous system (CNS) development and disease[75]. Additionally, "semi-guided" cortical organoids with robust neural oscillatory activity have been generated via optimized protocols with shortened induction and differentiation timelines, preserving cell type diversity while enhancing experimental reproducibility—making them ideal for disease modeling[76]. Whole-tissue lineage tracing studies in human cerebral organoids have further revealed dynamic clonal expansion and tunable tissue replenishment capacity, suggesting that intrinsic stem cell population plasticity ensures robust organoid development[77].

Human BBB assembloids, constructed by fusing brain organoids and vascular organoids derived from human PSCs, recapitulate the core physiological properties of the native human BBB—including tight junction integrity, transporter expression, and barrier function—and have been successfully used to unravel the pathogenic mechanisms of cerebral cavernous malformations (CCMs)[78]. This is particularly critical for neuroscience research, as the BBB serves as a major anatomical and functional barrier limiting the access of therapeutic agents to the CNS. Traditional brain organoids often lack a functional vascular network, which compromises their long-term survival, maturation, and physiological relevance; however, recent advances in engineering vascularized brain organoids (V-Organoids) have addressed this bottleneck by integrating functional vascular networks, significantly enhancing organoid survival, neural maturation, and translational utility in disease modeling, drug screening, and regenerative medicine, particularly for neurodevelopmental processes, BBB permeability, brain cancer, and regeneration[79].

Human midbrain organoids (hMLOs) have emerged as promising preclinical models for studying Parkinson's disease (PD)—a neurodegenerative disorder with elusive pathogenesis—facilitating PD-related mechanistic research, high-throughput drug screening, and the development of targeted therapeutic strategies[61]. In parallel, biomaterials-based spinal cord tissue engineering has advanced regenerative medicine applications by optimizing spinal cord organoid development and spinal cord

injury (SCI) repair: biomaterials that mimic the native ECM composition, mechanical properties, and biochemical cues promote lineage-specific differentiation of neural progenitors, enhance the structural integrity of spinal cord organoids, and facilitate neural regeneration at SCI lesions[80].

The integration of humanized brain organoids with microfluidic "organoids-on-chip" systems and biosensors is driving the development of high-throughput platforms for screening neuronal activity, neurotoxicity, and drug efficacy, while also opening new avenues for brain organoid intelligence and biocomputing research[81]. The integration of flexible electronics, such as kirigami electronics, with human neural organoids and assembloids enables long-term electrophysiological recording, allowing for investigation of disease and activity patterns underlying nervous system assembly[56].

3.1.3 Kidney Organoids

Kidney diseases affect hundreds of millions of individuals worldwide, and traditional preclinical animal models frequently lack sufficient predictive capacity for evaluating drug candidates, leading to high translational failure rates in renal drug development[84]. Kidney organoids and organ-on-a-chip systems, derived from induced pluripotent stem cells (iPSCs), provide more physiologically relevant models for dissecting renal tissue development and recapitulating patient-specific pathological responses, thus addressing the inherent limitations of conventional models[82].

A major bottleneck in kidney organoid technology lies in inadequate morphological uniformity and incomplete functional maturation, which severely hinder their standardization and translational applicability. To overcome this challenge, a 3D geometrically engineered permeable membrane-based platform, termed UniMat, has been developed for the scalable generation of kidney organoids[7]. Compared to conventional 3D cultures, UniMat-derived kidney organoids exhibit significantly enhanced morphological homogeneity, advanced functional maturation, and improved long-term culture stability—characterized by upregulated expression of nephron-specific transcripts, a physiological cell subtype composition mimicking native renal tissue, and robust vascular network formation[7]. This scalable platform enables the establishment of standardized kidney organoid models, which are well-suited for renal disease modeling, preclinical drug screening, and mechanistic investigations into renal organogenesis. Furthermore, microfluidic bioprinting technology has been employed to fabricate functional renal organoids derived from human induced pluripotent stem cells (hiPSCs), which exhibit predictable and reproducible responses to nephrotoxic agents—effectively overcoming the scalability constraints and batch-to-batch variability associated with manual organoid productio[39].

Kidney organoids have become indispensable tools in preclinical drug development, and concerted efforts are underway to integrate cutting-edge technological advancements with standardized culture protocols and functional validation assays to facilitate their robust implementation in preclinical drug screening pipelines[83]. Notably, the application of co-assembled supramolecular hydrogelators has been demonstrated to promote glomerulogenesis in kidney organoids by constructing a mechanoresponsive nanoenvironment. This biomaterial-based niche elicits biological responses that extend beyond the organoid-hydrogel interface, thereby further refining the functional maturation of kidney organoids—particularly in terms of glomerular structural integrity and physiological filtration capacity[47].

3.1.4 Lung Organoids

Lung organoids—miniaturized in vitro models of lung tissue—have emerged as pivotal tools in

respiratory research, facilitating in-depth investigations into the pathogenic mechanisms of respiratory diseases and the development of potential therapeutic strategies for conditions such as acute respiratory infections, chronic obstructive pulmonary disease, and pulmonary fibrosis[84]. Despite inherent limitations including insufficient cellular heterogeneity, incomplete structural complexity, and limited functional fidelity compared to native lung tissue, strategic advancements such as multi-cell type co-culture systems (incorporating epithelial cells, stromal cells, immune cells, and endothelial cells) and bioengineered culture platforms have significantly enhanced organoid functional maturation and physiological relevance. Notably, lung organoids (LOs) and lung-on-a-chip (LOC) technologies have effectively overcome the inherent shortcomings of conventional preclinical models in recapitulating the structural and functional complexity of the native lung, leveraging human pluripotent stem cells (hPSCs) to faithfully mimic key stages of lung morphogenesis and the biochemical, biophysical, and mechanical cues of the native pulmonary microenvironment[85]. Furthermore, these integrated model systems enable dynamic reconstruction of physiological respiratory microenvironments (e.g., air-liquid interface, cyclic mechanical stretch, and fluid shear stress), which not only deepens the mechanistic understanding of respiratory disease pathogenesis but also expedites the preclinical drug discovery pipeline and refines pharmacological efficacy and toxicity evaluations in respiratory medicine.

3.1.5 Endometrial Organoids

Endometrial regeneration is plagued by formidable clinical challenges, including intrauterine adhesions (IUAs), thin endometrium syndrome, and consequent infertility, where conventional therapeutic interventions often fail to fully restore the structural integrity and functional competence of the endometrial tissue. To address these unmet clinical needs, integrative bioengineering strategies that synergistically combine biomaterials, stem cells, organoids, and organ-on-a-chip technologies have emerged as promising translational approaches[11]. Natural polymers such as collagen, gelatin, and hyaluronic acid, alongside synthetic polymers including polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), and poly(lactic-co-glycolic acid) (PLGA), are rationally designed to recapitulate the biological, physical, and biochemical properties of the native extracellular matrix (ECM), thereby providing a biomimetic niche that facilitates cellular proliferation, angiogenesis, and precise modulation of immune responses. Notably, the strategic incorporation of mesenchymal stem cells (MSCs), MSC-derived extracellular vesicles (EVs), and pro-regenerative growth factors into these bioengineered scaffolds further potentiates regenerative efficacy by enhancing cell recruitment, promoting tissue remodeling, and accelerating functional recovery. Furthermore, endometrial organoids, 3D bioprinting technologies, and endometrium-on-a-chip systems collectively enable the construction of physiologically relevant in vitro models that recapitulate the dynamic cellular crosstalk and tissue microenvironment of the native endometrium, laying the foundation for precision regenerative medicine. These integrated approaches represent a next-generation therapeutic paradigm with the potential to effectively restore endometrial function and improve fertility outcomes in affected patients[11]. Recent advances in bioengineering technologies—encompassing organ-on-a-chip platforms, patient-derived organoids, advanced functional biomaterials, and high-resolution 3D bioprinting—have further empowered the in vitro reconstruction of functional endometrial models, which hold significant promise for advancing both reproductive health research and the development of targeted therapies for endometrial diseases[86].

3.1.6 Osteochondral Organoids

Osteochondral tissue repair is a significant challenge in regenerative medicine, and organoid technology offers a novel approach by mimicking osteochondral (OC) tissue architecture[87]. Bone/cartilage organoids, miniature tissues grown in vitro, enable the study of cellular interactions and disease pathology, offering opportunities for bone biology research.

The OC organoid biofabrication, particularly using 3D printing and microfluidics is focused on, outlining construction strategies and potential applications in OC disease treatment[87]. Bone/cartilage organoids find broad applications in osteochondral tissue reconstruction, disease modeling (e.g., osteoarthritis, osteonecrosis), and preclinical drug screening[48]. Challenges in this field include the rational selection of seed cells, matrix hydrogels, lineage-specific cytokines, and fabrication techniques, with emerging solutions involving artificial intelligence (AI)-aided optimization, heterotypic assembloid construction, and precision bioprinting. Continuous refinement of culture protocols and standardization of functional validation assays are crucial to unlocking the full potential of these organoids for patient-specific therapeutic interventions and advancing regenerative medicine[48]. Notably, human osteoarthritic cartilage organoids serve as physiologically relevant models for uncovering novel molecular drivers of cartilage degeneration and evaluating therapeutics targeting disease-associated signaling pathways[88]. Silk fibroin (SF)-based hydrogels, endowed with native extracellular matrix (ECM)-mimetic architecture, excellent biocompatibility, and tunable mechanical properties, are ideal scaffolds for cartilage organoid construction in osteoarthritis therapy, with iterative formulation optimization guided by AI-driven predictive modeling[20]. Hydroxyapatite (HAP) nanoparticles have been shown to promote the development of bone microtissues for accelerated bone regeneration by activating the FAK/Akt pathway, leading to self-organized trabecular bone organoids[89].

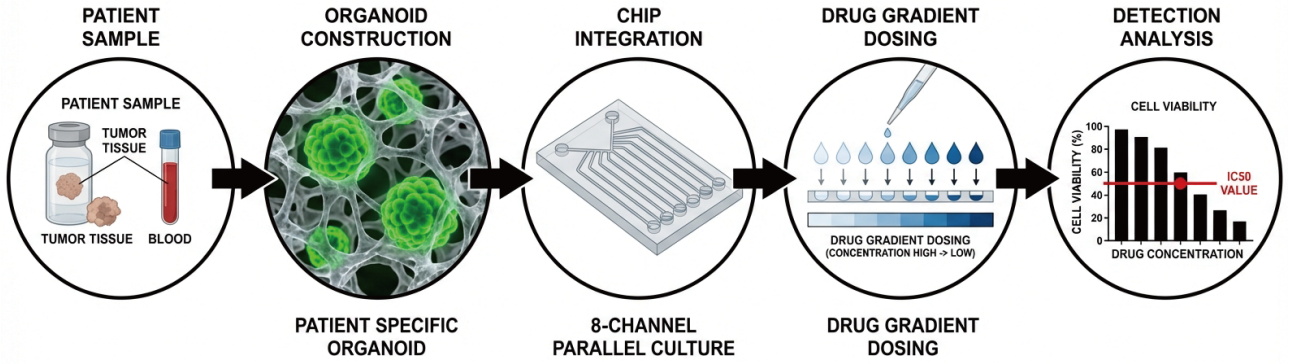
Understanding the skeletal microenvironment, including ECM components, mechanical cues, biochemical signaling, and cellular interactions, is indispensable for cellular behavior and tissue maturation in bone organoids. Recent advancements in biomaterial engineering and microstructural design have enabled the precise recapitulation of physiological niche cues, fostering the development of bone organoids with enhanced physiological fidelity for applications in drug screening, personalized medicine, and bone regenerative therapy—highlighting the transformative potential of niche-mimetic engineering approaches[90]. The future perspectives for bone/cartilage organoid technology, utilizing stem cells, biomaterials, and external factors, show promise in disease modeling and therapy, poised to enhance cartilage repair and bone regeneration[91].

3.2 *Drug Discovery and Precision Medicine*

Biomaterial-enhanced organoids are transforming drug discovery and precision medicine by providing physiologically relevant, patient-specific in vitro models that optimize preclinical testing, high-throughput drug screening, and personalized therapeutic stratification.

Notably, organoids—especially when integrated with microfluidic organ-on-a-chip (OOC) systems to form organoid-on-a-chip (OrgOC) platforms—offer unparalleled advantages over conventional 2D cell monolayers and preclinical animal models for preclinical assays and drug development[33,34]. These "OrgOCs" combine human organoids with microfluidic chips to mimic organ extrinsic characteristics and tissue-specific properties, providing a more reliable platform for drug safety assessment and efficacy testing[33,36](Fig.3). For instance, an automated microfluidic chip-based system has been developed for longitudinal monitoring of drug responses in organoids,

Figure 3. Illustration of high-throughput drug screening using organoid-on-a-chip.



with a specific focus on lung cancer preclinical testing; this integrated platform streamlines organoid establishment, long-term culture, drug administration, and ATP-based viability assessment, significantly improving data reproducibility and analytical accuracy compared to traditional discontinuous monitoring methods[37].

In terms of personalized medicine, the ability to generate patient-derived organoids (PDOs) within biomimetic biomaterial scaffolds enables the construction of patient-specific disease models that recapitulate the molecular, phenotypic, and functional characteristics of the native pathology[34,62,69]. This technological breakthrough is particularly transformative in oncology, where PDOs can predict individual patient responses to chemotherapeutic agents, targeted therapies, and immunotherapies, as well as identify synergistic drug combinations–translating to higher overall response rates and prolonged progression-free survival in patients receiving matched "hit" treatments[69]. Furthermore, the fusion of organoid culture with microfluidic OOC systems provides a powerful tool for advancing personalized precision medicine, facilitating treatment optimization, precise disease modeling, mechanistic investigation of pathogenesis, high-throughput drug screening, and individualized therapeutic design[34]. This transformative potential redefines clinical healthcare paradigms and improves patient outcomes by integrating genomic medicine, transcriptomic profiling, and multi-omics data with functional organoid-based assays.

Beyond therapeutic development, organoids and OOCs serve as ethically sound alternatives to animal models, addressing longstanding ethical concerns while enhancing the translatability of preclinical findings to human physiology[82,92]. This shift is critical for accelerating the drug development pipeline and mitigating the high failure rates of drug candidates in clinical trials–an issue largely attributed to the poor physiological relevance of traditional models. For example, brain organoids have demonstrated substantial promise in toxicological assessment and central nervous system (CNS) drug development, transforming disease modeling of neurodevelopmental and neurodegenerative disorders while deepening mechanistic understanding of brain pathologies[72]. Additionally, the advancement of organoid technology in regenerative medicine plays a pivotal role in bridging preclinical and clinical studies, with profound implications for organ transplantation, tumor biobanking, and precision medicine implementation[2]. Biomaterial-driven regenerative drug delivery systems further emerge as a promising frontier, accelerating the translation of stem cell therapies, tissue engineering

strategies, and precision drug delivery platforms–with personalized medicine, organoids, and OOC systems serving as core pillars of this innovation[93]. Moreover, artificial intelligence (AI) models are increasingly integrated to optimize biomaterial scaffold design, predict tissue responses to therapeutic agents, streamline data analysis workflows, and simplify 3D cell culture system development–collectively revolutionizing the drug discovery and development landscape[94].

3.3 *Regenerative Medicine and Tissue Engineerin*

Biomaterials serve as the foundational scaffold for the translational application of organoids in regenerative medicine and tissue engineering, providing indispensable structural support and instructive biophysical/biochemical cues that govern tissue repair, functional reconstruction, and even clinical organ transplantation.

Biomaterials inspired by the native extracellular matrix (ECM) have emerged as pivotal candidates for tissue regeneration, as they not only offer structural scaffolding but also mediate cell adhesion, facilitate intercellular signal transduction, mitigate adverse immune responses, and modulate tissue remodeling[8]. This is evident in endometrial regeneration, where natural and synthetic polymers mimic the ECM to support cell proliferation, angiogenesis, and immune response modulation, enhancing regenerative efficacy when combined with stem cells and growth factors[11]. Among these, decellularized extracellular matrix (dECM) biomaterials exhibit unique potency, as they retain native tissue-specific bioactive components to exert chemotactic effects that stimulate in situ tissue repair, offering promising growth factor-free and cell-free tissue engineering strategies[18]. Collagen-based biomaterials, renowned for their versatility, have been widely applied in regenerative therapies for bone, cartilage, skin, dental, neural, corneal, and urological tissues, with chemical or physical modifications further enhancing their mechanical stability, biodegradability, and bioactivity for targeted tissue regeneration[9,12,16]. For instance, gelatin-based biomaterials have been shown to promote hemostasis, exert antibacterial and anti-inflammatory effects, and accelerate cellular regeneration in chronic wound healing[13].

Organoids, when supported by appropriate biomaterials, hold potential for transplantation. Allogeneic iPSC-derived cartilage organoids, for example, have been shown to survive and integrate with primate knee joint cartilage defects, eliciting no immune reaction and contributing to tissue repair for at least four months (Fig.4). These transplanted organoids not only prevented

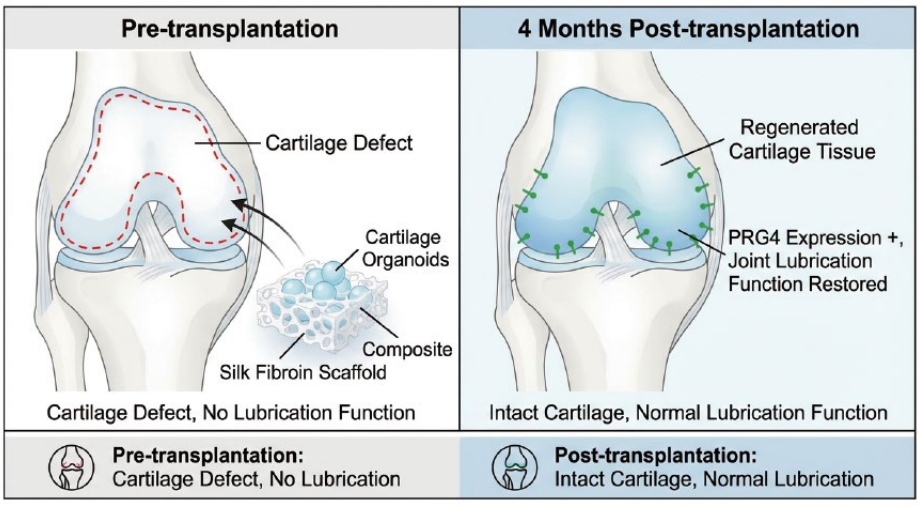


Figure 4. Schematic of cartilage organoid-biomaterial transplantation for repair.

progressive cartilage degeneration but also underwent lineage maturation, acquiring PRG4 expression—a key mediator of joint lubrication—highlighting their clinical applicability for treating chondral defects[95]. In diabetes therapy, extrahepatic transplantation of 3D-cultured stem cell-derived islet organoids on microporous biomaterial scaffolds effectively reduced blood glucose levels in diabetic mouse models, validating their potential as a cell-based therapeutic alternative[96]. For bone/cartilage organoids, their translational utility spans bone/cartilage reconstruction, disease modeling, and preclinical drug screening, with continuous refinement of construction protocols and standardization of functional assays being critical to unlocking their potential for patient-specific therapeutic interventions[48,91]. Furthermore, engineering bone tissues through microenvironment-mimetic strategies—leveraging bone organoids—has opened new avenues for bone biology research, disease modeling, and regenerative medicine, where advancements in biomaterial composition and microstructural design enable precise recapitulation of the native skeletal niche[90].

Advancements in biomaterial engineering have led to the development of sophisticated systems—including electroactive hybrid biomaterials and self-powered platforms—that are critical for recapitulating the natural electrophysiological microenvironments requisite for bone repair and regeneration[53]. These materials integrate triboelectric nanogenerators, piezoelectric components, or photovoltaic cells to generate localized electrical signals, which enhance osteogenic lineage commitment and extracellular matrix synthesis. Silicon-containing nanomedicine and biomaterials, including bioactive glass, are extensively explored for biomedical applications due to their bioactivity, biocompatibility, and facile surface functionalization, with multi-dimensional design enhancing their intrinsic biological effects and interactions with biological systems for regenerative medicine[97]. Additionally, CRISPR-based genetically modified scaffold-free biomaterials—including gene-edited organoids—have become pivotal tools in regenerative medicine and tissue engineering, with applications spanning gene therapy, disease modeling, tissue regeneration, organ xenotransplantation, organogenesis modeling, and drug screening, and several related clinical trials are currently underway[98]. Injectable hydrogels are promising for cartilage therapy in osteoarthritis, promoting cartilage repair and regeneration through targeted drug delivery and incorporating growth factors, anti-inflammatory drugs, and cells[99].

3.4 *Challenges and Future Directions in Clinical Translation*

Despite the remarkable progress, several significant challenges must be addressed to fully realize the clinical translational potential of biomaterial-enhanced organoids. These challenges span issues related to standardization, structural-functional complexity, multi-system integration, and ethical-regulatory frameworks.

Notably, the absence of standardized protocols for organoid derivation, culture, and functional validation constitutes a major bottleneck for widespread clinical adoption, leading to marked heterogeneity in organoid size, morphological uniformity, and functional fidelity[1,2]. While biomaterials offer a viable pathway to improve reproducibility by providing chemically defined and spatiotemporally tunable microenvironments, further efforts are imperative to establish robust, scalable, and automated production workflows[7,25,27]. Complementarily, AI-enabled real-time monitoring and precision drug delivery systems are emerging as transformative tools to advance precision regenerative medicine, facilitating standardized quality control and functional optimization[11].

Furthermore, current organoid models often lack functional, perfusable vascular networks, restricting nutrient perfusion and oxygen diffusion to the core regions of larger organoid constructs—this limitation hinders long-term survival, functional maturation, and physiological relevance[35,38,79]. Engineering perfusable vascular networks within organoids is therefore crucial for developing next-generation, high-complexity in vitro systems with applications in developmental biology, clinical diagnostics, and preclinical drug development[38]. Microfluidic platforms are making significant strides in this area by forming endothelial networks around 3D cell aggregates and establishing functional intravascular perfusion[35].

For transplanted organoids, modulating the host immune response and attenuating foreign body reactions (FBR) are critical prerequisites for long-term engraftment and functional integration[58]. Biomaterials rationally designed with immunomodulatory properties—via tailored surface chemical modifications or bioactive ligand presentation—can orchestrate immune cell recruitment, activation, and polarization, thereby reducing chronic inflammation associated with FBR and enhancing tissue repair[58,100]. An additional related challenge lies in inhibiting bacterial biofilm formation on biomaterial scaffolds, as biofilm colonization can induce device-related infections and subsequent implant failure[60].

While individual organoids faithfully mimic the structure and function of discrete organs, recapitulating systemic physiology and inter-organ crosstalk necessitates the integration of multiple organoid systems. Organoid-on-a-chip (OoC) technologies are advancing toward this goal by merging organoid culture with microfluidic platforms to model inter-organ communication, providing a more holistic view of systemic physiology and disease pathogenesis[33,34]. However, constructing larger, more complex tissue constructs and establishing functional vascular anastomosis between discrete organoid units remain key bottlenecks for modular organ building blocks and biofabrication strategies[32].

Long preparation times and inadequate cryopreservation methods hinder the widespread application of organoid technology. Recent advancements at the intersection of materials science and cryobiology—including the development of natural cryoprotective agents, ice growth-inhibiting biomaterials, and ultra-rapid rewarming technologies—are expanding the research scope and addressing these technical barriers, paving the way for organoid biobanking and off-the-shelf therapeutic applications[101].

As organoid, particularly brain organoids and assembloids, advances towards modeling higher cognitive functions (Organoid Intelligence, OI), ethical considerations become increasingly paramount[72,74]. Establishing robust ethical frameworks and regulatory guidelines is therefore essential for responsible research conduct and safe clinical translation, especially for genetically engineered organoids or those destined for xenotransplantation[26,98].

The complexity of organoid systems necessitates advanced computational and artificial intelligence (AI) tools for data analysis, model prediction, and design optimization[25,94]. AI-assisted real-time monitoring, 4D bioprinting, and computational-aided engineering strategies will play an increasingly pivotal role in optimizing biomaterial design, predicting organoid developmental trajectories, and streamlining preclinical drug discovery processes[11,20,41]. Moreover, integrating omics and computational methods (QSAR, AI/ML) with humanized in vitro co-culture models using biomaterials provides molecular insights for immunotoxicity and carcinogenicity assessments[102].

Finally, continuous innovation in biomaterials chemistry is indispensable, with a focus on developing novel materials with enhanced biofunctionalization, stimuli-responsiveness, and multi-dimensional engineering capabilities[8,55,103-105]. This includes exploring protein self-assembly strategies for fabricating multifunctional biomaterials and developing tricolor wavelength-selective photodegradable hydrogel systems for user-triggered therapeutic release and 4D spatiotemporal control over cell fates[103,104]. Additionally, the integration of advanced biomaterials with additive manufacturing technologies promises to revolutionize the production of dynamic, patient-specific constructs, reducing material waste and environmental footprint[105].

Conclusion

Biomaterials have emerged as indispensable components in the advancement of organoid research, fundamentally transforming our ability to engineer more physiologically relevant, reproducible, and functionally mature in vitro tissue models. This review has systematically highlighted the critical interplay between biomaterial design principles, their role in functional regulation, and their profound impact on the clinical translation of organoid technology.

In terms of design principles, the strategic selection of biomaterials, ranging from natural polymers like collagen, gelatin, hyaluronic acid, and decellularized ECM to synthetic polymers such as PCL, PLA, PEG, and bioorthogonally cross-linked hydrogels, is paramount. These materials are meticulously engineered to mimic the complex physicochemical and biological cues of the native extracellular matrix, providing essential structural support, cell adhesion sites, and biochemical signaling platforms[3,8,17,21]. Advanced fabrication techniques, including engineered hydrogel microspheres, 3D bioprinting, and microfluidic organ-on-a-chip systems, have further enabled the creation of intricate 3D architectures with precise spatial control, dynamic microenvironments, and enhanced scalability, addressing the limitations of traditional organoid culture methods[10,22,33].

The functional regulation of organoid development and maturation is profoundly influenced by the tunable properties of these biomaterials. Mechanical cues, such as matrix stiffness and topography, mediated by mechanomodulatory and mechano-responsive biomaterials, guide cell fate decisions and tissue organization, as demonstrated in studies on cancer organoids and kidney glomerulogenesis[42,47]. Biochemical signaling, facilitated by the controlled release of growth factors, extracellular vesicles, and bioactive molecules, or through the incorporation of ECM-mimicking peptides and specific inorganic materials like silicates, directs cell differentiation and enhances functional maturation, exemplified by oxygenated scaffolds for pancreatic islet organoids and BMOs[11,40,49,51]. Furthermore, the integration of electrical and other physical stimuli through electroactive biomaterials and flexible electronics, coupled with optogenetic tools, allows for precise control and monitoring of electrophysiological microenvironments, particularly crucial for neural organoids[52,56]. Surface chemistry and immunomodulatory properties of biomaterials also play a vital role in mediating cell adhesion, differentiation, and mitigating foreign body reactions, which are critical for long-term organoid viability and integration[46,58].

The clinical translation of biomaterial-enhanced organoids holds immense promise across diverse applications. In disease modeling, these platforms offer unparalleled fidelity for studying complex conditions like cancer, neurological disorders (e.g., Parkinson's, BBB formation), kidney disease, lung pathologies, and osteochondral defects, providing insights into pathogenesis and progression[48,66,78,82,84]. For drug discovery and precision medicine, organoids, especially patient-derived models integrated with microfluidic systems, serve as superior preclinical testing platforms, enabling high-throughput drug screening, personalized treatment optimization, and reducing reliance on animal models[33,34,69]. In regenerative medicine and tissue engineering, biomaterial-supported organoids are advancing towards tissue repair, reconstruction, and even transplantation, as evidenced by successful engraftment of cartilage and islet organoids in animal models, and the development of advanced biomaterial systems for bone and cartilage regeneration[90,95,96].

Despite these significant advancements, several research gaps and challenges remain. The lack of standardized protocols and inherent variability in organoid production continue to hinder widespread clinical adoption, necessitating further efforts in automation and quality control[1,2]. Achieving functional vascularization and long-term maturation within larger organoids remains a critical hurdle, although microfluidic and bioprinting strategies are making progress[35,38]. Integrating immune components and mitigating host immune responses for transplanted organoids are crucial for successful engraftment[58]. Furthermore, the complexity of multi-organ systems, the need for robust cryopreservation methods, and the establishment of comprehensive ethical and regulatory frameworks require continued attention[34,74,101].

Future directions in this rapidly evolving field will undoubtedly focus on several key areas. Continued innovation in biomaterials science will lead to the development of more sophisticated, stimuli-responsive, and multifunctional materials that can dynamically interact with organoids to guide complex developmental processes and therapeutic responses[55,104]. The integration of artificial intelligence and machine learning will be pivotal for optimizing biomaterial design, predicting organoid behavior, streamlining drug discovery, and enhancing the reproducibility and scalability of organoid production[25,94]. Advancements in biofabrication techniques, particularly 3D and 4D bioprinting, will enable the creation of increasingly complex and patient-specific tissue constructs, potentially leading to the biofabrication of entire functional organs[23,41]. Finally, the development of robust, vascularized, and immune-competent organoid-on-a-chip platforms will facilitate the creation of more accurate disease models and personalized drug screening tools, ultimately accelerating the translation of organoid research from the bench to the bedside, revolutionizing healthcare and improving patient outcomes.

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