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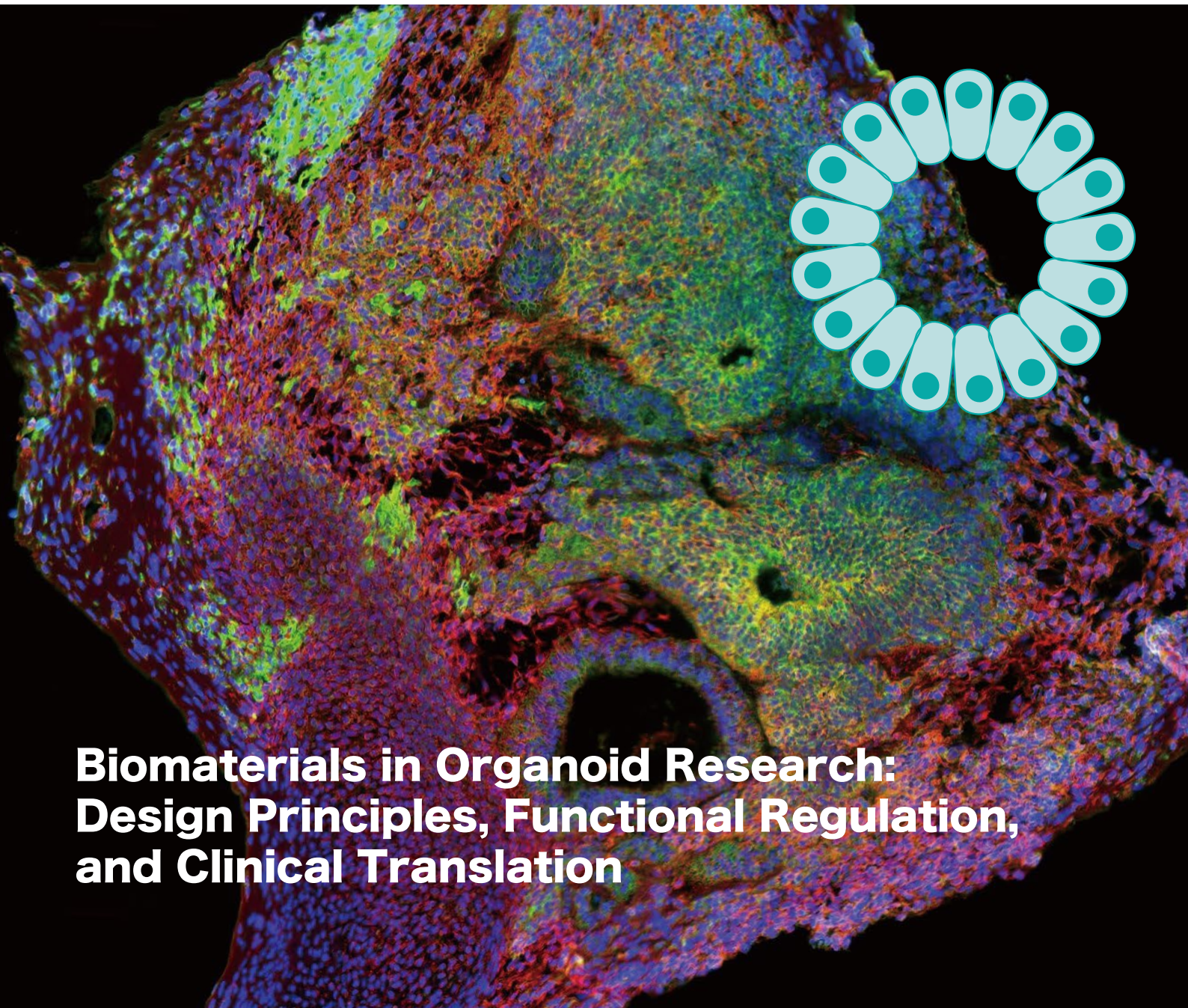

Biomaterials in Organoid Research: Design Principles, Functional Regulation, and Clinical Translation

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Review

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

Wenjing Gao[2], Baohua Zhong[2], Yuehua Xu[2], Zhiyuan Lan[1,2*]

[1] Institute of Biomaterials and Tissue Engineering, Huaqiao University, Xiamen, Fujian, China

[2] Xiamen Rekey Medical Technology Co., Ltd, Xiamen, Fujian, China

*Correspondence: zhiyuanlan@hqu.edu.cn (Zhiyuan Lan)

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).

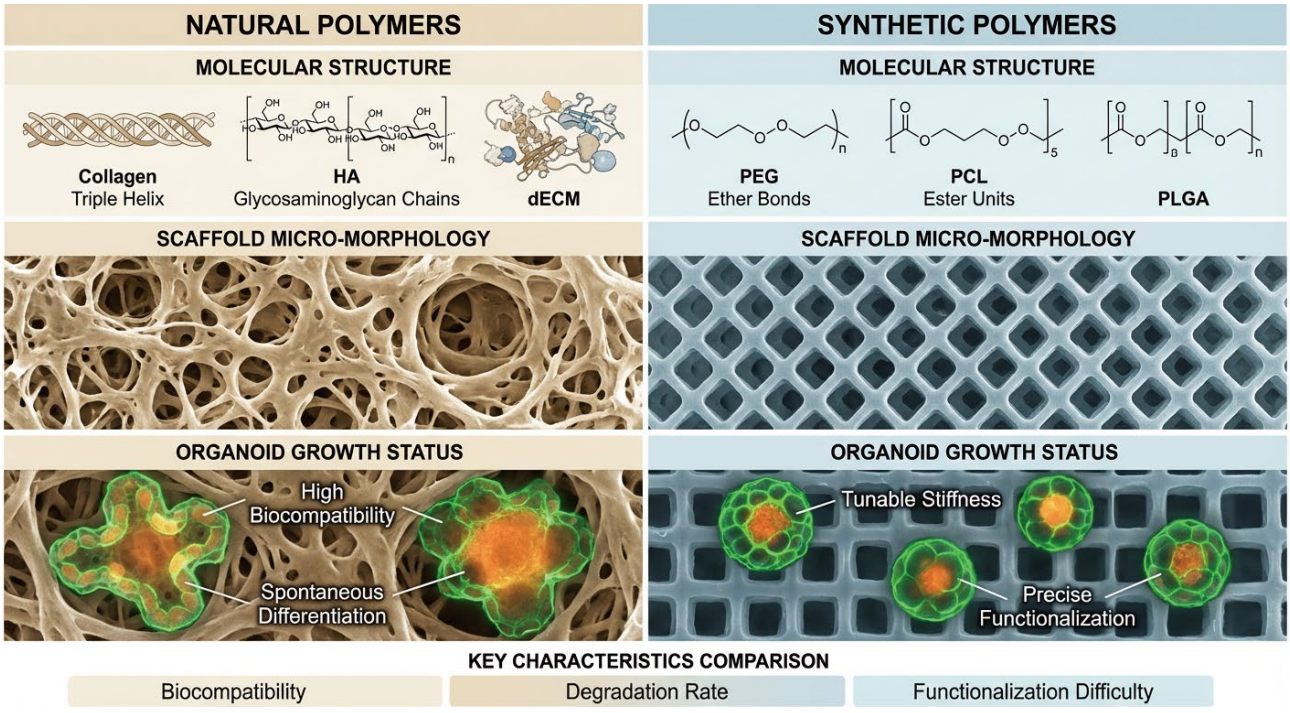


Figure 1. Comparison of natural and synthetic polymer-based organoid scaffolds.

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.

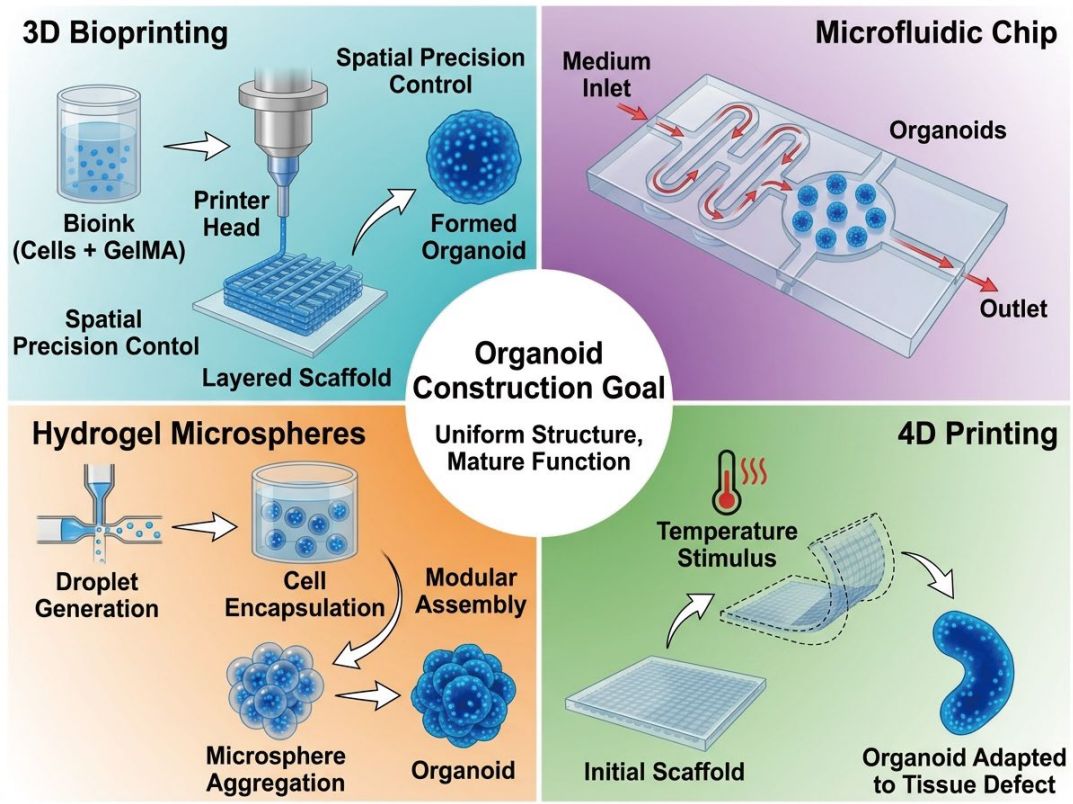


Figure 2. Integrated flowchart of advanced organoid fabrication techniques.

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].

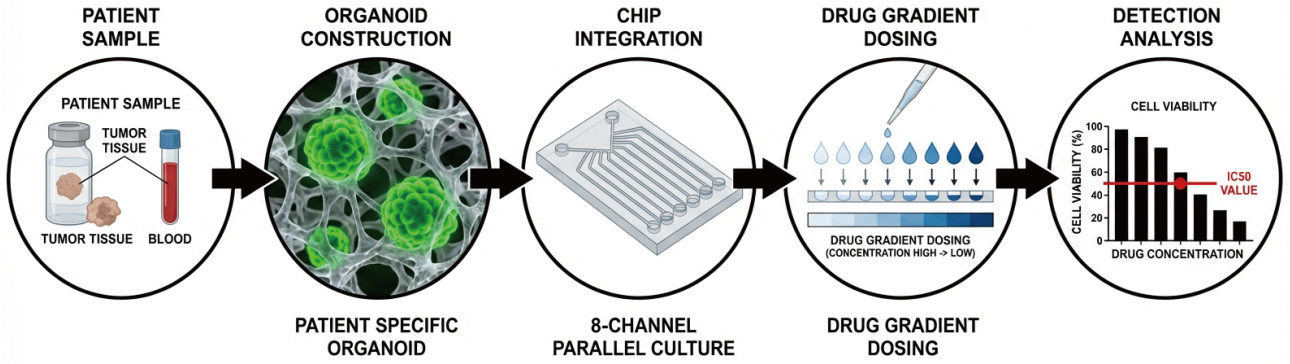
Understanding the skeletal microenvironment, including ECM components, mechanical cues, biochemical signaling, and cellular interactions, is indispensable for cellular behavior and tissue maturation in bone organoids. Recent advancements in biomaterial engineering and microstructural design have enabled 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

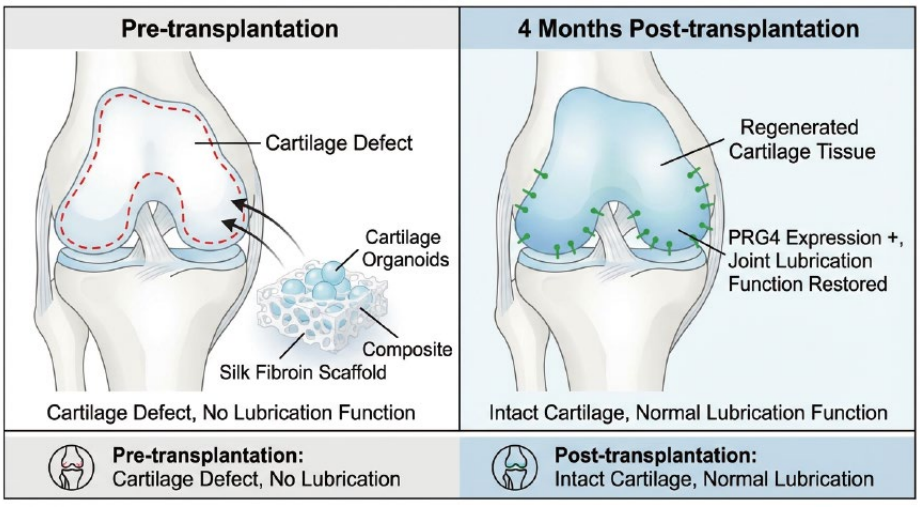


Figure 4. Schematic of cartilage organoid-biomaterial transplantation for repair.

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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Industry News

NIH Shift Away from Animal-Only Research Signals a Major Opportunity for Organoids

ISoOR Insight Team

*E-mail address: info@isoor.org

Abstract

In April 2025, the U.S. National Institutes of Health (NIH) announced a landmark shift that will reshape biomedical research for decades: the agency will no longer issue Notices of Funding Opportunities (NOFOs) that rely exclusively on animal models. Instead, all future funding calls must include—or explicitly permit—the use of non-animal methods (NAMs), including organoids, microphysiological systems, computational models, human-derived tissues, and advanced in vitro approaches. This policy, formalized at the first FDA-NIH "Workshop on Reducing Animal Testing" on July 7, 2025, marks an unprecedented reorientation of federal funding priorities toward human-relevant, ethical, and translationally predictive model systems. For the organoid field, the implications are vast: expanded funding, accelerated standardization, infrastructure scaling, enhanced regulatory relevance, and deeper integration into drug development and precision medicine. Yet the shift also presents scientific and practical challenges, including issues of reproducibility, biological complexity, and global regulatory acceptance. This article analyzes the motivations behind the NIH decision, its transformative significance for organoid science, the challenges ahead, and the role of standards such as ISoOR-ISOB and the newly funded Standardized Organoid Modeling (SOM) Center in shaping the next era of biomedical research.

Keywords

Organoids; New Approach Methodologies (NAMs); NIH policy; animal research reduction; microphysiological systems; FDA toxicology modernization; organoid biobanking; translational modeling; precision medicine; regulatory science.

1. Introduction

The April 29, 2025, announcement by the U.S. National Institutes of Health (NIH) that it will no longer solicit or fund new research proposals relying solely on animal models represents a turning point

in the history of biomedical science. Elaborated and formalized at the inaugural FDA-NIH "Workshop on Reducing Animal Testing" on July 7, 2025, this policy—championed by Acting NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives Dr. Nicole Kleinstreuer—has implications that extend far beyond administrative policy. It signals a profound reshaping of the scientific ecosystem, one that places human-relevant model systems such as organoids at the center of research innovation.

This decision reflects a longstanding recognition of two realities. First, animal models carry inherent ethical, logistical, and regulatory burdens. Second, and perhaps more importantly, animal models often fail to predict human outcomes reliably, particularly in oncology, immunology, neurology, toxicology, and emerging therapeutic modalities.

In this context, organoid technologies and other non-animal methods (NAMs) are no longer alternative or supplementary—they are becoming foundational to the future of biomedical discovery. As Dr. Kleinstreuer stated during the workshop, "All new NIH funding opportunities moving forward should incorporate language on consideration of NAMs... NIH will no longer seek proposals exclusively for animal models."

For organoid researchers, this policy shift is more than an endorsement; it is a structural repositioning that will accelerate adoption, standardization, and regulatory integration. It marks a new chapter in which organoids are poised to move from innovative niche tools to mainstream pillars of biomedical science. With the NIH committing to prioritize human-focused approaches across its $47 billion annual budget, organoid-centric proposals stand to gain a competitive edge, potentially unlocking billions in funding for scalable, reproducible models that better mirror human biology.

2. The Policy Shift: What NIH Actually Changed

2.1 End of Animal-Only Research Solicitations

Under the new NIH framework, as of July 2025:

- No Notice of Funding Opportunity (NOFO) may mandate exclusively animalbased research.
- Investigators are required to justify their model selection scientifically, rather than defaulting to historical norms such as rodent or primate models.
- This requirement is not merely bureaucratic; it represents a deep rethinking of the assumptions underpinning decades of preclinical and translational research practice.

The policy builds on the NIH's April 29, 2025, initiative to prioritize human-based research technologies, ensuring that all NOFOs related to animal model systems also support human-focused approaches like clinical trials, real-world data, or NAMs. NOFOs excluding animal use entirely may also be issued, allowing institutes to tailor calls to emerging priorities. As Dr. Kleinstreuer emphasized at the July 7 workshop, "The intent is to ensure investigators consider the models most appropriate for understanding human states of health and disease and are not constrained by the NOFO."

2.2 Inclusion and Encouragement of NAMs

All future NOFOs must include language that encourages the use of NAMs such as:

- Organoids and organ-on-chip systems
- Tissue-derived human in vitro models
- Computational/AI-based biological modeling
- Real-world human data
- Advanced microphysiological systems

By embedding NAMs directly into funding language, NIH is signaling institutional commitment to human-based model systems across the research pipeline. Examples of NAMs explicitly highlighted include ex vivo human-based approaches like perfused organs and precision-cut tissue slices, alongside in vitro methods such as organoids and computational tools. This shift is projected to redirect a significant portion of the NIH's extramural research budget—historically over $20 billion annually—toward proposals incorporating these technologies, fostering innovation while addressing the 90% failure rate of preclinical candidates in human trials.

2.3 Establishment of ORIVA and Agency-Wide Coordination

NIH will establish the Office of Research Innovation, Validation, and Application (ORIVA), a centralized effort aimed at the development, benchmarking, validation, and dissemination of NAMs. Its responsibilities include:

- Creating validation frameworks
- Coordinating inter-institute efforts
- Supporting scale-up of human-based models
- Facilitating interactions with regulatory agencies

As proposed in the April 29 announcement and elaborated at the July 7 workshop, ORIVA will formalize NIH's commitment to NAM integration, partnering with the FDA and other agencies to streamline validation processes. Complementing ORIVA, the September 25, 2025, award of $87 million in contracts for the Standardized Organoid Modeling (SOM) Center—housed at the Frederick National Laboratory for Cancer Research (FNLCR) under the National Cancer Institute (NCI)—will develop reproducible organoid protocols using AI and robotics, initially focusing on liver, lung, heart, and intestine models, with expansion to brain and thymus systems. Together, these reforms demonstrate NIH's commitment to transforming the research infrastructure—not just revising its policies—ensuring affordable, open-access protocols under FAIR principles for NIH-funded researchers nationwide.

3. Why the Policy Matters: Ethical, Scientific, and Translational Drivers

3.1 Ethical and Regulatory Pressures

Animal research has long been challenged by ethical concerns, heightened regulatory scrutiny, and increasing public expectations for humane science. The use of nonhuman primates, in particular, has faced growing legal, societal, and economic pressure. By encouraging alternatives, NIH aligns itself with global scientific and ethical momentum. Aligning with FDA's April 10, 2025, phase-out of mandatory primate testing for monoclonal antibodies—further detailed in the December 2, 2025, draft guidance on waiving six-month non-human primate (NHP) toxicity studies for monospecific antibodies—this policy reduces the ethical burden of using over 100 NHPs per typical monoclonal antibody program, at costs exceeding $50,000 per animal.

3.2 Scientific Limitations of Animal Models

Animal models often fail to:

- Reflect human tumor microenvironments
- Model complex neurological disorders
- Capture patient-specific heterogeneity
- Recapitulate human immune responses
- Predict human toxicity or drug metabolism

These shortcomings have contributed to high attrition rates in drug development and have driven researchers toward human-derived model systems, particularly organoids. Up to 90% of drugs succeeding in animals fail in humans, as highlighted by FDA workshop discussions in July 2025. Efficacy and safety issues account for 52% and 24% of Phase II/III failures, respectively, underscoring the translational gap.

3.3 NAMs as Scientifically Superior Alternatives

By formalizing support for NAMs, NIH acknowledges the increasing evidence that organoids, tissue chips, and human-derived in vitro models offer:

- Greater mechanistic fidelity
- Enhanced translational predictiveness
- Relevance to patient-specific biology
- Capacity for high-throughput drug screening
- Potential to reduce ethical burdens

This scientific reasoning underpins the shift as much as ethical considerations, with NAMs projected to cut preclinical costs by up to 30% while improving success rates.

4. Implications for Organoid Research

The NIH policy shift opens a new frontier for organoid science.

4.1 Expansion of Funding Opportunities

Organoid-based proposals are likely to:

- Gain a competitive advantage
- Receive increased funding allocation
- Attract multi-institute initiatives
- Integrate more deeply into clinical and translational pipelines

Fields likely to see the greatest growth include oncology, toxicology, developmental biology, precision medicine, and immunology. With NIH's $47 billion budget, organoid projects could capture 10–15% more extramural funds by 2027, especially through targeted NOFOs like those under ORIVA.

4.2 Infrastructure and Standardization

A major bottleneck for organoids is inconsistency across laboratories. The NIHfunded Standardized Organoid Modeling (SOM) Center is positioned to address this by:

- Developing standardized protocols
- Establishing national biobanking infrastructure
- Creating reproducibility frameworks
- Supporting cross-laboratory quality control
- Facilitating data governance and metadata standards

Awarded $87 million on September 25, 2025, and housed at the Frederick National Laboratory for Cancer Research (FNLCR) under NCI, SOM will use AI and robotics for real-time protocol optimization, starting with liver, lung, heart, and intestine models before expanding to brain and thymus. Open-access under FAIR principles, it ensures minimal-cost access for NIH-funded researchers, aligning with FDA for regulatory validation. This infrastructure will enable scalable production and data sharing, addressing reproducibility gaps that currently affect 40–60% of organoid studies.

4.3 Enhancing Interdisciplinary Collaboration

The organoid field increasingly intersects with:

- Bioengineering
- Single-cell and spatial omics
- Machine learning

- Immunology and oncology
- Regulatory science

NIH's new policy encourages these interdisciplinary collaborations by placing NAMs at the forefront of federal funding, with ORIVA coordinating cross-institute efforts and SOM integrating AI for protocol refinement.

5. Regulatory and Translational Impact

The NIH announcement aligns with recent FDA toxicology modernization decisions, including the April 10, 2025, phase-out of mandatory primate testing for monoclonal antibodies and the December 2, 2025, draft guidance waiving six-month NHP toxicity studies for monospecific antibodies (using three-month data from NHPs, dogs, or mini-pigs supplemented by weight-of-evidence assessments). The July 7 workshop committed to publishing NAM "use cases" for IND/BLA submissions, potentially integrating organoid data into safety assessments.

Together, NIH and FDA reforms may transform:

- IND submission expectations
- Preclinical safety assessment
- Mechanistic toxicology
- Early-phase drug development strategies

In the future, organoid-derived data may become an expected component of translational pipelines, rather than an optional supplement, reducing the 90% preclinical-to-clinical attrition rate.

6. Challenges, Limitations, and Scientific Realities

Despite the optimism, experts warn of several challenges.

6.1 Biological Complexity

Organoids still lack:

- Fully functional vasculature
- Mature immune components
- Endocrine cross-talk
- Systemic metabolic interactions

For certain studies—particularly systemic toxicology—animal systems currently offer capabilities that NAMs cannot yet match. As noted by experts at the July 2025 workshop, NAMs like organoids are "very premature" for complex multi-system studies (e.g., Eliza Bliss-Moreau, UC Davis: "too simplistic for multi-system toxicology").

6.2 Reproducibility and Standardization Gaps

Variability in:

- Culture conditions
- Donor tissue quality
- Differentiation protocols
- Analytical methods

can significantly affect reproducibility. Without coordinated standards, organoid data may be difficult to compare across institutions. FASEB's July 14, 2025, comments urged greater transparency in NOFO implementation to address these gaps.

6.3 Regulatory Pathways Still Evolving

Regulators worldwide are cautious. Many jurisdictions still require animal data for:

- Long-term toxicity
- Pharmacokinetics
- Developmental and reproductive toxicology

Thus, organoids must undergo rigorous validation before obtaining universal regulatory acceptance. The FDA's December 2 draft guidance represents progress but applies only to monospecific mAbs, leaving broader scopes for future action.

7. The Role of ISoOR, ISOB, and Global Standardization

International collaboration is essential. Organizations such as:

- ISoOR
  (International Society of Organoid Research)
- ISoOR-ISOB
  (International Standards for Organoid Biobanking)

are creating standards for:

- Culture reproducibility
- Biobanking and cryopreservation
- Data annotation
- Cross-lab comparability
- Regulatory-ready documentation

ISoOR's September 12, 2025, ILAC Stakeholder status enhances this effort, providing access to global accreditation networks for ISO/IEC 17011 alignment and future MRA recognition. ISoOR-ISOB, building on ISO 20387 with pilot validations, ensures organoid data meets reproducibility thresholds critical for NIH/FDA integration.

These frameworks will be critical to ensuring that organoids move from research tools to validated preclinical systems, bridging the translational gap that contributes to 90% of drug failures.

8. Implications for Cancer Research and Precision Oncology

Oncology stands to benefit immensely. Organoids offer:

- Patient-specific tumor modeling
- Accurate representation of tumor heterogeneity
- Co-culture with immune cells and stroma
- Real-time drug sensitivity profiling
- Analysis of resistance mechanisms
- Exploration of rare cancer subtypes

Given the high failure rate of oncology drugs in clinical trials—up to 95% attrition from preclinical to Phase III, with animal models succeeding in only 8% of cases that reach humans—NIH's new funding environment may accelerate the integration of patient-derived tumor organoids (PDTOs) into precision oncology workflows. Supported by NCI's leadership in the SOM Center for tumor microenvironment modeling, PDTOs could reduce oncology's 52% efficacy failure rate by enabling personalized screening before trials.

9. A Call to Action for the Organoid Community

To seize the opportunity, the field must:

1.Expand organoid infrastructure through biobanks, automation, quality control, and scalable production.

2.Strengthen interdisciplinary collaboration to integrate organoids with computational, engineering, and clinical frameworks.

3.Develop and adopt global standards to support reproducibility and regulatory acceptance.

4.Engage regulators early to co-design validation and qualification pathways.

5.Acknowledge limitations transparently and use complementary models where necessary.

This shift demands leadership, coordination, and scientific rigor. With SOM's $87 million investment and ORIVA's coordination, the community has unprecedented resources to act.

10. Conclusion

The NIH's decision to eliminate animal-only research solicitations and elevate NAMs marks an inflection point in biomedical science. It reflects an evolving understanding that human-relevant, ethical, and mechanistically faithful models—especially organoids—are essential to advancing translational research. The April 29 announcement, workshop formalization, ORIVA proposal, and SOM Center award collectively redirect resources toward innovation, addressing the 90% preclinical failure rate that has plagued drug development.

For the organoid field, the implications are transformative. With increased funding, strengthened infrastructure, deeper regulatory engagement, and global standardization initiatives like ISoOR-ISOB, organoids are now positioned to become a cornerstone of 21st-century biomedical research. The transition will be complex, but the opportunity is unparalleled. As organoids become more physiologically integrated—incorporating vasculature, immune components, multi-organ interactions, and computational modeling—their capacity to replace or complement animal models will only grow.

The age of organoid-centered biomedical innovation has begun, and the NIH's 2025 policy shift marks the official start of this new scientific era.

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Industry News & Perspectives

ISoOR Gains ILAC Stakeholder Status: Advancing Global Standards in Organoid Biobanking

ISoOR Insight Team

*E-mail address: info@isoor.org

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The International Society of Organoid Research (ISoOR) has strengthened its role in shaping global standards for organoid biobanking. On September 12, 2025, ISoOR was formally accepted as a Stakeholder member of the International Laboratory Accreditation Cooperation (ILAC), the world's leading authority on laboratory and inspection-body accreditation. Achieved just six months after the launch of the ISoOR-ISOB International Standard for Organoid Biobanking at the society's March 2025 congress in Shanghai, this membership provides ISoOR with a platform to contribute to international accreditation discussions, align its standards with globally recognized frameworks, and support the long-term goal of establishing organoid biobanking as a robust, reproducible, and trusted platform for clinical and commercial applications.

Organoids - self-organizing, three-dimensional structures derived from stem cells that recapitulate the architecture and function of human organs - have transformed disease modeling, drug screening,and regenerative medicine. Yet their widespread adoption has been limited by the absence of universally accepted biobanking and qualitycontrol standards. ISoOR's entry into ILAC directly addresses this gap by aligning the field with the same rigorous accreditation framework that underpins confidence in millions of laboratory results worldwide every day.

The Origins and Evolution of ILAC: From 1977 Vision to 2025 Global Authority The International Laboratory Accreditation Cooperation traces its roots to a pivotal conference held in Copenhagen, Denmark, from October 24–28, 1977. At that time, rapid growth in international trade exposed a critical problem: differing national calibration and testing standards forced exporters to undergo costly, redundant assessments in every market. Representatives from 15 countries gathered to advocate for mutual recognition of accredited test results, laying the philosophical and practical foundation for what would become ILAC.

In 1996, ILAC transitioned from an informal network into a formal international cooperation with a charter focused on peer evaluation and harmonized accreditation practices. The defining moment arrived on January 31, 2001, when 36 accreditation bodies from 28 economies signed the inaugural ILAC Mutual Recognition Arrangement (MRA) in Washington, D.C. This multilateral agreement created the principle of "accredited once, accepted everywhere."

The MRA has since expanded in scope and depth:

- October 2012 – inclusion of inspection bodies (ISO/IEC 17020)
- May 2019 – proficiency testing providers (ISO/IEC 17043)
- May 2020 – reference material producers (ISO 17034)

As of November 2025, the ILAC MRA comprises 121 signatories from 122 economies, covering more than 114,600 accredited laboratories, 15,600 inspection bodies, 700 proficiency testing providers, and 300 reference material producers. The arrangement directly supports World Trade Organization (WTO) objectives by eliminating technical barriers to trade and is recognized by regulators in fields ranging from food safety and environmental monitoring to medical diagnostics and advanced therapeutics.

Importantly, ILAC itself does not accredit laboratories or conformity assessment bodies (CABs). That responsibility lies with its Full Member accreditation bodies, which operate under the peer-evaluated discipline of the MRA. National or regional bodies (e.g., UKAS in the UK, A2LA in the US, SAC in Singapore) perform the actual accreditations, while ILAC ensures their competence through rigorous evaluation against ISO/IEC 17011 and supplementary requirements.

ISoOR's Strategic Roadmap Toward Global Alignment

ISoOR is actively working to align its organoid biobanking standards with international accreditation frameworks. In March 2025, the society unveiled ISoORISOB – the world's first dedicated international standard for organoid biobanking – which builds on ISO 20387:2019 (general biobanking) and addresses organoidspecific challenges, including long-term viability, genetic fidelity, phenotypic stability, ethical provenance, and data interoperability.

To guide its long-term development toward potential regional and international recognition, ISoOR has outlined a **multi-year roadmap**, which includes:

1.Internalization of ISO/IEC 17011 requirements

conducting a gap analysis focused on impartiality, conflict-of-interest mitigation, and structural separation of commercial and accreditation functions.

2.Deployment of a Quality Management System (QMS)

developing publicly available documentation, appointing an independent Quality Manager, and establishing governance structures to ensure accreditation decisions are insulated from revenue-generating activities.

3.Legal and governance restructuring

updating statutes, financial safeguards, and governance policies to reinforce impartiality and transparency.

4.Operational rollout of the ISoOR-ISOB accreditation scheme

piloting processes for assessor training, surveillance, complaints, and appeals.

5.Engagement with Asia Pacific Accreditation Cooperation (APAC) and ILAC

submission of relevant documentation and standards for feedback and alignment; ILAC Stakeholder membership, achieved in September 2025, marks an initial step in this ongoing process.

6.Commitment to continuous improvement

implementing regular audits, stakeholder workshops, and transparent reporting to refine processes over time.

Each of these steps is part of a **long-term initiative**; full international recognition and potential accreditation remain future objectives. ILAC Stakeholder membership provides ISoOR with a platform for early participation in global accreditation discussions and alignment with best practices, supporting the society's ongoing development.

Understanding ILAC Membership Categories and the Path to MRA Signatory Status

ILAC membership is structured in four categories (full criteria: https://ilac.org/ilacmembership/membership-criteria/):

- Stakeholder (ISoOR's current status): For international, regional, or national organizations with legitimate interests in accreditation (e.g., laboratory associations, regulators, industry bodies). No peer evaluation required; application via email to the ILAC Secretariat.
- Associate: Developing accreditation bodies operating schemes and demonstrating conformity with relevant standards.
- Full Member (MRA Signatory): Mature accreditation bodies successfully peer-evaluated against ISO/IEC 17011 and capable of accrediting CABs to ISO/IEC 17025, 15189, 17020, 17043, and/or 17034.
- Recognised Regional Cooperation Bodies (e.g., APAC, EA, IAAC): Regional groups whose own MRAs are evaluated and recognized by ILAC.

Acceptance as a Full Member and MRA signatory is contingent on a rigorous peer evaluation process conducted by senior staff from established accreditation bodies. Evaluations include:

- Headquarters office assessment for ISO/IEC 17011 conformity
- Witnessing of the applicant body's assessors performing actual accreditations at CAB sites
- Verification that accredited CABs meet the relevant technical standards with sufficient depth

Regional bodies such as APAC typically conduct these evaluations under delegated ILAC authority, although direct ILAC evaluation is available for bodies without regional affiliation.

The Peer Evaluation Process: Ensuring Global Confidence The ILAC MRA's credibility rests on an intensive, transparent evaluation cycle governed by publications such as IAF/ILAC A-series documents. Key commitments of every MRA signatory include:

- Maintenance of conformity with the current version of ISO/IEC 17011 and supplementary requirements
- Accreditation of laboratories to ISO/IEC 17025 and/or ISO 15189
- Accreditation of inspection bodies to ISO/IEC 17020
- Accreditation of proficiency testing providers to ISO/IEC 17043

- Accreditation of reference material producers to ISO 17034
- Immediate notification to peers of significant changes (name, legal status, key personnel, scope, etc.)
- Designation of a liaison officer for consistent communication

Annual reports and four-year re-evaluations ensure ongoing compliance, preserving the phrase "accredited once, accepted everywhere."

Stakeholder members like ISoOR play a vital complementary role

Shaping standards, providing technical input, and preparing the ground for future accreditation schemes (such as ISoOR-ISOB-based organoid biobank accreditation) that can eventually be operated by Full Member bodies under the ILAC MRA umbrella.

Looking Forward: From Stakeholder to Potential Accreditation Body ISoOR's Stakeholder membership is explicitly the first phase of a longer-term vision: to evolve into a recognized accreditation body for organoid biobanking worldwide. With ISoOR-ISOB already adopted by leading institutions and the society's governance now demonstrably ISO/IEC 17011-aligned, the path toward Associate and ultimately Full Member status within APAC and ILAC is clearly mapped.

When that milestone is reached, an organoid biobank accredited under the ISoORISOB scheme by an ILAC MRA signatory will carry the same international weight as any ISO/IEC 17025-accredited testing laboratory – a transformative prospect for drug developers, regulators, and clinicians relying on organoid data.

As ILAC prepares its own transition to the Global Accreditation Cooperation in 2026, the inclusion of a forward-looking organization like ISoOR illustrates how accreditation infrastructure is adapting to the next generation of biomedical technologies. For the organoid community, September 12, 2025, will be remembered as the day the field formally entered the global accreditation ecosystem.

The ILAC-IAF Merger: Birth of the Global Accreditation Cooperation and Its Implications for ISoOR

In a parallel development that amplifies the timing and strategic value of ISoOR's ILAC Stakeholder status, the accreditation landscape is undergoing its most profound structural change in decades. On October 24, 2024, following unanimous approval at their respective annual meetings in Vancouver, **the International Accreditation Forum (IAF)** and ILAC formally initiated the merger process, culminating in the incorporation of the **Global Accreditation Cooperation Incorporated (GAC)** as a legal entity in New Zealand. Provisionally set to become operational on January 1, 2026, the GAC represents the fusion of IAF – the global association for certification body accreditation since 1993 – and ILAC, creating a unified, single international organization overseeing all aspects of conformity assessment accreditation.

This merger, years in the making, addresses longstanding fragmentation in the global accreditation ecosystem. IAF has historically focused on management systems, product certification, and personnel certification (e.g., ISO/IEC 17021 for management systems certification bodies), while ILAC has specialized in laboratory, inspection, proficiency testing, and reference material accreditation. The resulting GAC will integrate the **IAF Multilateral Recognition Arrangement (MLA)** and ILAC MRA into a single

GAC Mutual Recognition Arrangement (MRA), streamlining peer evaluation, signatory status, and global acceptance of accredited results across all scopes. As outlined in the joint IAF/ILAC Constitution and General Rules approved in 2024, the GAC aims to enhance efficiency, reduce duplication, and strengthen advocacy for accreditation's role in sustainable development goals, WTO compliance, and emerging technologies like biotechnology.

The relevance of this merger to the broader accreditation community cannot be overstated. By consolidating operations, GAC will foster a more cohesive voice in international forums, such as the WTO Technical Barriers to Trade Committee and ISO technical committees. It promises operational synergies: unified peer evaluations, shared resources for digital transformation (e.g., traceability in analytical chemistry via CITAC), and a single MRA Mark to replace the IAF MLA and ILAC MRA logos by 2029. Regulators and specifiers are encouraged to update references to "ILAC/IAF accreditation" with "GAC accreditation" post-transition, ensuring seamless continuity. The provisional January 2026 launch date allows for a phased handover, with both organizations continuing parallel operations through 2025 to minimize disruption.

For ISoOR, the merger is strategically timely. As a new ILAC Stakeholder, the society enters the accreditation ecosystem at a moment of structural renewal, positioning itself to participate in and benefit from GAC's unified framework.

The merger may influence ISoOR in several ways:

- **Enhanced global advocacy:** GAC's unified platform amplifies Stakeholder voices like ISoOR's in shaping future standards, including potential extensions to biotech-specific scopes (e.g., ISO/TC 276 for biotechnology). ISoOR could contribute to initiatives such as digital traceability for organoid data, aligning with GAC's focus on emerging risks like AI-driven lab automation.

- **Early engagement in a consolidated accreditation ecosystem:** Being part of GAC's Stakeholder network allows ISoOR to observe, participate, and align its organoid biobanking standards with global best practices, positioning the society for future regional or international recognition.

While these developments are prospective, the merger provides ISoOR with an early opportunity to engage with a consolidated global accreditation framework, helping to inform its ongoing development of organoid biobanking standards and eventual alignment with regional and international accreditation practices.

Overall, the ILAC-IAF fusion via GAC is a boon for ISoOR, transforming its timely Stakeholder entry into a launchpad for leadership in biotech accreditation. By embedding organoid standards into a unified global MRA, ISoOR not only safeguards the field's reproducibility but also positions it as a pillar of the next accreditation era – one where miniature organs inform therapies trusted across borders.

Conclusion

ISoOR's acceptance as an ILAC Stakeholder represents a strategic milestone inthe society's long-term plan to advance global standards for organoid biobanking. While this membership does not confer accreditation authority, it provides a platform for engagement with the international accreditation ecosystem and alignment with best practices. Looking ahead, ISoOR's transition into a recognized accreditation body seeks to eventually achieve MRA signatory status, positioning organoid biobank accreditation for international recognition, reproducibility, and trust in clinical and research applications.

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Industry News & Perspectives

Genmab Acquires Merus for $8 Billion: The First Organoid-Discovered Clinical Asset Drives the Largest European Oncology Deal of 2025

ISoOR Insight Team

*E-mail address: info@isoor.org

COPENHAGEN & UTRECHT – September 29, 2025 – In the largest European oncology acquisition of 2025, Genmab A/S (Nasdaq: GMAB) has agreed to acquire Merus N.V. (Nasdaq: MRUS) for approximately $8 billion in cash, or $97.00 per share. The transaction instantly delivers full ownership of petosemtamab (MCLA-158), a first-in-class EGFR × LGR5 bispecific antibody that represents a historic milestone: it is the first therapeutic candidate discovered, prioritized, and advanced into Phase III clinical trials exclusively through patient-derived organoid (PDO) screening. With two FDA Breakthrough Therapy Designations already secured and Phase III trials actively enrolling globally, petosemtamab has rapidly emerged as one of the most promising investigational therapies in head-and-neck squamous cell carcinoma (HNSCC) and is projected to achieve multibillion-dollar peak sales. Breakthrough Therapy Designation is granted to expedite the development and review of drugs that show substantial improvement over existing therapies for serious conditions.

The $97.00 per-share offer carries a 41% premium to Merus' closing price of $68.89 on September 26, 2025, and a 44% premium over the 30-day volume-weighted average price of $67.42. Genmab will finance the deal through a combination of approximately $5.5 billion in newly issued non-convertible senior unsecured notes and existing cash reserves, eliminating any financing contingency. The tender offer is scheduled to commence in October 2025, with closing anticipated in the first quarter of 2026, subject to customary antitrust clearances and acceptance by at least 80% of outstanding shares (potentially reducible to 75% under Dutch law provisions).

Genmab Chief Executive Officer Jan van de Winkel described the acquisition as "a transformational step that instantly establishes a robust, wholly owned late-stage pipeline and accelerates our evolution into a fully integrated oncology company capable of delivering multiple innovative medicines this decade." Merus Chief Executive Officer Bill Lundberg emphasized the strategic and cultural alignment, noting that both organizations have pioneered Biclonics® and common-light-chain bispecific antibody technologies for over fifteen

years and share an unwavering commitment to precision oncology driven by deep biological insight.

Petosemtamab (MCLA-158): From Organoid Screen to Phase III in Under a Decade

Petosemtamab is a full-length human IgG1 bispecific antibody that simultaneously binds extracellular domains of EGFR and LGR5. LGR5, a Wnt pathway co-receptor and established marker of adult stem cells, is selectively overexpressed on cancer stem cells in colorectal, head-and-neck, esophageal, gastric, and certain lung adenocarcinomas. By co-engaging both targets, petosemtamab triggers potent internalization and lysosomal degradation of EGFR specifically on LGR5-positive malignant cells, thereby blocking two orthogonal survival pathways (independent signaling mechanisms that promote cancer cell survival; dual targeting reduces the risk of compensatory resistance mechanisms) while sparing healthy LGR5-positive stem cells in the intestine and skin – a critical differentiation from conventional EGFR inhibitors that cause dose-limiting rash and diarrhea.

The molecule originated in 2015 from a multi-year collaboration between Merus and the Institute for Research in Biomedicine (IRB Barcelona), led by Eduard Batlle. The team had established one of the world's largest living biobanks comprising more than 150 colorectal and head-and-neck cancer PDO lines that faithfully preserved tumor heterogeneity, stem cell hierarchy, and metastatic potential. Rather than screening candidates in immortalized 2D cell lines or xenografts, Merus applied high- throughput functional testing directly on three-dimensional PDOs, evaluating both tumor-killing potency and selectivity against matched healthy organoids from the same patients. From hundreds of Biclonics® candidates, MCLA-158 was selected as the sole molecule that eradicated LGR5-high tumor spheres while completely sparing normal intestinal crypt organoids – a selectivity profile that preclinical mouse models had failed to predict for prior EGFR-targeted therapies.

Preclinical validation, published in *Nature Cancer* in 2022, demonstrated that petosemtamab completely blocked organoid initiation from residual LGR5+ cells after chemotherapy, prevented liver and lung metastasis in orthotopic PDO-xenograft models, and synergized with PD-1 blockade. These findings translated rapidly into the clinic. Updated Phase 1/2 results presented at ASCForename 2025 showed a 63% confirmed objective response rate and >90% clinical benefit rate when petosemtamab was combined with pembrolizumab in first-line PD-L1-positive recurrent/metastatic HNSCC (n=43). As monotherapy in later lines, durable responses were observed in 37- 40% of cetuximab- and checkpoint-refractory patients, with median duration of response exceeding six months and a manageable safety profile dominated by infusion-related reactions largely confined to the first dose.

The strength and consistency of these data prompted the FDA to grant Breakthrough Therapy Designation twice in 2025 – first for the first-line combination and subsequently for second-line and beyond monotherapy – paving the way for accelerated development and review. Two pivotal Phase III trials are now underway (Table 1).

Table 1. Ongoing Phase III trials of petosemtamab

Trial	Indication	Design	Primary Endpoints	Target Enrollment
PETTONC-1	1L PD-L1+r/m HNSCC	Petosemtamab + pembrolizumab vs. pembrolizumab + platinum/5-FU	ORR, PFS	>400
PETTONC-2	2L/3L HNSCC	Petosemtamab monotherapy vs. investigator's choice	ORR, OS	>300

Top-line readouts are expected in 2026, positioning petosemtamab for potential regulatory submissions in 2027 and first commercial launch in 2027–2028 across multiple indications.

Why Organoids Proved Decisive in De-Risking the Program

Traditional discovery paradigms that rely on engineered cell lines or patient-derived xenografts routinely overestimate efficacy and underestimate toxicity because they fail to recapitulate native stem cell niches and tumor–stroma interactions. The Merus–IRB Barcelona PDO platform circumvented these limitations by preserving the exact cellular hierarchy and mutational landscape of individual patients. Screening in matched tumor-versus-normal organoids provided an unprecedented early readout of therapeutic window, eliminating dozens of otherwise promising EGFR-targeted molecules that proved toxic to healthy tissue. This rigorous human-first selection process is widely credited with petosemtamab's remarkably clean safety profile and high response rates in molecularly unselected, real-world populations – outcomes that have historically eluded the EGFR class, and demonstrates the potential of PDOs to reduce attrition in oncology drug development by several years.

Broader Industry Validation and Perfect Regulatory Timing

The acquisition occurred just four days after the NIH officially launched the Standardized Organoid Modeling (SOM) Center at the Frederick National Laboratory on September 25, 2025, with an initial $87 million commitment to develop reproducible, regulatory-grade organoid standards for major organ systems. The SOM Center directly implements NIH directive NOT-OD-26-004 (July 2025), which mandates prioritization of human-based New Approach Methodologies over animal testing, and dovetails with the FDA Modernization Act 2.0 framework that now explicitly accepts organoids and microphysiological systems as standalone nonclinical evidence packages. Regulatory frameworks are increasingly recognizing human-based models such as organoids as valid nonclinical evidence, with the FDA actively supporting the use of New Approach Methodologies (NAMs) to reduce reliance on animal testing, which may set new precedents for global clinical trial design, particularly in oncology [FDA, 2025; Zushin et al., 2023].

Genmab's decision to pay an $8 billion premium for a pipeline anchored by an organoid-originated asset sends an unequivocal message: large-cap biopharma now views mature organoid platforms as commercially derisked engines capable of delivering blockbuster oncology medicines faster, more predictively, and more ethically than legacy preclinical models.

Financial and Strategic Implications

Wall Street analysts currently project peak annual sales for petosemtamab in excess of $4 – 6 billion across HNSCC, colorectal, and esophageal indications, with significant additional upside from earlier lines and combination regimens. The

transaction also adds three earlier-stage wholly owned programs (MCLA-145, MCLA-129, MCLA-138), instantly expanding Genmab's late-stage portfolio from two partnered assets to seven wholly owned or co-commercialized programs. The deal is expected to be accretive to EBITDA by 2029 and reinforces the resurgence of high-value oncology M&A following a prolonged drought.

Future Outlook

When petosemtamab reaches the market – potentially as early as 2027 – it will mark the first blockbuster oncology therapy whose discovery, candidate selection, and preclinical validation were driven end-to-end by living human organoid models. This precedent is poised to catalyze massive investment into next-generation organoid biobanks, vascularized and immune-competent systems, multi-organ chips, and AIaugmented phenotypic screening. For organoid researchers worldwide, the Genmab–Merus transaction validates PDO biobanks as indispensable tools for the design of tomorrow's precision medicines.

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Industry News

Development of Patient-Derived Organoids from NUT Carcinoma: A Robust and Fully Documented Culture System

Mingzhu Yin[1]*, Chongyang Shen[1], Minghui Zhang[1], Xin Li[1], Zhuomiao Ye[1], LiangDong[1], Jun Fu[1]

[1] Clinical Research Center, Medical Pathology Center, Cancer Early Detection and Treatment Center, and Translational Medicine Research Center,Chongqing University Three Gorges Hospital, Chongqing, China

*Correspondence: mingzhu.yin@cqsyhospital.cn

Approved for compliance with the ISoOR-ISOB International Standard by the ISoOR-ISOB Technical Committee (March 2025 release)

Abstract

NUT carcinoma is an aggressive, poorly differentiated malignancy defined by NUTM1 rearrangements. Median survival remains 6–7 months and preclinical models are essentially nonexistent. Here we report the first patient-derived organoid platform for this disease. Starting material included resected tumors, pleural effusions, CTguided fine-needle aspirates, and transbronchial biopsies. Using a defined medium supplemented with Wnt3a, R-spondin-1, Noggin, FGF10, EGF, bFGF and smallmolecule inhibitors (A83-01, Y-27632, and Losmapimod), we successfully established long-term cultures from all four specimen types. Organoids retained characteristic nuclear NUT expression (≥80% positive cells), preserved the original fusion by FISH and NGS, and remained stable for at least 10 passages. Drug testing against BET inhibitors yielded clear, reproducible dose-response curves. All procedures, quality controls, and banking steps were performed according to the recently released ISoOR-ISOB international standard. This platform should facilitate mechanistic studies and drug screening for a tumor that currently lacks tractable models.

1. Introduction

NUT carcinoma (previously called NUT midline carcinoma) is driven by reciprocal translocations that fuse NUTM1 most commonly to BRD4 or, less often, BRD3 or NSD3. The resulting oncoproteins trigger global histone acetylation and block differentiation, producing a highly lethal squamous cancer that affects children and adults alike. More than 90% of patients present with stage III or IV disease, and median overall survival is still under seven months despite intensive chemotherapy and radiation.

Until now, researchers have relied on a handful of immortalized cell lines or patientderived xenografts that poorly reflect the original tumor heterogeneity and rapidly lose the fusion oncoprotein in culture. Patient-derived organoids have transformed drug discovery in many carcinomas, but no robust protocol existed for NUT carcinoma. We therefore set out to build a reliable culture system that works with the limited material clinicians can obtain from these patients and that meets the new ISoOR-ISOB biobanking standard from day one.

2. Materials and Methods

2.1 Ethics and ISoOR-ISOB compliance

The study was approved by the Ethics Committee of Chongqing University Three Gorges Hospital (approval 2023-047). Written informed consent was obtained from all adult patients or from parents/legal guardians of minors. The complete protocol, including quality-control thresholds and banking workflow, was reviewed and approved by the ISoOR-ISOB Technical Committee in February 2025.

2.2 Clinical specimens

Between June 2023 and October 2025 we collected fresh tumor tissue (n=12), malignant pleural effusions (n=9), CT-guided fine-needle aspirates (n=5), and transbronchial biopsies (n=7). All cases were confirmed NUT carcinoma by NUT immunohistochemistry and FISH or NGS.

2.3 Tissue processing

Resected specimens were transported on ice in DMEM/F12 + Primocin and processed within 30 min. Tissue was minced to ≈0.5 mm^3 fragments and digested 30–60 min at 37 °C in collagenase/dispase (1 mg/mL), hyaluronidase (0.1 mg/mL), and DNase I (40 µg/mL). Pleural effusions were centrifuged, red blood cells lysed when necessary, and tumor cell clusters enriched by brief digestion.

2.4 Organoid culture medium (final concentrations)

Advanced RPMI-1640 or DMEM/F12 supplemented with: B27 (1×), N2 (1×), GlutaMax (1×), N-acetylcysteine (1.25 mM), nicotinamide (2 mM), EGF 50 ng/mL, bFGF 20 ng/mL, FGF10 50 ng/mL, Wnt3a 50 ng/mL, R-spondin-1 100 ng/mL, Noggin 200 ng/mL, A83-01 500 nM, Y-27632 10 µM, Losmapimod 1 µM (found essential in pilot experiments to prevent early differentiation), Penicillin/streptomycin 100 U/mL and Primocin 100 µg/mL.

2.5 Embedding, passaging, and cryopreservation

Cell clusters were suspended in growth-factor-reduced Matrigel (Corning), dispensed as 10–25 µL domes in pre-warmed 24-well plates, and overlaid with 500 µ L complete medium after polymerization. Medium was refreshed every 2–4 days. Organoids were passaged at ≈200 µm diameter by cold PBS wash, 5–10 min TrypLE digestion at 37 °C, and mechanical disruption into small fragments (never single cells). Typical split ratios 1:2 to 1:4. For banking we used DMEM/F12 + 40% FBS + 10% DMSO, controlled-rate freezing (–1 °C/min) to –80 °C, then transfer to vapor-phase liquid nitrogen.

2.6 Quality control (ISoOR-ISOB thresholds)

- Morphology: compact structures 80–250 µm, <40% central necrosis, <30% vacuolation
- Viability (trypan blue): ≥80% before banking
- Sterility: mycoplasma PCR (every 3 passages), bacterial/fungal broth culture
- Identity: NUT IHC (rabbit mAb C52B1, CST #3625) ≥80% nuclear positivity; fusion confirmed by break-apart FISH or targeted NGS
- Post-thaw recovery: ≥50% viability accepted

2.7 Drug sensitivity

2,000–3,000 organoids/well in 96-well plates, 72 h drug exposure, viability by CCK-8, curves fitted in GraphPad Prism.

3. Results

Patient-derived organoids were successfully established from all four types of clinical specimens, demonstrating the feasibility of this platform across diverse sample sources. Tumor tissues yielded the highest establishment efficiency, with 11 of 12 samples generating organoids that could be expanded beyond ten passages. Pleural effusion-derived samples also produced viable organoids in 8 of 9 cases, highlighting the potential for minimally invasive sampling in patients with advanced disease. Organoids from FNAs and TBLBs were more challenging due to lower cellularity, yet 3 of 5 FNAs and 6 of 7 TBLBs produced expanding cultures. These observations confirm that the platform can accommodate the limited material often obtainable from NUT carcinoma patients.

Morphologically, organoids formed compact, densely packed spheroid-like structures with irregular outer surfaces, reminiscent of poorly differentiated squamous carcinoma. Over the first 7–14 days in culture, organoids displayed progressive enlargement and branching, reflecting active proliferation while maintaining structural integrity. High-resolution microscopy revealed uniform nuclear-tocytoplasmic ratios, minimal central necrosis, and absence of excessive vacuolation. Notably, omitting Losmapimod from the medium during pilot experiments resulted in rapid cystic degeneration and early loss of nuclear NUT staining, indicating that MAPK inhibition is essential for maintaining differentiation blockade and molecular fidelity in culture.

Molecular characterization confirmed that organoids preserved key tumor features. Immunohistochemistry demonstrated robust nuclear NUT expression in >85% of cells across passages 1–10, aligning with parental tumor profiles. Break-apart FISH and targeted NGS verified that the original NUTM1 fusion was retained in every line, while RNA sequencing indicated stable transcriptional signatures that closely mirrored those of the source tumors. These findings underscore the fidelity of the organoids in recapitulating both genetic and phenotypic hallmarks of NUT carcinoma.

Cryopreservation experiments further demonstrated the robustness of the platform. Post-thaw viability ranged between 55–70%, and organoids recovered their original morphology within 3–5 days, confirming that long-term storage does not compromise structural or molecular integrity. Drug-sensitivity assays using BET inhibitors such as iBET-762 and OTX015 produced reproducible dose-response curves, with IC_{50} values consistently in the low nanomolar range across independent organoid lines. These results validate the organoids as a functional preclinical model suitable for pharmacologic testing.

4. Discussion

The development of a standardized, ISoOR-ISOB–aligned organoid platform for NUT carcinoma represents a significant advance in modeling this rare, aggressive malignancy. Previous reliance on immortalized cell lines and patient-derived xenografts has been limited by rapid loss of NUTM1 fusion expression, poor preservation of tumor heterogeneity, and restricted scalability. Our study demonstrates that organoids can be reliably established from multiple patient-derived specimens, including surgically resected tumors, pleural effusions, FNAs, and TBLBs, thereby overcoming challenges associated with limited sample availability.

The culture system preserves key histopathologic and molecular characteristics of parental tumors. Dense, squamous-like morphology and high nuclear NUT expression are maintained over multiple passages, indicating that the combination of defined growth factors, Wnt signaling activators, and small-molecule inhibitors effectively
supports tumor identity while preventing premature differentiation. The addition of Losmapimod proved particularly critical, as pilot experiments without it led to rapid morphological degradation and loss of NUT expression, emphasizing the importance of MAPK pathway modulation for maintaining oncogenic fusion-driven phenotypes.

Cryopreservation protocols also proved highly effective, enabling long-term biobanking without significant loss of viability or molecular fidelity. Post-thaw recovery rates of 55–70% and restoration of normal organoid morphology within days confirm the feasibility of establishing a shared organoid repository for international research collaboration. Drug-sensitivity testing further demonstrated that these organoids respond predictably to BET inhibitors, providing a robust platform for preclinical screening and precision medicine initiatives.

5. Conclusion

We provide a practical, rigorously documented protocol for generating, characterizing, and banking NUT carcinoma organoids. The platform is already being used in our center for BET-inhibitor combination screens and should help fill a critical gap for this orphan disease.

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Conflicts of interest

None declared.

Data availability

Detailed culture logs, QC records, and sequencing data are available from the corresponding author on reasonable request and after MTA execution.

Volume 4 (2025)

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Industry News & Perspectives

United Kingdom Launches £75 Million National Roadmap to Phase Out Animal Testing by 2030: A Defining Moment for Human-Relevant Research

ISoOR Insight Team

*E-mail address: info@isoor.org

Abstract

On 11 November 2025, the United Kingdom released its unprecedented "Roadmap for Replacing Animals in Science", announcing a structured transition toward humanrelevant, non-animal scientific methods by 2030. Supported by £75 million in dedicated government funding, the roadmap positions organoids, microphysiological systems (MPS), AI-driven toxicology, and advanced in vitro human models as central components of future regulatory science. This article summarizes key milestones, scientific frameworks, regulatory mechanisms, and sector-wide implications of the UK roadmap. The initiative represents one of the most comprehensive national strategies for animal testing reduction ever implemented by a G7 country, offering a blueprint for global transition toward human-specific research platforms.

Introduction

The United Kingdom has taken a decisive step toward reshaping the scientific and regulatory landscape by announcing a national strategy to accelerate the phase-out of animal testing. Jointly released by the Department for Science, Innovation and Technology (DSIT), DEFRA, and the Home Office on 11 November 2025, the "Roadmap for Replacing Animals in Science" lays out clear goals, timelines, and investments aimed at replacing animal experiments with validated non-animal methodologies (NAMs).

With global momentum building around organoids, organ-on-chip systems, and AIbased predictive methodologies, the UK strategy provides both direction and infrastructure for transitioning these technologies from research environments into regulatory practice. The roadmap fulfills a key Labour Party manifesto pledge and builds on the UK's post-Brexit leadership in animal welfare, including the Animals (Scientific Procedures) Act 1986 and NC3Rs initiatives. It targets a 35% reduction in animal procedures by 2030, from the 2.8 million recorded in Great Britain in 2023.

A Structured Timeline for Phasing Out Animal Testing (2026–2030)

The roadmap outlines measurable and enforceable milestones, using a tiered model to prioritize low-risk tests first. This approach ensures safety while accelerating adoption of NAMs.

Table 2

Year	Milestone	Primary NAMs Involved
2026	Complete elimination of animal testing for skin irritation, skin sensitisation, and serious eye damage/irritation	Reconstructed human epidermis models, corneal organoids, EpiSkin assays
2027	Termination of mouse LD50 assays for botulinum toxin (Botox) potency	Cell-based neuronal organoids, in vitro potency tests
2030	35% reduction in use of dogs and nonhuman primates in pharmacokinetic (PK) and toxicology research	Multi-organ MPS, vascularised organoids, AI-driven PBPK models

Table 2: This timeline represents one of the most detailed national commitments to animal testing reduction on record, with annual progress reports to Parliament.

Scientific Pillars of the UK Roadmap

The strategy rests on three interconnected pillars, with organoids and MPS as foundational tools for human-specific modeling.

1. Human Organoids and Microphysiological Systems (MPS)

Organoids are prioritized for toxicity and safety assessment, disease modeling, drug-response profiling, PK/PD evaluation, and preclinical modeling of biologics and complex modalities. Their ability to mimic human-specific phenotypes—such as zonal liver architecture or intestinal crypt-villus structures—provides distinct advantages over rodent or primate systems, reducing translational failures (estimated at 92% in oncology from preclinical to clinic).

2. AI and Computational Toxicology

AI-driven models will support in silico prediction of compound-target interactions, physiologically based pharmacokinetic (PBPK) modeling, digital toxicology pipelines, and risk assessment based on integrated biological and computational data. For example, machine learning algorithms trained on organoid-derived multiomics datasets could predict hepatotoxicity with >85% accuracy, per NC3Rs pilots.

3. 3D-Bioprinted Human Tissues

Applications include skin irritation testing, hepatotoxicity screening, absorption/penetration studies, and wound healing/reconstructive biology. Bioprinted skin equivalents, validated by EURL ECVAM, have already replaced rabbit Draize tests in cosmetics.

These technologies form an interconnected human-relevant testing ecosystem, with organoids bridging in vitro precision and MPS for systemic interactions.

A £75 Million Investment into National Infrastructure

The funding allocation targets validation, translation, and capacity-building, addressing key barriers like reproducibility and regulatory acceptance.

- **£60 Million: Validation and Translation Centers**
  This supports two major hubs: the Preclinical

Translational Models Hub and the UK Centre for the Validation of Alternative Methods (UKCVAM). Their mandates include NAM validation, inter-laboratory reproducibility initiatives, regulatory interface development, and industry adoption pathways. For instance, UKCVAM will standardize organoid protocols for hepatotoxicity, building on OECD Test Guideline 497.

- **£15.9 Million: National Human In Vitro Disease Model Program**
  Funded by the Medical Research Council (MRC), Innovate UK, and Wellcome Trust, this program supports consortia developing human models for liver disease, neurological disorders, cancer, pain mechanisms, and vascular pathology. Early projects include liver organoid chips for NASH modeling, with £5 million earmarked for biobanking and AI integration.

Governance and Policy Framework

Oversight will be coordinated by a cross-government committee chaired by Lord Patrick Vallance, responsible for publishing national KPIs in 2026, conducting biennial progress reviews, updating regulatory priorities, and streamlining approval pathways for human-relevant methods. The roadmap also includes early-career researcher training (e.g., 500 fellowships in NAMs) and technical workforce development programs, aiming to upskill 2,000 scientists by 2028.

Stakeholder Perspectives

- **NC3Rs:** Praised the roadmap as a "strategically aligned effort that maintains high scientific standards while accelerating innovation," highlighting its integration with the 2023–2028 NC3Rs strategy.
- **UK Pharmaceutical Sector (ABPI):** Highlighted benefits including improved human predictivity, reduced clinical failure rates (potentially 20–30% via organoid screening), and more efficient preclinical workflows.
- **Royal Society of Biology (RSB):** Called the roadmap a model for "ethically aligned scientific progress" and encouraged adoption in other regulatory jurisdictions, noting its alignment with global 3Rs principles.

Industry and academia, including organ-on-chip developers and computational toxicology groups, emphasize that the roadmap provides regulatory clarity, expands validation infrastructure, offers new funding pathways, and creates confidence for industrial investment. However, experts like Dr. Kathy Niakan (stem cell biologist) caution that delivery depends on addressing organoid variability.

Implications for Global Human-Relevant Research

1.Regulatory Transition Toward Human Biology

For the first time, organoids and MPS platforms are being positioned as primary evidence-generation tools, not supplementary methods. This could reduce reliance on the ~2.8 million annual animal procedures in GB (2023 Home Office data).

2.Increased Demand for Standardization

Growth in harmonized SOPs, biobanking best practices, QC/QA frameworks, reference materials, and inter-laboratory reproducibility studies. Challenges include batch variability (e.g., 20–30% in organoid gene expression), addressed via UKCVAM ring trials.

3.Global Competitive Pressure

The UK roadmap is likely to accelerate policy and regulatory responses in the EU (EURL ECVAM's 2024 validation push), US (NIH SOM Center, $87M, September 2025), Japan, Singapore, and South Korea, fostering international consortia.

4.Major Investment Shifts

Expected increases in venture capital (e.g., £100M+ in UK NAM startups by 2027), consortia-based translational programs, industry–academia partnerships, and commercial organoid/MPS platforms. Case study: NC3Rs-funded organoid vaccine testing replaced rabbit pyrogen assays, cutting timelines by 6 months.

Global Outlook

Taken together, these developments signal a broader movement toward human relevant scientific ecosystems, with consequences for clinical translation, drug development success rates, ethical modernization, predictive toxicology, and harmonization of global regulatory frameworks. Compared to the US NIH SOM Center (organoid standardization) or EU REACH revisions (NAM integration), the UK approach uniquely combines funding with enforceable KPIs.

Conclusion

The United Kingdom's Roadmap for Phasing Out Animal Testing by 2030 represents a pivotal moment in modern biomedical research. Combining clear policy directives, targeted financial investment, and scientifically validated alternatives, the roadmap establishes a foundation for human-specific, ethically aligned, and more predictive biological research. Organoids, MPS platforms, AI-driven models, and bioprinted tissues are poised to become central pillars of this new framework–reshaping preclinical research for decades to come. If effectively implemented, the UK roadmap could set a global benchmark for transitioning away from animal-based research systems, potentially reducing failures in oncology and toxicology by 20–30%.

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Volume 4 (2025)

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Industry News

Major Shift in U.S. Research Policy: CDC to End All Nonhuman Primate Experiments by 31 December 2025

ISoOR Insight Team

*E-mail address: info@isoor.org

Abstract

On 21 November 2025, the U.S. Centers for Disease Control and Prevention (CDC) received an internal directive from the Department of Health and Human Services (HHS) ordering the complete termination of all in-house research involving nonhuman primates – approximately 200 macaques – by the end of the calendar year. This is the first time since the NIH chimpanzee retirement in 2015 that a major federal agency has fully shuttered an active, government-owned NHP colony. The decision, driven by persistent primate shortages, documented biosafety incidents, translational failures of NHP models, and the accelerating maturity of human-relevant alternatives (organoids, microphysiological systems, organ-on-chip platforms, and AIintegrated digital twins), constitutes one of the most far-reaching policy realignments in U.S. biomedical research since the Animal Welfare Act of 1966 and the FDA Modernization Act 2.0 of 2023. This Industry News analysis places the CDC directive in full scientific, ethical, and regulatory context, evaluates the evidence base, addresses remaining challenges, and explores the transformative opportunities this shift creates for the organoid and bioscience sectors.

Keywords

Organoids; microphysiological systems; nonhuman primates; CDC policy; translational research; human-relevant models; organ-on-chip; infectious disease; FDA Modernization Act 2.0; ISoOR standards; NAMs

Introduction

For more than seven decades, rhesus and cynomolgus macaques have been considered the gold-standard model for HIV, tuberculosis, Zika, Ebola, and biodefence research within the CDC.

On 21 November 2025, however, Science magazine published an exclusive report revealing that HHS Secretary Robert F. Kennedy Jr., through deputy chief of staff Sam Beyda and the "Make America Healthy Again" (MAHA) initiative, had ordered the CDC to end all monkey experiments and decommission its remaining colonies by 31 December 2025 [1]. Subsequent reporting in Scientific American,Nature, FierceBiotech, and STAT confirmed the directive and revealed that the approximately 200 animals currently housed at the Roybal Campus in Atlanta and associated facilities face either retirement to accredited sanctuaries or, in the likely event of insufficient sanctuary capacity, euthanasia [2,3].

Background:Four Converging Crises That Made Continuation Untenable

1.Translational discordance – Decades of comparative genomics and immunology have documented systematic species differences in ACE2 receptor affinity, innate immune signalling (e.g., type I interferon pathways), cytokine storms, and drug metabolism that frequently invalidate NHP findings in human trials.

2.Supply-chain collapse and biosafety incidents – Between 2021 and 2024, the CDC documented 69 cases of tuberculosis in newly imported macaques during quarantine, highlighting ongoing zoonotic and reverse-zoonotic risks. Import restrictions implemented during and after the COVID-19 pandemic reduced annual U.S. primate imports by >80 %, driving per-animal costs above $100,000 [1].

3.Ethical and political pressure – Sustained public advocacy made continued federal funding politically radioactive [4,5].

4.Maturation of alternatives – By mid-2025, more than 40 organoid and MPS assays had achieved formal context-of-use validation under FDA and NIH NAM programmes, many of them directly relevant to CDC mission areas.

The CDC Directive: Timeline and Details

Internal CDC documents leaked to Science state explicitly that "nonhuman primate research no longer meets the agency's optimal scientific, operational, biosafety, and ethical criteria" [1]. The directive mandates:

- Immediate freeze on new NHP protocol approvals
- Termination of all ongoing studies by 31 December 2025
- Full decommissioning of primate housing facilities
- Reallocation of the estimated $20–30 million annual NHP budget toward New Approach Methodologies infrastructure

HIV researchers such as Jonah Sacha (Oregon Health & Science University) and Dan Barouch (Harvard) have publicly warned that the abrupt timeline could "set back HIV cure and prevention research by a decade" [2]. Conversely, the Physicians Committee for Responsible Medicine and PETA have launched campaigns urging Congress to appropriate dedicated sanctuary funding to prevent euthanasia [4,5].

Scientific Evidence Supporting the Transition

High-profile failures have eroded confidence in NHP models:

- SARS-CoV-2 causes only mild, self-limiting disease in most macaque species, severely limiting utility for severe COVID-19 or long COVID studies
- HIV-1 mucosal transmission efficiency, viral set-point, and elite-controller rates differ markedly from human epidemiology

- Multiple tuberculosis vaccine candidates that protected macaques failed spectacularly in human efficacy trials

In parallel, human organoid platforms have achieved unprecedented fidelity:

- Cerebral organoids recapitulate Zika microcephaly and SARS-CoV-2 neurotropism with patient-specific genetic backgrounds
- Airway and alveolar organoids support full replication cycles of influenza A/B, RSV, and human metapneumovirus
- Intestinal organoids sustain norovirus, rotavirus, and enterovirus propagation – pathogens that historically required primates or gnotobiotic animal models
- Vascularised, multi-lineage lung- and liver-on-chip platforms now integrate circulating human immune cells, mechanical breathing, and perfusion, enabling modelling of cytokine storms and antibody-dependent enhancement

Rise of Human-Relevant Alternatives

The FDA Modernization Act 2.0 (2023) and the subsequent 2024–2025 FDA/NIH NAM Roadmaps have created a clear regulatory pathway for organoid and MPS data in IND and BLA submissions. By December 2025, the following platforms had achieved formal qualification or context-of-use letters:

- Emulate Lung-Chip for viral infectivity and drug-induced pulmonary injury
- HUB multi-organoid systems for hepatotoxicity and intestinal barrier function
- TISSUSE Humimic Chip 4 for multi-organ pharmacokinetics

In March 2025, the International Society for Organoid Research (ISoOR) published the ISoOR-ISOB international biobanking and quality-control standards, providing the first globally harmonised framework for organoid identity, viability, and functional benchmarking – a critical step toward regulatory-grade replacement of NHP cohorts [1,2].

Implications for Biomedical Research and Public Health

1.Infectious-disease modelling - Organoid panels now enable same-week, highthroughput pathogenicity screening of novel isolates with human-specific receptor usage.

2.Vaccine development - HLA-typed lymphoid organoids and tonsil organoids permit precise measurement of germinal-centre reactions and neutralising antibody maturation without cross-species artefacts.

3. Biodefence - Multi-organ chips with integrated immune compartments can model select-agent pathogenesis under BSL-4 conditions using far lower biocontainment burdens.

4. Resource reallocation - The CDC's liberated budget is expected to seed major new initiatives, including a rumoured FY2027 NIH "Moonshot for Human- Relevant Infectious Disease Models".

Remaining Challenges

Full systemic physiology (neuro-immune-endocrine axes, long-term chronic infection, pregnancy models) remains difficult. Standardisation of vascularisation and immune-cell integration is still evolving. However, 2025 high-throughput droplet,

microwell, and bioreactor platforms have reduced per-assay costs below those of many historical NHP studies, and reproducibility metrics now routinely exceed those of primate cohorts.

Ethical, Regulatory, and Global Dimensions

The CDC decision aligns with Europe's parallel trajectory: the Netherlands announced closure of its Biomedical Primate Research Centre by 2028, and the European Parliament is debating a 2030 phase-out roadmap. Sanctuary capacity remains the immediate humanitarian bottleneck; only ~500 lifetime spaces exist in accredited U.S. facilities for the thousands of federally owned primates[3,4].

Outlook for Organoid Science and Biotechnology

The CDC directive is expected to catalyse:

- Multi-hundred-million-dollar funding lines for organoid biomanufacturing and MPS scale-up
- Expanded pre-competitive consortia (ISoOR, IQ Consortium, NC3Rs, FDA ISTAND)
- Commercial launch of cryopreserved, ready-to-use, HLA-diverse organoid panels targeting the $2–3 billion infectious-disease modelling market
- Accelerated regulatory acceptance of multi-organoid platforms as standalone evidence for vaccine efficacy and countermeasure licensure

Conclusion

The CDC's decision to end all nonhuman primate research by 31 December 2025 marks the end of an era and the decisive beginning of another. It is a policy built on decades of evidence that NHP models frequently mislead rather than illuminate human disease, compounded by supply, safety, and ethical crises that have become insoluble. For the organoid and bioscience communities, the responsibility is immense: to deliver standardised, reproducible, regulatorily accepted human platforms at scale within the next 3–5 years. The opportunity is historic: to redefine infectious-disease research, vaccine development, and public health preparedness on the unshakable foundation of actual human biology.

References

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Conflicts of interest

The authors declare no conflicts of interest.

ISoOR International Society of Organoid Research


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@ ISoOR-WeChat


info@isoor.org


www.isoor.org