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Nanomaterials in organoid research: Advancements and applications

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Abstract

In recent years, organoids have demonstrated immense potential as three-dimensional in vitro models of human tissue, capable of simulating physiological and pathological environments. Nanomaterials, owing to their unique physicochemical properties, have become pivotal tools in advancing organoid research and applications. By integrating nanomaterials, scientists can more effectively explore disease mechanisms, optimize drug delivery systems, and develop novel therapeutic strategies. For example, nanoparticle-based metabolic reprogramming techniques offer novel avenues for regulating organ function, while advances in gene editing technologies have markedly enhanced the precision and complexity of organoid models. Furthermore, organoids demonstrate broad application prospects in fields such as virology research, cardiac tissue engineering, and cancer therapy. These advances not only propel fundamental scientific inquiry but also provide crucial support for clinical translation. The future holds promise for achieving more precise, personalized medical solutions through the integration of nanotechnology and organoid models.

Keywords: Nanomaterials; Organoid models; Drug delivery; Disease modeling; Personalized medicine

1. Introduction

1.1. Background and importance of organoids

Over the past few decades, traditional cell lines have been the most commonly used experimental models in cell biology and medical research, playing a crucial role in many major medical discoveries.[1] However, as research questions become increasingly complex, traditional cell lines have begun to reveal significant limitations, making them inadequate for modern biomedical research. This is especially true in areas such as drug pharmacology assessment for complex diseases and the study of the mechanisms of organogenesis and development. The applicability of classical cell lines is constrained by their limited differentiation ability, homogeneous cell sources, and inability to replicate the multicellular composition and dynamic changes typical of in vivo tissues.[2]

Thus, the development of new research models that more closely mimic real physiological states has become a critical issue in modern biomedical research. In recent years, as stem cell technologies have progressed, organoid technology has matured, offering a new approach in this

field.[3] Organoids are three-dimensional cell aggregates formed by stem cells in vitro and have a defined spatial structure.[4] These structures have the ability to self-renew and self-organize, closely mimicking the structure and function of actual tissues.[5] By cultivating stem cells derived from normal or diseased tissues, it is possible to recreate key features of tissues or tumors in vitro, providing an effective model for studying their development mechanisms.[6,7]

Compared with traditional two-dimensional cell culture systems, organoid models have significant advantages in mimicking the tissue microenvironment. By enhancing interactions between cells, they more accurately replicate the spatial configuration and functional characteristics of in vivo tissues.[8] As such, organoids bridge the gap between two-dimensional cell models and animal experiments, offering a more physiologically relevant experimental platform for drug screening, toxicity assessments, and disease mechanism studies.[9]

1.2. Role of nanomaterials in organoid engineering

Nanomaterials are materials that have at least one dimension in the range of nanometers (1–100 nm), positioned between atomic, molecular, and macroscopic structures. These materials are composed of nanoparticles and possess unique physicochemical properties, making them widely applied in various biomedical fields. Studies have shown that nanomaterials offer greater targeting precision, therapeutic accuracy, and safety in cancer treatment.[10] Additionally, owing to the size effects of nanotechnology, nanomaterials play a significant role in drug delivery, medical imaging, and immunotherapy.[11-13] Their optical, magnetic, and electrical properties have made them a focal point in biotechnology and bioengineering research, further promoting the development of organoid-related studies.[14]

In organoid research, nanomaterials have been extensively applied in various functional modulations. For example, in liver organoid models, iron oxide nanoparticles are used for non-invasive dynamic tracking of hepatocyte differentiation.[15] Moreover, nanomaterials responsive to physical stimuli, such as light and electrical signals, have been developed to directly modulate stem cell surface receptor activity, providing new technological means for exploring the complex signaling networks involved in organoid construction and differentiation. However, the incorporation of nanomaterials into organoid research does not simply confer technical advantages but also introduces additional challenges associated with system complexity. On the one hand, nanomaterials provide new strategies for addressing key limitations that are difficult to overcome using conventional approaches, such as precise delivery to deep tissue regions, real-time non-invasive monitoring of the organoid microenvironment, and spatiotemporal regulation of stem cell fate. On the other hand, their integration may increase the physicochemical complexity of the system, alter local microenvironmental parameters, and potentially disturb the intrinsic physiological homeostasis of organoids.[16] Therefore, the integration of nanotechnology into organoid systems should be guided by clearly defined mechanistic objectives or practical therapeutic needs, rather than by simple technical accumulation. Overall, such interdisciplinary integration is of substantial mechanistic and translational value only when the biological insights gained or therapeutic benefits achieved clearly outweigh the added complexity introduced by nanomaterials.[17] However, systematic reviews focusing on the interaction between nanomaterials and organoids are still relatively scarce, particularly research reports centered on using nanoscience and nanotechnology to construct organoid microenvironments.[18,19] There remains a lack of comprehensive reviews on how nanomaterials directly influence stem cell fate decisions and how they can provide a three-dimensional biomimetic microenvironment for organoids.[20]

Therefore, the role of nanomaterials—both inorganic and carbon-based—in regulating organoid structure and function requires further investigation. This paper reviews the latest advancements in nanomaterials in organoid research, discussing aspects such as material design, functionality, and applications in biomedical fields (Figure 1).

2. Design of nanomaterials in organoid engineering

2.1. Types and properties of nanomaterials: Inorganic/organic/composite nanomaterials

2.1.1. Inorganic materials

Inorganic nanomaterials, due to their unique physicochemical properties, exhibit significant advantages in the diagnosis and treatment of diseases. For example, gold nanoparticles exhibit exceptional biocompatibility, a high surface-to-volume ratio amenable to functionalization, and superior optical and surface plasmon resonance characteristics, rendering them highly attractive for photothermal therapy and drug delivery applications.[21] In photothermal therapy, gold nanoparticles exhibit the capacity to absorb light at specific wavelengths and convert it efficiently into thermal energy, enabling localized thermal ablation of tumor tissue with minimal collateral damage to adjacent healthy tissues.[22]

Silica nanoparticles, especially mesoporous silica nanoparticles (MSNs), are increasingly used as multifunctional carrier platforms due to their regular porous structure, high surface area, and tunable pore sizes[23] (Figure 2). These features allow them to effectively load

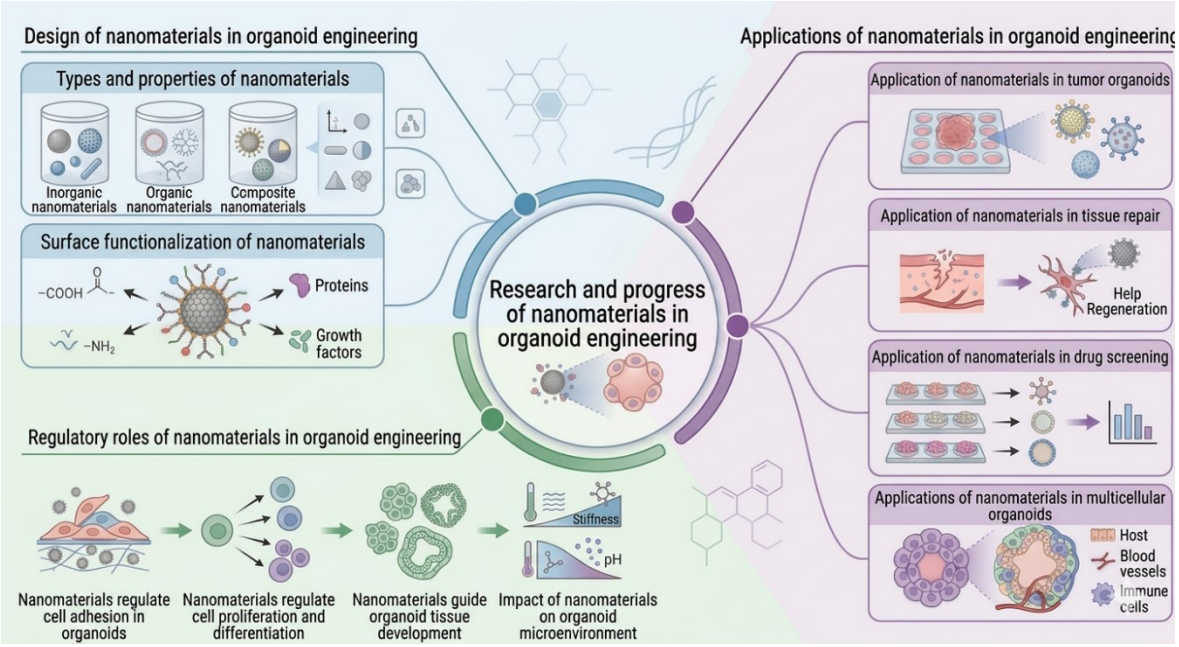

Figure 1. Research and progress of nanomaterials in organoid engineering. Image created by the authors with Nano Banana Pro.

various therapeutic molecules, including small molecules and biological macromolecules. Furthermore, MSNs are often designed as theranostic systems that integrate both diagnostic and therapeutic functions, enabling simultaneous disease imaging and drug delivery.[24] Owing to their distinctive optical characteristics—including broad excitation spectra, narrow emission bands, and tunable emission wavelengths—quantum dots have emerged as pivotal tools in biomedical applications.[25] These advantages make them excellent for high-sensitivity fluorescence labeling, widely used for protein and nucleic acid detection and analysis. Quantum dots also serve as high-resolution imaging probes for live-cell single-molecule tracking and studying intracellular dynamic behaviors.[26]

2.1.2. Organic materials

Lipid-based nanodelivery systems are mature and widely used in drug delivery platforms due to their excellent biocompatibility and efficient drug encapsulation capabilities.[27] Liposomes, as a typical representative, consist of phospholipid bilayer vesicles capable of carrying both hydrophilic and hydrophobic drugs.[28] Doxil exemplifies a liposomal formulation that exhibits preferential accumulation at tumor sites via the enhanced permeability and retention effect, thereby enhancing therapeutic efficacy.[29] Solid lipid nanoparticles are composed of biocompatible solid lipids and are suitable for delivering poorly soluble drugs. Their structure helps improve drug stability, reduce enzymatic degradation, and enable controlled release, improving the solubility of drugs.[30] Nanostructured lipid carriers integrate the advantageous characteristics of both solid and liquid lipids, thereby improving drug-loading capacity and encapsulation efficiency, while enabling precise modulation of drug release kinetics[31,32] (Figure 3).

2.1.3. Composite nanomaterials

Polymer nanoparticles constructed from biodegradable and biocompatible materials, such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone, and chitosan, serve as important platforms for drug delivery. They are commonly used for sustained and controlled drug release, extending treatment durations and reducing dosing frequency.[33] By adjusting the composition ratio and molecular weight of the polymer, the degradation behavior and drug release kinetics can be precisely controlled.[34] For example, PLGA nanoparticles are widely used for delivering anti-inflammatory and anti-tumor drugs, enhancing targeting efficiency, reducing systemic side effects, and improving therapeutic efficacy.[35] Chitosan-based nanoparticles, recognized for their outstanding biocompatibility and versatile chemical modifiability, hold significant promise for non-oral drug delivery applications.[36]

2.2. Surface functionalization of nanomaterials

Through surface functionalization, nanodrug delivery systems can achieve active targeting capabilities, enhancing their selective accumulation in specific tissues or cells.[37] This is typically done by conjugating antibodies, peptides, aptamers, or small-molecule ligands to the surface of nanoparticles, enabling them to recognize and bind to

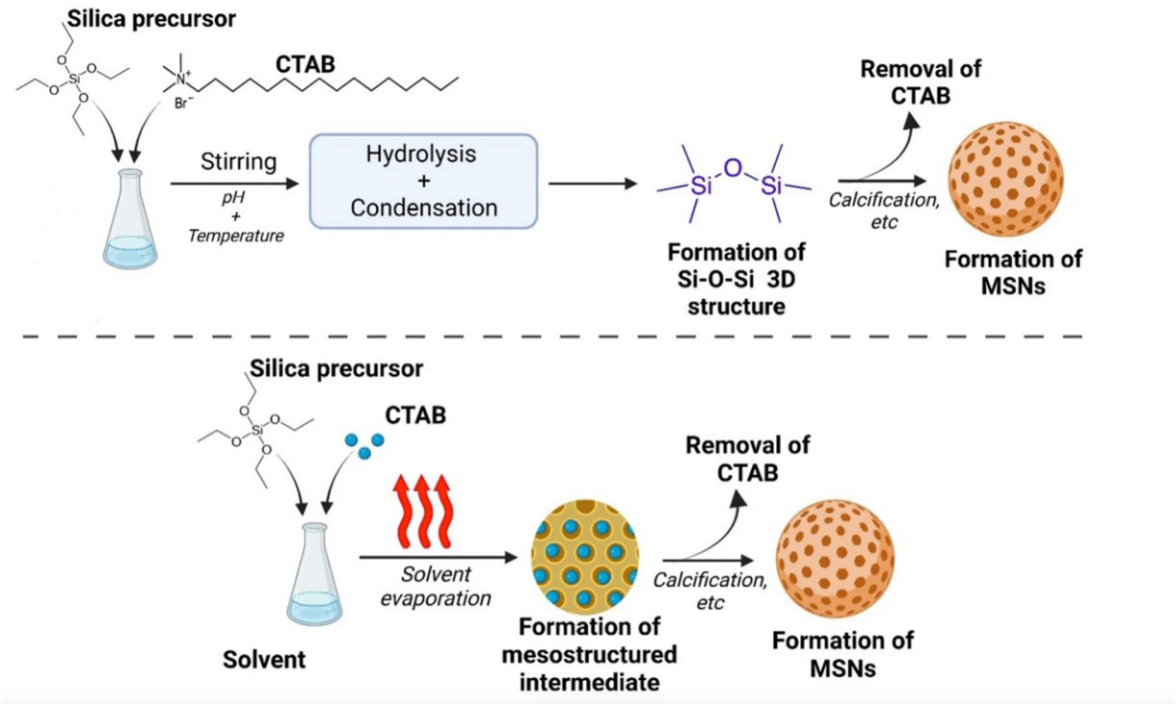

Figure 2. Mesoporous silica nanoparticle (MSN) synthesis via sol–gel method and evaporation-induced self-assembly. Reprinted from Dutta Gupta *et al.*[23]
Abbreviation: CTAB: Cetyltrimethylammonium bromide.

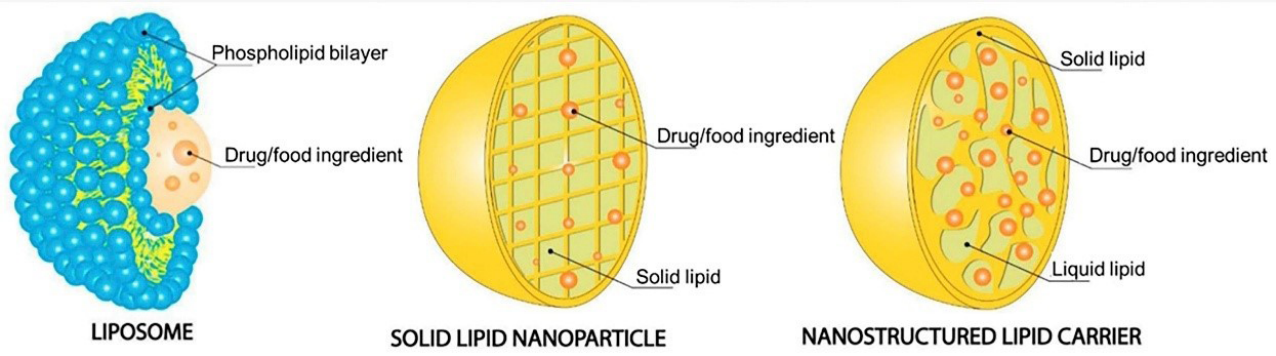

Figure 3. Structural features of liposomes, solid lipid nanoparticles, and nanostructured lipid carriers. Reprinted with permission from Barroso *et al.*[31]

overexpressed receptors or specific biomarkers in disease cells. This molecular recognition strategy not only improves therapeutic efficiency but also reduces nonspecific toxicity to normal tissues.

Antibodies, known for their highly specific antigen-binding abilities, are widely used in the construction of targeted nanoparticle platforms. For example, cetuximab-conjugated polysaccharide-ester nanoparticles have demonstrated enhanced anti-tumor efficacy in murine models.[38] Hyaluronic acid-functionalized nanoparticles have also demonstrated enhanced targeted delivery by binding to receptors overexpressed on tumor cells.[39] Furthermore, polyethylene glycolation (PEGylation) diminishes the recognition and clearance of nanoparticles by the mononuclear phagocyte system, thereby extending their circulation half-life and improving their stability and bioavailability.[40] However, the role of PEGylation in in vitro models such as organoids should be re-evaluated in the context of the specific experimental setting. Although organoid systems cannot recapitulate systemic circulation or mononuclear phagocyte system-mediated clearance in vivo, PEG modification remains relevant under in vitro conditions. In particular, PEGylation can improve the colloidal stability of nanoparticles, reduce nonspecific

adsorption in the culture system, and minimize particle aggregation. In addition, the PEG layer may modulate nanoparticle interactions with the extracellular matrix (ECM), thereby indirectly influencing their distribution and penetration within organoids. Nevertheless, it should be noted that the well-recognized advantages of PEGylation in prolonging circulation time and reducing immune clearance cannot be fully assessed in static organoid systems. Therefore, when PEGylated nanoparticles are investigated using organoid models, their physicochemical effects in vitro should be clearly distinguished from their biological functions in systemic in vivo delivery, in order to avoid overinterpretation of their overall performance.[41] By combining targeting molecules with pharmacokinetic control strategies, rationally designing the surface structure of nanoparticles helps overcome biological barriers and achieve precise spatial control and efficient drug delivery (Figure 4).

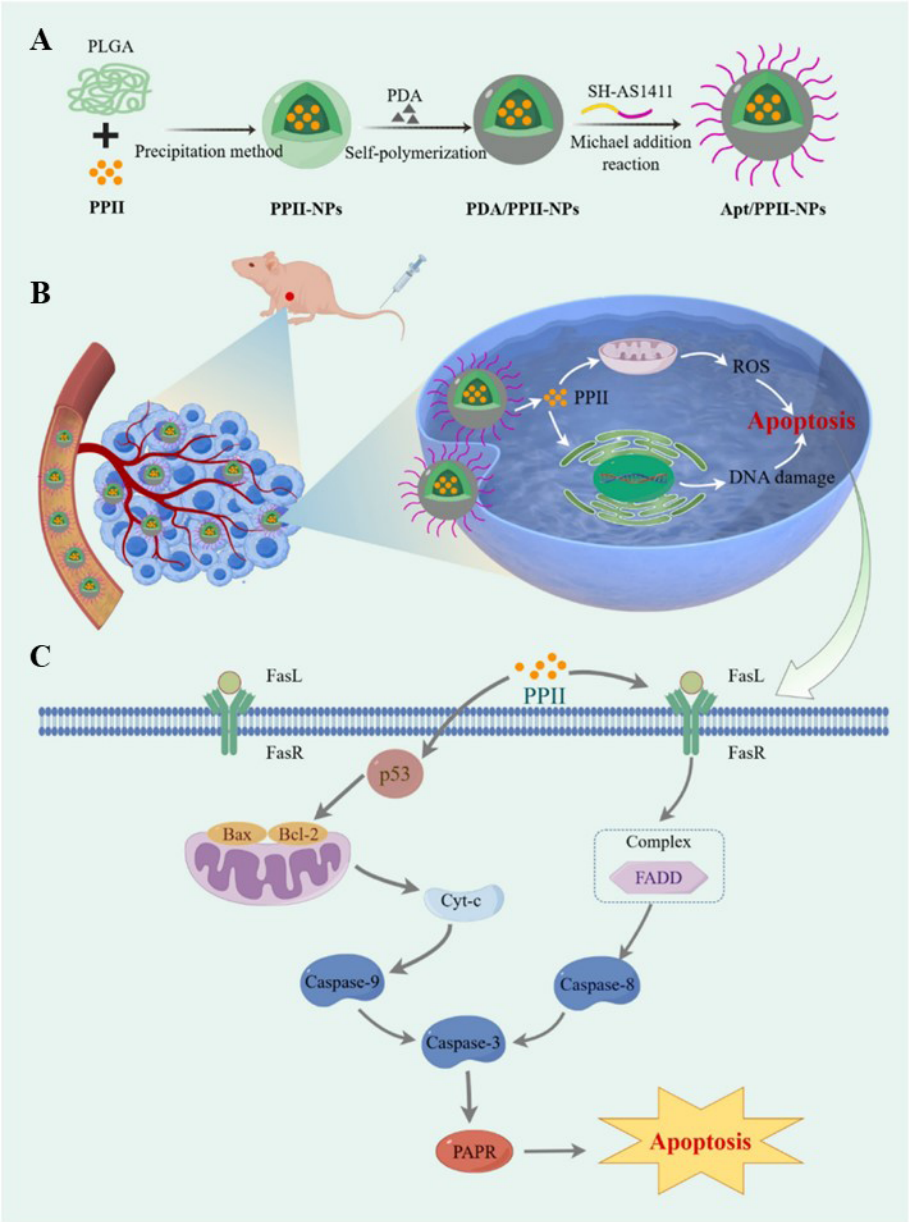

Figure 4. Schematic diagram of the treatment of liver cancer through inducing cell apoptosis using Apt/PPII-NPs. (A) Synthesis process. (B) Anti-tumor effect of Apt/PPII-NPs. (C) Apoptosis mechanism induced by Apt/PPII-NPs. Reprinted from Huang *et al.*[27]
Abbreviations: Apt: Aptamer AS1411; Bax: Bcl-2–associated X protein; Bcl-2: B-cell lymphoma 2; Cyt-c: Cytochrome c; FADD: Fas-associated protein with death domain; FasL: Fas ligand; FasR: Fas receptor; NP: Nanoparticle; PARP: Poly (ADP-ribose) polymerase; PDA: Polydopamine; PPII: Polyphyllin II.

2.3. Conceptual framework for nanomaterial selection

A practical design of nanoparticle–organoid systems requires an integrated conceptual framework for nanomaterial selection. Such a framework should consider the intended application type, the biological characteristics of the organoid model, the presence of biological barriers, payload compatibility, targeting requirements, and safety considerations. Specifically, material choice should be aligned with the research objective, such as therapy, imaging, sensing, or tissue engineering, while also accounting for tissue-specific and pathological features of the organoid model.[42] In addition, barriers such as dense ECM, elevated interstitial pressure, and hypoxic cores may critically influence nanoparticle penetration and distribution. Carrier selection should also match the properties of the intended payload, whereas surface functionalization strategies should be tailored to the need for active targeting of specific cell populations. Equally important is the evaluation of biodegradability, long-term toxicity, and unintended effects on organoid development. By standardizing these considerations, this framework may support the development of more precise and application-oriented nanoengineered organoid platforms.[43]

3. Distribution of nanomaterials in organoids

The spatial distribution of nanoparticles within the body is one of the key factors determining their therapeutic efficacy, as their localization in tissues directly influences the recognition efficiency of specific target cells and the subsequent activation of biological responses. In this process, the ECM plays a crucial role as a physical barrier. ECM is composed of proteins and polysaccharides that form a dense, complex network structure, significantly limiting the diffusion and penetration of nanoparticles within tissues. To address these limitations and enhance research consistency, engineered and chemically defined matrices are increasingly employed to standardize nanoparticle transport studies. Researchers are increasingly turning to engineered and chemically defined matrices. Compared with naturally derived matrices such as Matrigel, these synthetic or semi-synthetic matrices can improve standardization by allowing precise control over several key parameters.[44] These include matrix density and porosity, which determine the physical channels available for nanoparticle diffusion through modulation of polymer concentration and crosslinking density; stiffness, which enables the simulation of tissue-specific mechanical properties and thereby standardizes the influence of biomechanical cues on nanoparticle uptake; and biochemical composition, where defined ligand densities and spatial organization of biochemical factors help reduce nonspecific interactions and render transport studies more controllable.

Nevertheless, it should be noted that full standardization remains challenging, because matrix effects interact in complex ways with the intrinsic variability of organoids themselves, including differences in cellular organization and secretory profiles.[45] In organoid systems, particularly tumor organoids, the ECM not only replicates the structural environment of solid tumors but also mimics typical mechanical features, such as increased tissue stiffness and elevated interstitial fluid pressure. These factors have been shown to reduce the penetration ability of nanoparticles, leading to uneven drug distribution.

The intricate three-dimensional architecture within organoids—encompassing stratified cellular organization, nutrient and oxygen gradients, and a hypoxic core—further modulates the spatial distribution and diffusion dynamics of nanomaterials (Figure 5). In tumor organoids specifically, hypoxic regions frequently establish significant additional barriers to drug delivery. It should also be noted that conventional tumor organoid models cannot fully recapitulate the complex vascular architecture in vivo. Most current organoid systems primarily reproduce tissue structural features and the associated diffusion barriers, but lack authentic vascular networks, limiting their ability to accurately model nanoparticle delivery in vivo.

In recent years, vascularized organoids and microfluidic perfusion systems have partially addressed this limitation.[46] By incorporating endothelial cells or dynamic fluidic environments, these models can simulate certain aspects of vascular-associated transport, thereby improving the accuracy of nanoparticle delivery studies. However, these advanced systems still fall short of fully reproducing the complex hemodynamic properties and vascular–tissue interactions found in vivo, and therefore remain limited in their ability to predict nanoparticle biodistribution and delivery efficiency. Accordingly, when organoid models are used to evaluate nanoparticle delivery performance, their limitations in vascular simulation should be explicitly recognized, and the results should ideally be interpreted in combination with in vivo or other physiologically relevant models to obtain more reliable conclusions.[47]

To overcome limitations in nanoparticle distribution within complex tissues, advanced imaging technologies are widely used to evaluate and optimize nanoparticle localization and penetration behaviors. For example, multiphoton microscopy (MPM) and optical coherence tomography (OCT) enable high-resolution, three-dimensional imaging of nanoparticles within organoids. By employing nonlinear fluorescence excitation mechanisms and long-wavelength lasers, MPM overcomes the resolution and tissue penetration constraints inherent in conventional single-photon microscopy.[48] This technology has demonstrated significant efficacy in studies of brain

organoids in vivo, facilitating the observation of cell migration, neuronal network anomalies, differentiation impairments, and the progression of neurodegenerative diseases and tumor models.[49] Similarly, in retinal organoid research, MPM has been instrumental in elucidating human-specific neurodevelopmental mechanisms and related disease processes.[50]

On the other hand, OCT technology, based on interference measurement principles, offers high spatial resolution and non-invasive imaging advantages, making it valuable for three-dimensional structural reconstruction and real-time dynamic monitoring in organoid research.[51] For example, OCT has been used for real-time three-dimensional imaging of retinal organoids, providing detailed structural information on cell dynamics and tissue remodeling.[52] Despite these advantages, both techniques have inherent limitations in the context of nanoparticle–organoid interaction analysis.

To more accurately evaluate the penetration capacity and spatial heterogeneity of nanoparticles within organoids, a variety of quantitative analytical approaches have recently been developed, thereby improving the rigor and reliability of related studies. First, three-dimensional fluorescence imaging-based methods, such as confocal microscopy and MPM, are widely used. Through three-dimensional reconstruction of organoids, the fluorescence intensity of nanoparticles can be quantified at different depths, providing an overall assessment of their penetration behavior.[53] In addition, radial penetration analysis is commonly applied by using the organoid center as a reference point and calculating the decay profile of fluorescence signals along the radial axis, thereby quantitatively describing the diffusion efficiency of nanoparticles from the periphery toward the core. Furthermore, core-to-periphery distribution metrics can be used to assess the uniformity of nanoparticle distribution within organoids. For example, comparing fluorescence intensity ratios between the core and peripheral regions can directly indicate whether nanoparticles effectively penetrate into deeper structures. At the single-cell level, organoids can be dissociated into individual cells and combined with flow cytometry or single-cell sequencing techniques to quantify nanoparticle uptake. Such approaches help reveal uptake heterogeneity among different cell types and thus provide deeper insight into nanoparticle distribution in complex multicellular systems. In addition, quantitative techniques such as inductively coupled plasma mass spectrometry (ICP-MS) can be employed to precisely measure the metal content of nanoparticles, thereby determining their overall or region-specific accumulation in organoids.[54] Owing to its high sensitivity and accuracy, this method often serves as a powerful complement to fluorescence imaging.

Collectively, these multiscale and multimodal quantitative strategies are essential for comprehensively evaluating nanoparticle penetration and distribution heterogeneity in organoids, while also providing a more robust basis for cross-study comparison.[55]

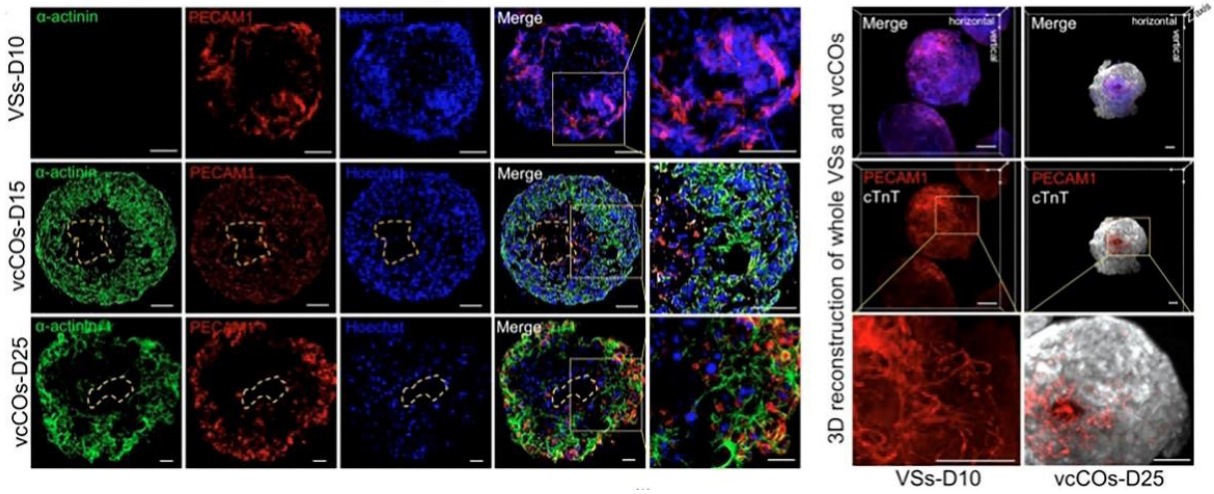

Figure 5. Whole-mount staining of vascular spheres (VSs) and cardiac organoids (vcCOs) for endothelial cells (platelet endothelial cell adhesion molecule 1 [PECAM1], red), cardiomyocytes (α-actinin, green), and the nucleus (Hoechst 33342, blue) at indicated days (D10, D15, and D25). Scale bars: 50 μm. The right panel shows the three-dimensional reconstruction of whole VSs (D10) and vcCOs (D25) using a light plate microscope. Scale bar: 100 μm. Reprinted from Yang *et al.*[56]

4. Nanomaterials regulating cell proliferation and differentiation in organoids

Organoid models have the capacity to reconstruct tissue-specific three-dimensional structures and microenvironments in vitro, providing an important platform to study the regulatory mechanisms of cell proliferation and differentiation. However, in complex three-dimensional systems such as organoids, ligand–receptor interactions do not always operate in a stable or uniform manner, and their effects are often highly dependent on the local microenvironment.

In organoid models, these interactions are regulated by multiple factors and exhibit marked context dependence.[57] First, receptor expression levels are often heterogeneous among different cell types and differentiation states, potentially leading to substantial differences in targeting efficiency. Second, the ECM can exert a matrix-shielding effect on nanoparticles, thereby limiting their effective contact with receptors on target cell surfaces. Third, dynamically changing microenvironmental factors within organoids, such as pH, oxygen tension, and metabolic status, may alter the affinity and stability of ligand–receptor binding. Fourth, nanoparticles may undergo surface modifications in biological environments, such as protein corona formation, further affecting their recognition capability and binding behavior. Therefore, ligand–receptor-mediated targeting in organoid systems should be considered a dynamic process that depends on specific experimental conditions, rather than a universally stable mechanism.

Recognizing this context dependence is important for optimizing nanoparticle design strategies and for improving the interpretation of experimental findings.[58] For example, in reconstituted testicular organoids, spermatogonial stem cells (SSCs) have the potential for proliferation and differentiation. To study the proliferation and differentiation abilities of SSCs in testicular organoids, researchers have conducted immunohistochemical staining.[59] Proliferating cell nuclear antigen (PCNA) and Ki67-positive SSCs indicate their proliferative potential (Figure 6). Zhang *et al.*[60] found that the expression patterns of Ki67 and PCNA in SSCs from testicular organoids resembled those in normal mouse testis tissues. C-kit, a marker of differentiating spermatogonia, especially A1–A4 type spermatogonia, was found in testicular organoids, suggesting that SSCs differentiate into A1–A4 spermatogonia within eight weeks. Therefore, testicular organoids can promote the proliferation and initial differentiation of SSCs within seminiferous tubules.

Further reverse transcription-polymerase chain reaction and Western blot analyses confirmed the expression of multiple germ cell and somatic markers, such as *PLZF*, *GFRA1*, *THY1*, *SYCP3*, and *MLH.1*[61] This indicates that organoids not only maintain the stem cell population but also support the developmental progression toward spermatocytes and more mature stages. It is important to note that cell seeding density and hormonal environments of recipient animals significantly influence the self-renewal and differentiation efficiency of stem cells within organoids. Moderate cell density (4×10^7 cells/mL) is conducive to the formation of seminiferous tubule-like structures, while excessively high or low cell densities may affect tissue reconstruction efficiency.[62] Hormonal status also regulates SSC differentiation potential, highlighting the critical role of microenvironmental factors in stem cell fate determination.[63]

5. Nanomaterials guiding organoid tissue development

Nanomaterials in organoid engineering are not intended to replace advanced ECM-based culture systems, but rather to serve as powerful complementary tools that endow these platforms with dynamic functions that cannot be readily achieved by ECM alone.[64] The integration of nanomaterials with ECM-based systems enables the construction of a microenvironment that is both more physiologically relevant and more controllable.[65] While ECM provides structural support and essential biochemical cues, nanomaterials introduce several unique engineering advantages. Owing to their precisely tunable physicochemical properties, including size, shape, and surface chemistry, nanomaterials can be optimized to enhance biocompatibility and regulate cell–material interactions in accordance with the specific requirements of different tissues.[66]

In addition, stimulus-responsive nanomaterials, designed to respond to light, magnetic fields, or electrical signals, allow non-invasive and remote modulation of the local microenvironment within organoids or direct activation of cellular receptors. The incorporation of imaging probes, such as quantum dots and magnetic nanoparticles, also enables long-term and real-time monitoring of cell migration, cell differentiation, and neuronal network abnormalities without disrupting organoid architecture. Furthermore, through surface functionalization with antibodies or ligands, nanoparticles can actively target specific cell subpopulations within organoids,[67] thereby increasing the local concentration of therapeutic agents while reducing nonspecific effects.

Beyond these functions, nanoplatforms can integrate multiple therapeutic and imaging components within a single system, allowing seamless combination of disease modeling, drug delivery evaluation, and real-time therapeutic monitoring.[68] Looking forward, embedding nanocarriers with spatiotemporally controlled release

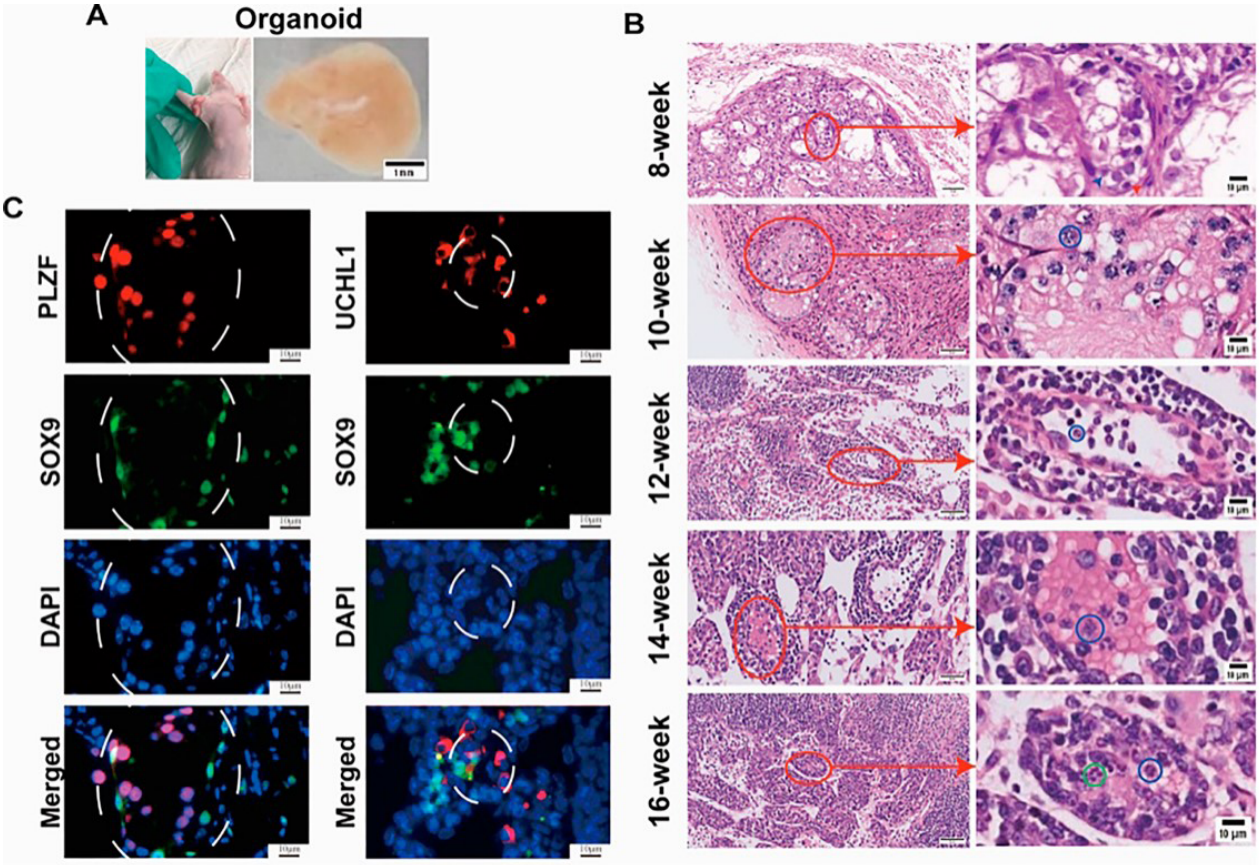

Figure 6. Morphological features of mouse testicular organoids. (A) The precise localization of transplantation (left panel) and a representative testicular organoid (right panel) at 8 weeks post-transplantation. Scale bar: 1 mm. (B) Hematoxylin and eosin staining of testicular organoids at 8, 10, 12, 14, and 16 weeks of cell transplantation. The red arrowhead indicates spermatogonial stem cells (SSCs), while the blue arrowhead denotes Sertoli cells; blue circles indicate spermatocytes, and green circles denote spermatids. Scale bars: 10 μm. (C) Double immunostaining of SOX9+ Sertoli cells and PLZF+ SSCs, as well as SOX9+ Sertoli cells and UCHL1+ SSCs, in the eighth testis organoids. White circles denote seminiferous tubules. The red arrows referred to a local zoomed-in image. Scale bars: 10 μm. Reprinted from Zhang *et al.*[60]
Abbreviations: DAPI: 4′,6-diamidino-2-phenylindole; PLZF: Promyelocytic leukemia zinc finger; SOX9: Sex-determining region Y-box 9; UCHL1: Ubiquitin C-terminal hydrolase L1.

properties into engineered ECM scaffolds may offer a more realistic means of recapitulating morphogen gradients and dynamic mechanical changes during in vivo development. Such deep integration of nanomaterials with ECM is advancing organoids from static culture models toward dynamic and predictive preclinical platforms.[69]

5.1. Nanomaterials as precision delivery tools for organoids

Studies have shown that organoid systems can simulate the structure and signaling networks of in vivo tissues, supporting stem cell proliferation and lineage differentiation.[70] These systems provide an ideal platform for exploring the regulatory mechanisms of exogenous factors (such as nanomaterials, bioactive molecules, and mechanical signals) on cell fate. Under the context of nanomaterial applications, these systems can be used to evaluate the effects of nanocarriers on stem cell self-renewal, differentiation direction, and microenvironment remodeling, thus laying the experimental foundation for developing nanostrategies to regulate tissue regeneration and functional reconstruction.[71]

5.2. Active regulatory mechanisms of nanomaterials on organoid fate

In organoid engineering, the role of nanomaterials has evolved from that of passive carriers to active components capable of modulating cell fate. This active regulation can be achieved through several interconnected mechanisms. At the receptor level, nanomaterials can directly interfere with or activate cell-surface signaling pathways through their specific physicochemical properties;[72] for example, stimulus-responsive nanomaterials that react to light, magnetic fields, or electrical signals can non-invasively

activate specific receptors on stem cell surfaces, thereby influencing lineage commitment, while controlled nanoparticle arrangement on the cell membrane may further induce receptor clustering and trigger downstream signaling cascades. In addition, nanomaterials can regulate cell behavior through mechanotransduction by altering the local mechanical environment within organoids.[73]

The incorporation of nanocomposite materials into ECM-based scaffolds can locally modulate stiffness and mimic dynamic mechanical changes during tissue development, whereas magnetic nanoparticles exposed to external magnetic fields can exert subtle mechanical forces on selected cell populations, thereby guiding tissue morphogenesis.[74] Nanomaterials may also influence organoid fate through redox and metabolic regulation, as certain nanoparticles have been shown to induce metabolic reprogramming in stem cells or diseased cells, while redox-active nanomaterials, such as specific metal oxides, can regulate local reactive oxygen species levels and thereby affect cell survival, proliferation, and differentiation.[75]

Furthermore, unlike conventional passive diffusion, nanosystems enable spatiotemporal control of bioactive signal delivery. By responding to local cues within organoids, including pH gradients, enzyme activity, and hypoxic conditions, nanomaterials can achieve on-demand release of signaling molecules at defined developmental stages or pathological regions. At the same time, the non-uniform distribution of nanoparticles within three-dimensional structures may be exploited to mimic in vivo morphogen gradients, thereby promoting the establishment of more complex spatial patterning and polarity. Collectively, these mechanisms indicate that nanomaterials are not merely auxiliary delivery tools but functional regulators capable of reshaping the biochemical, biophysical, and spatiotemporal signaling environment of organoids, thus providing new opportunities for directing organoid development and enhancing the precision of disease modeling and regenerative strategies.[17]

6. Impact of nanomaterials on the organoid tissue microenvironment

To systematically evaluate the physicochemical properties and biological effects of nanodrugs, it is essential to construct high-fidelity models that accurately replicate the complex disease microenvironment.[76] This is because microenvironmental factors directly determine the in vivo behavior, therapeutic response, and safety of nanoparticles. Traditional two-dimensional monolayer cell cultures, due to their simplicity, lower cost, and suitability for high-throughput screening, have been widely used in nanomedicine research for many years (Figure 7). However, this system is primarily limited to preliminary analyses of nanoparticle–cell interactions and cytotoxicity, failing to accurately predict their clinical efficacy.[77] The fundamental issue is that two-dimensional models lack a three-dimensional ECM, which plays a key role in regulating nanoparticle tissue penetration, diffusion kinetics, and intracellular uptake.[78]

In contrast, three-dimensional organoid models, by reconstructing the natural tissue's spatial structure, cell diversity, and functional characteristics,[79] provide a more physiologically relevant experimental platform for nanodrug research. Organoids, which are typically derived from stem cells or patient tissues, can self-organize to form multicellular systems with organ-specific structures and functions, providing a microecological environment similar to that in vivo for preclinical studies.[80,81] Disease-specific organoids—including models for cancer, neurodegenerative disorders, and infectious diseases—provide a pathologically relevant platform for investigating nanodrug behavior.[82] Automated bioreactors can markedly improve the size uniformity and production throughput of organoids by precisely controlling parameters such as hydrodynamics and oxygen tension. However, standardization of the external culture environment does not necessarily translate into uniformity of nanoparticle distribution within organoids. Physical barriers persist, as the dense cellular organization and ECM inside organoids continue to restrict nanoparticle penetration even in scaled-up systems. Therefore, in large-scale organoid platforms, the penetration depth and intratissue distribution of nanoparticles should still be directly validated using three-dimensional imaging or quantitative analytical techniques to ensure the reliability of efficacy assessment.[83]

7. Applications of nanomaterials in organoid engineering

In organoid engineering, the application of nanomaterials has become an important area of research due to their unique physicochemical properties, making them highly applicable in tumor models, tissue repair, drug screening, and multicellular organoids. Nanomaterials, with their tunable size, shape, and surface chemistry, play a significant role in organoid engineering, enhancing biocompatibility and regulating growth, development, and functionality. This section provides a detailed exploration of the application of nanomaterials in tumor organoids, tissue repair, drug screening, and their integrated role in multicellular organoids (Figure 8).

7.1. Applications in tumor organoids

The core goal of cancer nanomedicine is to construct nanocarriers that can accurately deliver drugs to the tumor site, thereby enhancing anti-tumor efficacy while

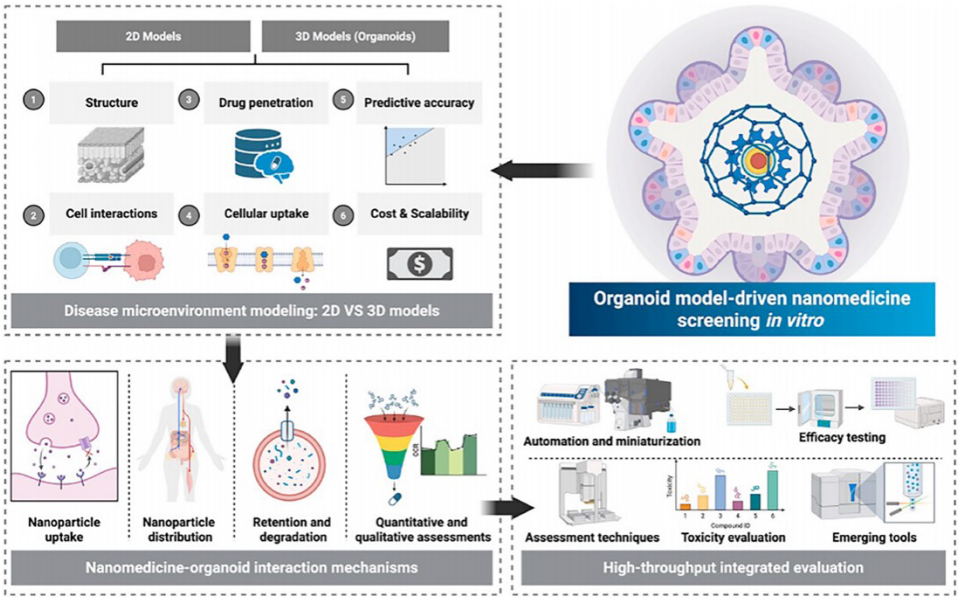

Figure 7. Organoid model-driven nanomedicine screening in vitro. The study provides a comparative evaluation of two-dimensional (2D) and three-dimensional (3D) organoid models for nanomedicine screening, underscoring distinctions in structural organization, cellular crosstalk, drug penetration efficiency, and predictive accuracy. The 3D organoid systems demonstrate superior physiological relevance and more reliable predictions of drug efficacy and toxicity, advantages that are further enhanced by automated screening platforms and high-throughput evaluation methodologies. Reprinted with permission from Wang *et al.*[84]

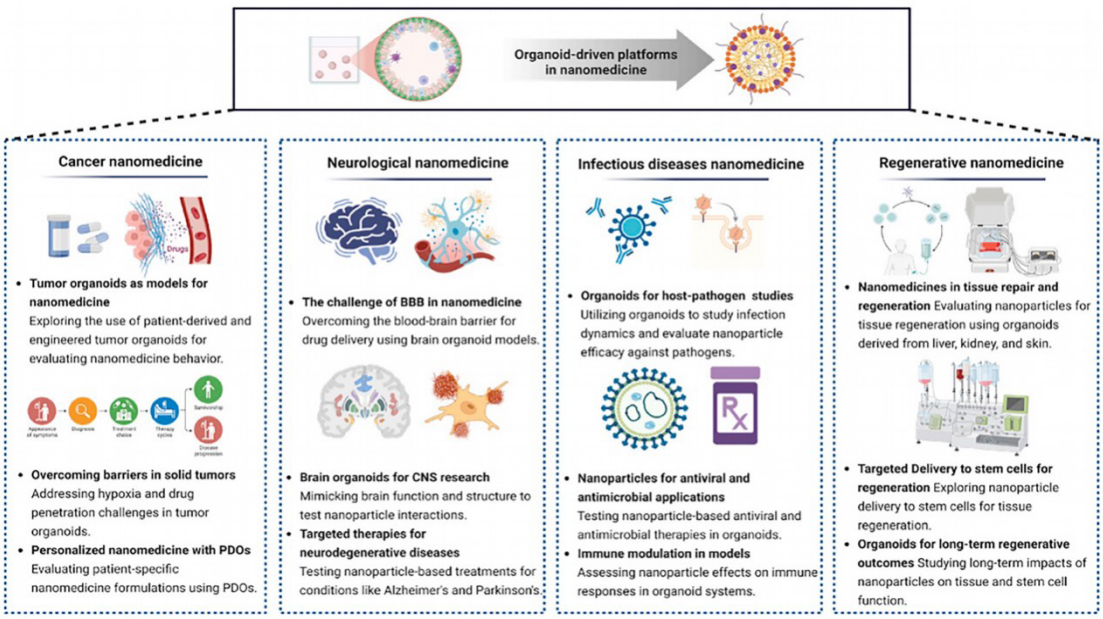

Figure 8. Applications of organoid-driven platforms in nanomedicine. The application of organoid platforms in personalized nanomedicine has expanded across diverse fields, including cancer treatment, neurological diseases, infectious disorders, and tissue regeneration. Reprinted with permission from Wang *et al.*[84]

Abbreviations: BBB: Blood–brain barrier; CNS: Central nervous system; PDO: Patient-derived organoid.

minimizing damage to normal tissues.[85] Tumor organoids, derived from patient biopsy specimens or tumor cell lines, serve as physiologically relevant three-dimensional platforms for investigating nanoparticle behavior within the complex and dynamic tumor microenvironment. By maintaining critical features of the parental tumor, including cellular heterogeneity, epithelial–mesenchymal interactions, and tumor-specific ECM components, these models offer an advantageous platform for evaluating the delivery performance, tissue distribution, and therapeutic efficacy of nanomedicines.[86]

Beyond the well-established pathway of apoptosis, emerging modalities of programmed cell death, including ferroptosis and cuproptosis, have recently attracted considerable interest within cancer research and nanomedicine.[87] Nanomaterials are capable of initiating these cell death pathways through the modulation of iron and copper homeostasis, the induction of lipid peroxidation, and the instigation of mitochondrial proteotoxic stress, offering a promising strategy to circumvent tumor resistance and augment anti-tumor efficacy.[54] Tumor organoid models, which retain three-dimensional tissue architecture, cellular heterogeneity, and key elements of the tumor microenvironment, represent a physiologically relevant in vitro platform for assessing these nanomaterial-induced cell death mechanisms, thereby refining and expanding our comprehension of nanomaterial-mediated anti-tumor actions.[88]

By reconstructing the complexity of tumor tissue in terms of spatial structure and biochemical signals, tumor organoids provide crucial tools for studying the interactions between nanoparticles, cancer cells, and ECM components, helping deepen understanding of drug uptake mechanisms, intracellular transport pathways, and local therapeutic responses.[89] In solid tumors, the hypoxic core is of particular importance because it is marked by low oxygen levels, dense ECM deposition, and poor vascular perfusion, all of which pose substantial obstacles to drug penetration.[90] Tumor organoids can faithfully recapitulate oxygen and nutrient gradients, providing a reliable model for assessing the capacity of nanoparticles to penetrate and exert therapeutic effects within hypoxic regions.[91]

Although patient-derived organoids hold considerable promise for optimizing nanoformulations in a personalized manner, their broader application remains constrained by several practical factors.[92] First, resource and time limitations are major challenges, as access to primary tumor tissues is often uncertain, and the establishment and expansion of organoids can be time-consuming, which may not be compatible with the urgent therapeutic window of some patients with advanced cancer. Second, the cost and scalability of individualized screening remain substantial barriers, as this approach requires intensive culture and analytical resources, while standardized automated workflows for processing large numbers of patient samples are still lacking. Finally, successful clinical translation requires the establishment of standardized procedures covering tissue processing, nanoparticle administration protocols, and efficacy evaluation criteria, in order to ensure the reproducibility of predictive results and their clinical relevance.[93]

7.2. Applications in tissue repair

In regenerative medicine research, nanoparticles have gradually become an important tool for promoting tissue repair and functional reconstruction, primarily by delivering growth factors, regulating local microenvironments, and targeting stem cell populations to enhance tissue regeneration.[94] Organoid models can reconstruct the spatial structure, cell composition, and some functional characteristics of natural tissues, providing a highly relevant three-dimensional experimental platform for evaluating the biological effects of nanomaterials in the regeneration process.[95]

Organoids derived from tissues such as the liver, kidney, and skin provide suitable platforms for functionally validating nanocarriers intended for tissue repair applications.[96] These models can simulate tissue microenvironments under damaged or pathological conditions. On this basis, nanoparticles loaded with growth factors—such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF)—can be used to assess their ability to promote cell proliferation, induce angiogenesis, and drive tissue remodeling in organoid systems, particularly in the context of fibrosis or chronic injury.[97]

7.3. Applications in drug screening

In drug screening, nanomaterials serve not only as therapeutic carriers but also as essential tools for constructing efficient screening systems. By loading antiviral, anti-malaria, or immune-modulating molecules onto nanocarriers, their delivery efficiency, cellular uptake capacity, and therapeutic potential can be systematically evaluated in vitro, enabling more targeted drug screening strategies.[98] However, the clinical translation of organoid-based nanodrug screening remains incompletely validated. Although organoid-based studies of drug response have shown some correlation with patient treatment outcomes, direct clinical validation specifically for nanodrug screening remains limited. Most existing evidence has been derived from studies of conventional small molecules or chemotherapeutic agents, whereas nanocarrier-based systems, owing to their more complex delivery mechanisms and in vivo behaviors, have not yet been sufficiently validated in terms of how organoid responses correspond to clinical outcomes.[99] In contrast to

traditional two-dimensional cell culture models, organoids derived from tissues such as the lung and intestine provide physiologically relevant three-dimensional platforms for nanodrug screening and more accurately recapitulate host–pathogen interactions in native tissues.[100]

Organoids can reconstruct tissue-specific structures and functions, including epithelial barrier integrity, mucus secretion, and immune response patterns, thus forming infection models that closely mimic the in vivo environment.[101] For example, lung organoids have been widely used to evaluate nanodrug candidates targeting respiratory pathogens, such as the influenza virus, respiratory syncytial virus, and SARS-CoV-2.[102] In these systems, nanoparticles loaded with small-molecule drugs, peptides, or small interfering RNA (siRNA) can be used to address targeting efficiency, viral replication inhibition, and immune-modulating effects, thereby optimizing nanomedicine design.

Moreover, organoid models can reproduce key microenvironmental factors in infected tissues, such as pathogen storage regions, hypoxic conditions, and immune cell involvement, thereby aligning nanomaterial screening more closely with clinical scenarios.[103] For example, nanoparticles with surface-modified specific ligands can be validated in organoids to determine their selective binding to infected cells or pathogens, thereby selecting candidates with superior targeting ability.[104] Additionally, the multicellular dynamic environment helps analyze immune responses induced by nanoparticles, such as changes in cytokine secretion and macrophage activation levels, providing a basis for comprehensive evaluation of drug safety and efficacy.[105]

At present, organoid-based nanotoxicology research is primarily focused on acute toxicity, while the evaluation of long-term effects is still in its early stages. To improve clinical translational value, future studies should prioritize the following: chronic and repeated dosing designs, including the establishment of long-term exposure models that simulate clinical treatment cycles to assess the cumulative toxicity of nanoparticles within organoids; functional and genomic stability, with attention extending beyond cell viability to the effects of prolonged exposure on organoid physiological functions, such as barrier integrity, as well as on genomic stability; and dynamic monitoring technologies, such as organ-on-a-chip platforms, to enable real-time and dynamic monitoring of long-term interactions between nanoparticles and organoids.[106]

Organoid-driven nanomedicine platforms hold enormous promise; however, most current organoid systems still lack complex immune components, greatly limiting the comprehensive evaluation of nanoparticle immunogenicity and immune-mediated therapeutic effects.[107] To address this limitation, research is evolving toward a higher level of physiological complexity. One key challenge is the limitation in immunogenicity evaluation: the absence of endogenous immune cells makes it difficult for researchers to observe critical biological responses induced by nanoparticles, such as cytokine storms, macrophage polarization, and complement activation. Immune cell co-culture strategies offer one potential solution: by introducing peripheral blood mononuclear cells, T cells, or macrophages into organoid systems, it becomes possible to simulate immune infiltration within the tumor microenvironment and thereby more accurately assess the cytotoxic efficacy of immuno-nanomedicines.[108] Another important approach is the organoid-on-a-chip strategy: microfluidic-based organoid chip systems can simulate dynamic blood circulation and immune cell recruitment, providing a valuable tool for investigating the real-time interactions between nanoparticles and the immune system. Through the integration of these strategies, organoid models will more faithfully reflect the immune response mechanisms of nanomedicines in vivo, thereby significantly enhancing the translational value of preclinical research.

Based on three-dimensional organoid systems, the nanodrug screening platform can more accurately reflect the in vivo microenvironment compared to traditional two-dimensional cultures, improving the predictive accuracy of nanomedicine performance and reducing the gap between in vitro screening and clinical application.[109] Therefore, the combination of nanomaterials and organoid technology is becoming a key strategy for precise drug screening and optimization in anti-infective drug development.[110]

7.4. Applications in multi-cell line organoids

Three-dimensional multicellular organoids, as highly biomimetic in vitro models, can reconstruct the spatial structure, cell heterogeneity, and microenvironment characteristics of tissues or tumors. Compared to traditional two-dimensional cell culture systems, they offer greater physiological relevance and clinical predictive value in nanomaterial research. Multicellular organoids typically include cancer cells, fibroblasts, immune cells, and ECM components, enabling the simulation of cell–cell and cell–matrix interactions that occur in real tissues.[111]

In multicellular organoids, different cell types exhibit differential nanoparticle uptake behaviors. For example, in tumor organoids, cancer cells, stromal fibroblasts, and infiltrating immune cells show significant differences in their uptake patterns.[112] This variation provides important insights for the precise design of targeted nanodrugs. Organoids reflect the complex tissue microenvironment, including the ECM, oxygen gradient, nutrient gradient, and spatial structural barriers, all of which influence

nanoparticle distribution and penetration.[113] Therefore, organoids can more accurately reflect the transport behavior of nanodrugs in vivo. Nanoparticle size, surface charge, and functional modifications significantly affect their diffusion, penetration, and retention within organoids.[114] Research has shown that negatively charged nanoparticles generally exhibit better tissue penetration in organoids, and multivalent ligand or targeting molecule modifications can enhance their endocytosis efficiency in specific cell populations.[114]

Overall, multicellular organoids, by reconstructing complex tissue microenvironments and cellular heterogeneity, provide a highly biomimetic research platform for evaluating nanoparticle uptake, distribution, and therapeutic efficacy in biological systems.[77] However, it is important to clarify that current organoid models only partially reproduce the intricate stromal and vascular interactions found in vivo. Although the integration of multicellular organoids, vascularized platforms, and microfluidic technologies represents a major advance in bioengineering and has substantially improved the physiological relevance of these models,[115] it must be acknowledged that current organoid systems can only partially reproduce the complex stromal and vascular interactions present in vivo. First, with regard to stromal complexity, although co-culture with fibroblasts and immune cells has enhanced cellular heterogeneity, these systems still struggle to fully recapitulate the highly dynamic and hierarchically organized ECM architecture of native tissues.[116] Second, in terms of vascularization, most current vascularized organoids rely on the integration of endothelial cells or on artificial scaffolds. While these approaches can improve nutrient and oxygen delivery to some extent, they remain insufficient compared with native vascular networks in terms of branching density, hemodynamic shear stress, and the fine microstructure of capillary beds. Third, microfluidic organ-on-a-chip platforms are capable of simulating certain hydrodynamic conditions and partially compensating for the limitations of traditional static culture systems; however, they still face significant technical challenges in maintaining long-term vascular stability and in reconstructing complex intertissue crosstalk. Overall, despite the substantial progress enabled by these advanced platforms, a considerable gap remains between current models and the full complexity of native stromal and vascular systems, and bridging this gap will be a critical priority for future translational research.[117] Their applications in mechanism studies, immunotherapy collaboration research, high-throughput screening, and precision medicine significantly enhance the clinical translation potential of nanomedicines, making the intersection of nanomedicine and organoids a key area of research development.[118]

However, this increase in complexity also poses serious challenges for experimental standardization, and the establishment of unified criteria covering the following parameters is a prerequisite for clinical translation. To improve interlaboratory reproducibility and enhance the translational potential of organoid-based studies, the standardization of experimental parameters is essential.[119] The following summarizes the core elements that should be standardized in studies of nanoparticle–organoid interactions: organoid characterization, including detailed documentation of organoid origin (such as patient biopsies and stem cell lines), passage number, culture duration, and quantitative size distribution to ensure baseline consistency of the biological model; microenvironmental control, including clear definition of the chemical composition, stiffness, and matrix components of the hydrogel or extracellular scaffold, as these physical properties strongly influence nanoparticle penetration kinetics and distribution heterogeneity; nanoparticle physicochemical properties, including precise characterization of particle size, surface charge, morphology, and surface modifications such as ligand density, since these features determine tissue diffusion and cellular uptake patterns; exposure protocols, including standardized dosing regimens based on mass concentration or surface area concentration, exposure duration, and the specific administration mode, such as static incubation or dynamic microfluidic perfusion; and analytical endpoints, including standardized quantitative metrics such as radial penetration depth, core-to-periphery distribution ratio, single-cell uptake rate, and absolute accumulation measured by ICP-MS.[120]

8. Challenges and future directions

Despite the promising potential of organoid-driven nanomedicine platforms, there are still many challenges in their biomedical research and therapeutic applications that require systematic optimization.[121-122] The foremost issue is the lack of a unified standard system.[123] Beyond insufficient standardization, batch-to-batch variability commonly observed in organoid systems is another major factor affecting the consistency of experimental outcomes.[106] Even under identical culture conditions, substantial differences may still arise between batches in organoid size, cellular composition, differentiation state, and ECM composition. In addition, the intratumoral-like microenvironment within organoids is highly heterogeneous, with pronounced spatial gradients in oxygen, nutrients, and metabolic byproducts. These factors can markedly influence nanoparticle uptake efficiency, penetration capacity, and subsequent biological responses.[124] For example, larger organoids usually exhibit a more pronounced diffusion barrier effect, thereby limiting nanoparticle access to the core region, whereas cells at different differentiation states may display

distinct nanoparticle uptake profiles, further increasing result variability. Accordingly, batch-to-batch variability has been recognized as one of the major sources of poor reproducibility in nanoparticle–organoid studies. At the current stage, effectively reducing inter-batch variability and establishing standardized evaluation frameworks remain critical challenges for the field. Future work should therefore place greater emphasis on the standardization of organoid preparation procedures, harmonization of experimental parameters, and incorporation of quantitative assessment methods to improve the reliability and comparability of experimental results.

In addition, although nanomaterials have shown considerable potential in regulating metabolic reprogramming in organoid systems, the reproducibility of these effects across different organoid models has not yet been sufficiently validated. Most existing studies have focused on specific models or single experimental settings, and no unified or broadly generalizable conclusions have yet been established. Therefore, this area remains largely exploratory, and the robustness and reproducibility of current findings still require systematic evaluation.

Available evidence suggests that nanomaterial-induced metabolic reprogramming is strongly influenced by multiple factors.[125] First, the origin of the organoids, such as whether they are patient-derived or stem cell-derived, as well as their differentiation status, can directly shape their metabolic features and responsiveness to external stimuli. Second, the physicochemical properties of the nanomaterials, including composition, particle size, surface charge, and surface modification, can alter their interactions with cells and thereby affect their metabolic regulatory capacity.[126] Third, experimental conditions, such as dosage and exposure duration, also play important roles in determining the magnitude and direction of metabolic reprogramming. Consequently, at present, the consistency of nanomaterial-mediated metabolic modulation across different organoid systems remains highly uncertain.

This issue is now regarded as a major limitation of the field. Future studies will need to improve reproducibility and comparability by standardizing organoid construction workflows, unifying nanomaterial characterization parameters, and optimizing experimental design, thereby supporting more reliable mechanistic investigations and facilitating clinical translation.[127] Currently, there are no general guidelines for organoid culture, maintenance, and functional characterization, leading to significant differences in size, cell composition, and functional characteristics across different laboratories.[128,129] This inter-laboratory variability weakens the reproducibility of models and affects their reliability as preclinical evaluation tools. Therefore, establishing standardized culture medium formulations, quality control systems, and functional verification standards is essential for enhancing model stability and comparability.[130]

Another major limitation is the insufficient level of clinical validation. Most current studies remain at the stage of preliminary toxicity and efficacy assessment, and the lack of large-scale clinical data makes it difficult to accurately predict the actual in vivo performance of these systems in patients. To validate the predictive accuracy of organoid models for patient clinical responses, researchers should adopt a systematic validation framework.[131] First, matched testing should be performed using paired patient-derived organoids to evaluate both free drugs and their corresponding nanoformulations, thereby assessing the therapeutic gain conferred by nanomedicine strategies.[132] Second, clinical correlation should be established by directly comparing in vitro organoid screening results with patients' actual clinical outcomes, either retrospectively or prospectively, in order to determine the predictive sensitivity and specificity of the model. Third, multi-parameter readouts should be integrated to encompass diverse indicators, including cell viability, morphological changes, gene expression profiles, and the tissue penetration depth of nanoparticles, to construct a comprehensive evaluation system. Finally, the clinical predictive value of organoid-based nanomedicine platforms should be confirmed through longitudinal patient follow-up and multicenter validation across laboratories.

Another major limitation is the lack of scalable production capacity.[133] At present, the organoid construction process requires high precision, involving directed differentiation of stem cells and fine-tuning of three-dimensional culture systems. The overall process is time-consuming and labor-intensive.[134] Although organoid models overcome some of the limitations of conventional two-dimensional cell models, their ability to bridge the gap between preclinical findings and clinical outcomes remains limited. The major advantage of organoid systems lies in their capacity to preserve three-dimensional tissue architecture, cellular heterogeneity, and disease-relevant microenvironmental features, thereby providing a more physiologically relevant platform for the in vitro evaluation of nanomedicines.[135] However, these models cannot fully recapitulate the complex systemic processes that occur in vivo, including pharmacokinetics, immune regulation, and inter-organ interactions. Therefore, while organoids may help narrow the gap between preclinical success and clinical failure to a certain extent, they cannot yet replace in vivo models and have significant limitations in predicting the clinical efficacy of nanomedicines.[136] Small fluctuations in oxygen tension, nutrient gradients, or fluid dynamics can induce heterogeneity among batches, making it difficult to ensure batch consistency.[137] This limitation restricts its application in high-throughput drug screening, where large

numbers of standardized and stable biological models are needed.[138]

To enhance scalability, automated bioreactors and microfluidic systems are considered key technological pathways. Studies have shown that automated stirred-tank bioreactors, by precisely controlling fluid dynamics, stirring rate, and oxygen tension, can stably produce billions of human-induced pluripotent stem cell aggregates of controllable size while maintaining their pluripotent state.[139] Additionally, modular organ-on-a-chip platforms show great promise. For example, Carvalho *et al.*[96] developed a LEGO-like microfluidic system that combines continuous perfusion with real-time monitoring of DO_2 and pH, enabling the cultivation of thyroid organoids for up to 10 days under strictly controlled conditions. These technologies combine automated scaling with precise environmental control, laying the foundation for the industrial-scale, high-quality, reproducible production of organoids.

9. Conclusion

Organoid-driven nanomedicine platforms, by addressing key issues such as insufficient standardization, limited scalability, and incomplete physiological complexity, have the potential to transition from experimental research tools to predictive preclinical models. These technological advancements will aid in the realization of personalized, precise, and highly safe therapeutic strategies, promoting the translation of preclinical research findings into clinical applications.

Organoid technology provides a more in vivo-like experimental platform for biomedical research, showing immense potential in drug screening, disease model establishment, and therapeutic method exploration. The application of nanomaterials in organoids will propel the field to new heights, offering new strategies for drug targeting and delivery, while also providing a solid foundation for the study of disease mechanisms and the development of precision medicine.[56] However, despite significant progress in both organoid and nanotechnology fields, challenges such as model standardization, scalability, and physiological complexity remain. Addressing these issues will drive deeper integration of organoid and nanomaterial research and promote their widespread application in biomedical fields.

In the future, as technology continues to advance, the combination of organoids and nanomaterials will enable breakthroughs in multiple directions. Firstly, the vascularization of organoids will become a key focus of research, particularly through the integration of endothelial cell co-culture systems, artificial vascular scaffolds, and microfluidic perfusion systems to support nanoparticle penetration and therapeutic efficacy in highly vascularized tissues. Secondly, nanodrug design will focus on microenvironment-responsive features, such as developing multifunctional nanoparticles that respond to hypoxia or pH changes to enhance targeting precision and reduce nonspecific side effects. Within the three-dimensional architecture of organoids, particularly in tumor organoids, pronounced hypoxic and redox gradients are commonly present. It should be clarified that nanoparticles do not biologically "adapt" to these changes on their own; rather, they can be molecularly engineered to exhibit physicochemical responsiveness to specific microenvironmental cues. In terms of hypoxia responsiveness, nanomaterials can be designed with hypoxia-sensitive chemical bonds or functional groups, enabling precise drug release or structural transformation within the hypoxic core regions of organoids and thereby helping to overcome the penetration barriers imposed by dense tissues. In addition, redox-sensitive designs can take advantage of variations in intracellular glutathione levels and other redox-related indicators within organoids, allowing engineered nanocarriers to undergo spatiotemporally controlled disassembly and thus improving the local bioavailability of therapeutic agents. Therefore, the key concept is not active adaptation, but intelligent sensing through environment-triggered mechanisms. This strategy provides a precise means of regulation in organoid research and enables the design of more predictive and pathology-oriented drug-delivery systems for complex microenvironments. Moreover, the construction of multi-organ models will provide more comprehensive data for systematic efficacy and safety studies, especially when combined with immune components and vascularized structures, significantly improving clinical translation potential.

In summary, with technological advancements and increasing interdisciplinary collaboration, organoid-driven nanomedicine platforms are expected to provide new solutions for personalized medicine and precision treatments, accelerating the development and clinical application of innovative drugs and ultimately benefiting human health.

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Conflict of interest

The authors declare they have no competing interests.

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