Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Harnessing Organoid Platforms for Nanoparticle Drug Development

Linanni Chen[1–4,*], Xinying Luo[1–4,*], Jiankang Zhang[1–4], Jinwen Zhang[1–4], Chunting Yang[1–4], Yunqi Zhao[1–4]

[1]College of Science, Mathematics and Technology, Wenzhou-Kean University, Wenzhou, Zhejiang, People's Republic of China; [2]Wenzhou Municipal Key Laboratory for Applied Biomedical and Biopharmaceutical Informatics, Wenzhou-Kean University, Wenzhou, Zhejiang, People's Republic of China; [3]Zhejiang Bioinformatics International Science and Technology Cooperation Center, Wenzhou-Kean University, Wenzhou, Zhejiang, People's Republic of China; [4]Dorothy and George Hennings College of Science, Mathematics and Technology, Kean University, Union, NJ, USA

*These authors contributed equally to this work

Correspondence: Yunqi Zhao, College of Science, Mathematics and Technology, Wenzhou-Kean University, 88 Daxue Road, Wenzhou, Zhejiang, 325060, People's Republic of China, Email yuzhao@kean.edu

Abstract: Cancer nanomedicine holds transformative potential, but its clinical translation remains hindered by the lack of preclinical models that accurately mimic human tumor complexity. Conventional approaches often overlook the dynamic tumor microenvironment (TME) and interpatient variability, leading to unreliable predictions of nanodrug behavior. Here, we present tumor organoids as a transformative solution. These three-dimensional cultures retain the original tumor's architecture, molecular profiles, and TME interactions. Through concrete examples spanning pancreatic, breast, and glioblastoma cancers, we showcase how organoids reliably evaluate nanodrug delivery efficiency, therapeutic effects, and safety profiles. In addition, the establishment of large-scale organoid biobanks further facilitates rapid drug screening and tailored treatment strategies, significantly improving preclinical success rates. Therefore, the organoid-driven paradigm not only overcomes long-standing challenges in tumor modeling but also paves a faster, more reliable path toward clinically effective nanotherapies.

Keywords: cancer, drug screening, nanoparticle, organoid, personalized medicine

Introduction

The advent of nanotechnology has heralded a new era in the field of cancer treatment, with nanoparticles emerging as promising candidates for improving efficacy and reducing side effects.[1] Despite the promise of nanoparticles in preclinical studies, translating these nanoscale drug delivery systems into clinical practice has been slow. Accurately evaluating the safety and efficacy of nanomedicine in preclinical studies is still a challenge. The complexity of the tumor microenvironment (TME) can impede the penetration and uptake of nanomedicines and influence tumor progression and metastasis. It also plays a crucial role in determining the therapeutic response.[2] Therefore, there is a critical need for more representative and predictive models that can accurately mimic human tumor pathophysiology to predict drug responses.

Traditional two-dimensional (2D) monolayer cultures have served as the foundation of cancer research for decades, with tumor cells typically grown as flat sheets on artificial surfaces. However, researchers now recognize that these systems cannot reproduce the intricate three-dimensional structure and cellular diversity found in actual human tumors.[3] Unlike living tumors, these simplified models lack essential biological features, including proper cell-to-cell communication, extracellular matrix networks, and the spatial organization that collectively determine how nanoparticles behave in real tissue. In this context, spheroids emerge as a cost-effective option for preliminary screening, similar to 2D models.[4] While both organoids and spheroids serve as 3D models for nanoparticle evaluation, they exhibit fundamental differences in biological relevance and application scope. Spheroids, formed through self-aggregation of tumor cell lines, provide a simplified 3D structure but lack heterogeneity.[5]

Received: 28 March 2025
Accepted: 5 July 2025
Published: 18 July 2025

Organoid technology has gained considerable attention as a powerful tool for cancer research and drug development.[6] By providing a more accurate representation of human tumors, organoids offer a valuable tool for predicting how tumors respond to nanoparticle-based treatments and identifying the factors that govern the success or failure of these therapies. This approach may accelerate the translational application process of nanoparticle drugs from the laboratory to the clinic.[7] The volume of scholarly articles related to organoids has significantly grown in the last decade (Figure 1). The Food and Drug Administration announced that organoid technology can replace animal studies, which are no longer mandatory for product safety approval.[8]

Integrating organoid technology with nanoparticle drug development is a significant step in improving cancer therapies.[9] The advent of organoid technology has provided new opportunities for the research and development of nanomedicine (Figure 2).[10–13] Organoid-nanoparticle systems represent an exciting breakthrough in cancer drug development. By combining the biological complexity of organoids with the precision targeting of nanoparticles, researchers can now tackle long-standing challenges across the entire drug development pipeline.[14] These hybrid systems faithfully recreate the tumor microenvironment's key characteristics, giving us unprecedented ability to study how nanoparticles actually behave in human-like conditions. This means we can better predict drug delivery effectiveness, tailor treatments

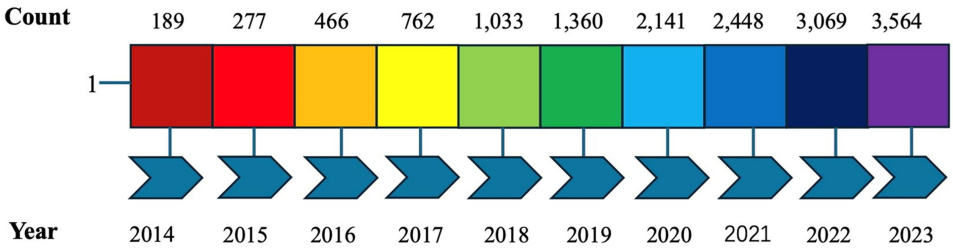

Figure 1 The number of organoid-related publications published in the past ten years (data obtained from PubMed).

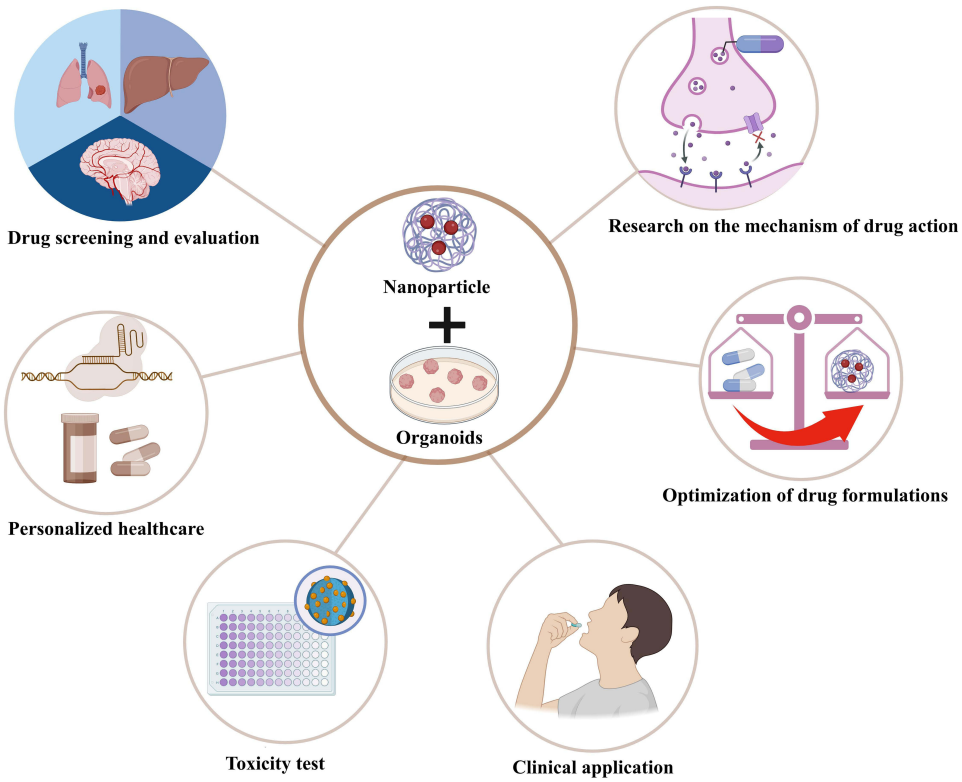

Figure 2 Application prospects of organoids in nanoparticle-based drug formulations.

https://doi.org/10.2147/DDDT.S530999

to individual patients, and identify potential toxicity issues earlier than ever before. The unique synergy between organoids and nanoparticles is revealing new insights into drug formulation and how nanotherapeutics work at a fundamental level. As our understanding of organoids and nanoparticles continues to evolve, we anticipate that this field will yield transformative advances in cancer treatment. Moreover, with the continuous progress and deepening of technology applications, we expect organoid technology to play a more important role in future cancer treatment, providing patients with more effective and personalized treatment options.

Recent advances in organoid technology have opened new possibilities for modeling human tumors.[15] However, their potential to transform cancer nanomedicine development remains largely untapped. This review synthesizes cutting-edge research to demonstrate how organoids are redefining preclinical testing paradigms for nanoparticle therapeutics. The protocols and validation frameworks presented here provide researchers with actionable strategies to harness organoids' predictive power, addressing the urgent need to improve the dismal clinical translation rates of nanotherapeutics. By bridging fundamental discoveries with translational applications, this work moves the field beyond proof-of-concept studies toward clinically meaningful implementation.

Transforming Cancer Research with Organoids

Preclinical cancer research is challenging because of the restrictions of traditional in vitro and in vivo methods. Cancer cells grown outside an organism, such as cell lines, cannot represent tumors in patients as accurately. A variety of organoid models have been established (Figure 3) in response to the limitations of traditional methods in preclinical cancer research.

Patient-derived tumor organoids form through a remarkable recapitulation of self-renewal and spatial organization processes observed in native tumors. This unique capability comes from cancer stem cells preserving their original epigenetic blueprints. Researchers typically culture these cells in a life-like extracellular environment, most often using Matrigel® or specially formulated collagen hydrogels. In this setting, the cells reactivate crucial developmental pathways like Wnt/β-catenin and BMP signaling, which guide them to form three-dimensional structures remarkably similar to real tumors.[16]

For these organoids to thrive while maintaining their tumor-like properties, scientists have developed specific culture protocols. These methods combine essential stem cell support factors with specialized growth additives tailored to different cancer types. Maintaining proper oxygen levels is equally critical, with researchers carefully controlling conditions to match the low-oxygen environment that tumors experience in the body.[17]

The physical properties of the growth environment, particularly matrix stiffness, are essential for tumor organoid cultures. Matrix stiffness varies significantly across different tumor types. For instance, the optimal matrix stiffness for softer malignancies like pancreatic carcinoma is around 4 kPa, while lung solid tumors require a stiffer microenvironment of

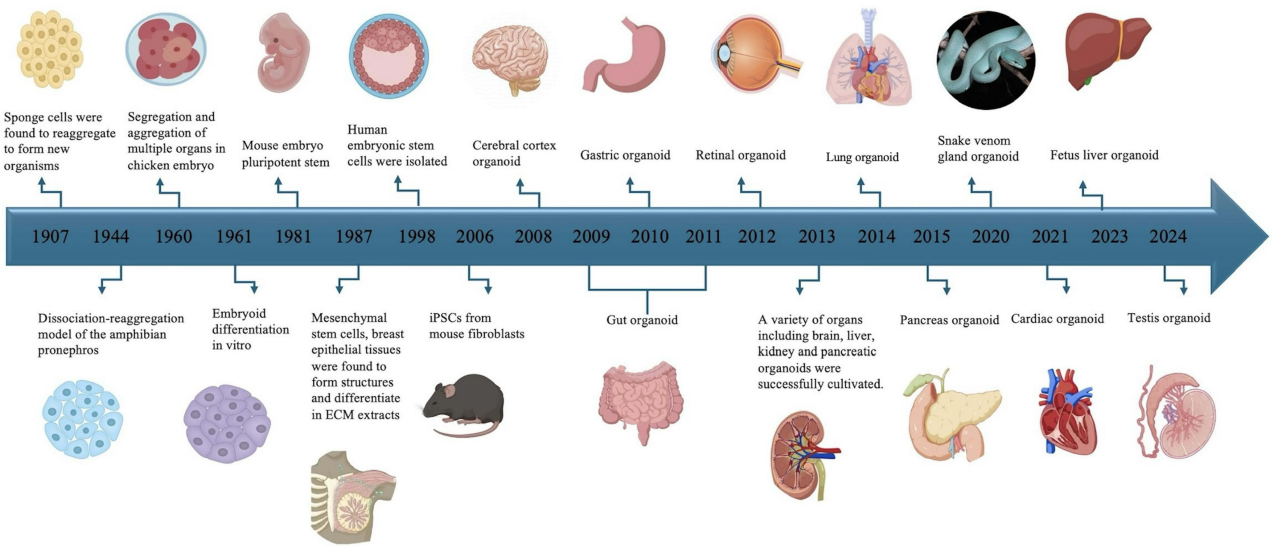

Figure 3 The development timeline of organoid models.

https://doi.org/10.2147/DDDT.S530999

approximately 20–30 kPa.[18] The stiffness is mainly dictated by the quantity and cross-linking extent of stromal components, which are crucial factors influencing tissue stiffness. Throughout tumor progression, heightened stiffness of the extracellular matrix (ECM) not only hinders drug delivery but also promotes cancer advancement by activating mechanical stimuli that influence cell membrane receptors and mechanosensitive pathways. These differences in stiffness significantly influence tumor cell behavior, including proliferation, migration, and responses to therapeutic interventions.[19]

Tumor organoids have proven effective in the determination of drug reactions and personalized therapy decisions.[20,21] Recent validation demonstrates that well-established liver cancer organoid models preserve >90% of the original tumor's genetic alterations under 2 months in vitro culture. In a study focusing on pancreatic ductal adenocarcinoma patient-derived organoid (PDO), 82.4% to 99.96% of the mutations identified in the primary tumor samples were successfully identified in the organoid cultures. The application of organoid modeling in oncology, particularly PDO pharmacogenomics, has significantly advanced by linking driver mutations to therapeutic responses. Research across cancers like breast, head and neck squamous cell carcinomas, prostate, pancreatic ductal adenocarcinoma, and bladder found that specific gene mutations in PDOs were associated with sensitivity to targeted drugs, offering potential guidance for patient treatment selection.[22] These results demonstrate the promise of organoid models as effective resources for forecasting clinical outcomes and informing personalized cancer treatments.

Since organoids are highly stable in terms of genome and phenotype, they are also useful for evaluating nanomedicine therapeutic efficacy and interactions within TMEs.[23–25] This can be achieved by establishing biobanks containing large PDO collections. Therefore, conducting comprehensive research on different aspects, such as drug development, tumorigenesis, and cancer pathobiology, is possible using established biobanks with high genetic stability over time.[26] Additionally, because organoids reflect actual human cancer complexity while recapitulating it simultaneously, these biobanks also offer an opportunity for testing nanoparticle-based drugs with a precision oncology approach toward personalized treatment against diverse types of cancers. This means that one can use this method to personalize treatment by testing various drugs on different types of tumors grown from PDOs.[27,28] Therefore, they have contributed greatly to advancing nanomedicine translational research.

Organoids follow intrinsic developmental procedures to replicate their counterparts' critical structural and functional properties.[29] Organoids from various tissues and cancers maintain their unique response profiles upon exposure to external stimuli. They still manifest normal sensitivities to therapies such as different chemotherapeutic agents.[30,31] Notably, organoid-on-a-chip (OOC) models have been developed with the help of technological advancements that position these models as potential platforms for precision medicine.[32]

OOC is a culture of organoid cells in a microengineered chip.[33] It contains a microfluidic chip that enables fluid flow control, nutrient exchange and other characteristics of the microenvironment to be precisely controlled.[34] This overcomes some of the main challenges associated with TME modeling, tissue-tissue interactions, and multiorgan communications by reducing experimental variation compared with static cultures.[35] OOC systems may benefit oncology drug development.[36] They are closely related to real tumor tissues, making them valuable during target evaluation at an early stage because they can capture heterogeneity within tumors. Furthermore, reproducible high-throughput screening for drug efficacy has become possible because of standardized microchip platforms.[37,38] Using a flexible in vitro model, such as organoids, with the rigidity and repeatability of the microchip environment provides OOC potential as an all-around preclinical platform. This combines organoid translational relevance with the need for standardization of nanostructured medicines. Therefore, OOC-personalized organoid cultures could be used throughout the nanomedicine development pipeline when placed in physiologically relevant contexts.[39]

Patient-derived xenograft organoids (PDXOs) can be derived from adult stem cells within established patient-derived xenograft (PDX) models.[40] Like their in vitro counterparts, PDXOs maintain key attributes of the original tumors, such as genomic profiles and histological features. On the other hand, they show excellent prediction ability for clinical response and have advantages over PDX models regarding high throughput screening for compounds.[41,42] Several studies have shown that existing libraries of PDXs have been changed into biobanks comprising cancerous cell lines derived from carcinoma organoids with parental organoids, confirming their similarity in terms of genomics, pathology, and pharmacology.[43] PDXOs serve as physiologically relevant in vitro platforms for high-throughput drug screening, overcoming the scalability limitations of in vivo models while preserving tumor microenvironment interactions. Establishing large collections of

organoids will help facilitate the integration of PDXO-based approaches into early-stage drug discovery programs and the creation of personalized treatment options guided by tumor profiling. Therefore, they are promising models for accelerating precision oncology drug development since they retain clinical relevance and compatibility with high-throughput platforms.[44]

Current culture methods have been successful in creating biobanks that encompass a variety of cancer types through the use of organoids. These organoids are derived from pancreatic,[45] gastric,[46] colon,[47] prostate,[48] kidney,[49] and breast[44] tumor tissues as well as metastatic biopsies. Multiple studies have shown that compared with tumors, PDOs retain many important morphological and genetic features of the original cancer throughout passages.[50] They could be used to determine how drug molecules can overcome barriers in the tumor microenvironment that prevent ordinary drugs from reaching their target, which is a key problem for drug delivery in oncology. Compared with traditional models, organoid biobanks reduced preclinical failure rates and research costs and timings.[50] They could speed up the clinical translation of nanoparticles by testing them in personalized laboratory dishes before they reach patients. In short, this remarkable technology has turned bottom-up approaches into powerful tools for fighting cancer at every stage.

Organoid Models in Nanomedicine Development

Nanoparticles serve as engineered carriers for various therapeutics, such as small molecule drugs, nucleic acids, proteins, and chemotherapeutics.[51] Compared with traditional chemotherapy approaches, their utility in drug delivery offers pharmacokinetic improvements and enables tumor-specific targeting, controlled drug release, and reduced off-target toxicity through engineered design features.[52] Some of the main benefits of nanoparticles are that they use an active targeting strategy to aid in delivery and make targeted ligand functionalization possible. This allows them to bypass various biological obstacles, frequently preventing systemically given drugs from accumulating well in cancerous tissues.[53]

Many advantages can be found with organoid models, as they serve as valuable tools for assessing nanoparticle-based drug delivery systems. Organoids recreate the physical barriers that nanoparticles meet in living organisms. This allows for investigating complicated cancer-stromal cell interactions that affect delivery.[54] In addition, compared with in vivo structures, one can easily image multiple scales of nanoparticle behavior using organoids as a model.[55] During the early stages of drug development, organoids could be used to test nanoparticle penetration ability as an avenue for accelerating lead optimization. The assessment of nanomedicine efficacy and toxicity individually can also be performed via personalized organoid platforms.[56] At the subcellular and cellular levels, it is possible to study nanoparticle-tumor interactions with the help of organoid systems.[57]

Organoid models uniquely maintain functional stromal networks that replicate the critical triad of nanoparticle, ECM, and cellular interactions governing therapeutic responses. These systems preserve native ECM components such as collagen IV and fibronectin that actively guide nanoparticle behavior.[58] Pancreatic cancer studies using fibrotic organoids have demonstrated how ECM architecture dictates nanoparticle penetration patterns and subsequent drug delivery efficiency.[59] Another study highlighted the potential of organoid models to predict drug responses, emphasizing that the preserved stromal networks within organoids can significantly influence nanoparticle uptake and distribution, thereby affecting treatment outcomes.[60] In addition, toxicity assessments confirm that organoid ECM integrity directly modulates cellular nanoparticle processing, validating these models for preclinical safety evaluation.[61]

Organoids represent a promising model for advancing personalized nanoparticle-based cancer therapies, offering distinct advantages over traditional 2D and animal models (Figure 4). Using organoid systems in nanomedicine opens new possibilities and challenges that must be continuously addressed. In this section, we review the applications of organoid platforms and their potential as versatile tools to transform nanomedicine into clinics.

Pancreatic Organoids

The poor prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) stems from the dense fibrous stroma and intricate multicellular microenvironment, which are challenging to replicate using traditional cell lines.[62] In contrast, PDAC organoids better represent real in vivo conditions, such as histoarchitecture or the microenvironment, than typical cell lines do.[63] Pancreatic organoid models have been generated from cancerous mice and human pancreas. These models can be used to understand the steps of pancreatic cancer progression at a molecular or cellular level.[64,65]

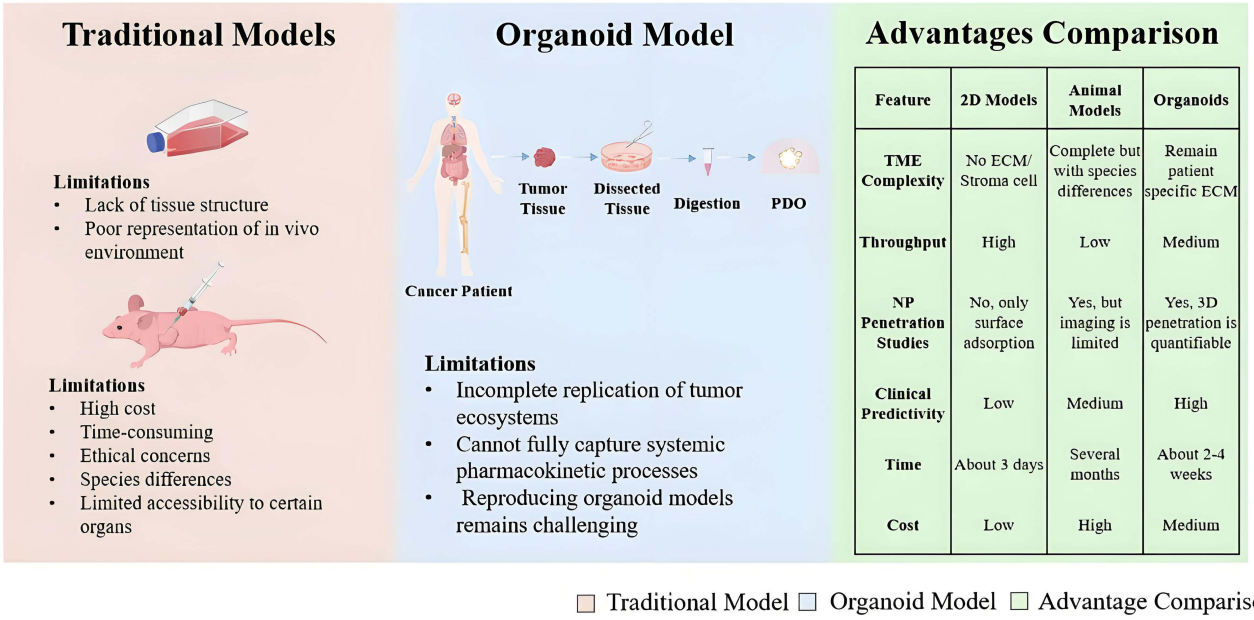

Figure 4 Advantages of Organoids in Nanoparticle Development Compared to Traditional in Vitro and In Vivo Models.

Researchers have successfully utilized organoid cultures to assess the effectiveness of targeted therapies and combination treatments, demonstrating a link between the responses of patient-derived PDAC organoids and patient sensitivity to these therapies.[65] Microfluidic organoid platforms, which utilize minimal tissue samples or PDOs obtained from PDAC biopsies, were developed for therapeutic evaluation. This discovery has many benefits in customizing cancer treatments and can be developed into a supplementary diagnostic method for chemotherapy or immunotherapy, thereby improving personalized cancer treatment.[66]

Building on this foundation, Julian Palzer et al investigated magnetic fluid hyperthermia (MFH) treatment of magnetic nanoparticles (MNPs) in PDAC via PDOs. The authors utilized phospholipid bilayer-coated superparamagnetic iron oxide nanoparticles (SPIONs) to form magnetoliposomes, which were then applied to human PDAC-derived organoids. This study revealed that the MNPs exhibited only surface adherence rather than cellular internalization. This finding provided valuable insights into the unique properties of PDAC organoids. Unlike traditional cell line cultures, these organoid models faithfully replicate the penetration barriers encountered in living systems, while simultaneously establishing an experimental platform for refining magnetic nanoparticle delivery strategies under physiologically relevant conditions.[67]

Extending the application of organoids in drug delivery optimization, Fan Lei et al developed polymeric micelles co-encapsulating the active metabolites of two potent chemotherapy agents, 7-ethyl-10-hydroxycamptothecin and 1,2-diaminocyclohexane-platinum (II). The performance of these dual-drug-loaded micelles was examined via a sophisticated PDAC model originating from mouse tumor organoids. The findings were encouraging since, when loaded with both drugs at a synergistic ratio, these micelles showed significantly improved cytotoxicity against the tumor organoids relative to either single drug-loaded micelles or conventional cocktails of free drugs. This study highlighted the potential of organoid models for screening complex drug delivery systems while supporting the clinical translation of targeted micellar formulations to reduce chemotherapy-induced systemic toxicity.[68]

To address the penetration limitations observed in previous studies, Justin H. Lo et al designed PEGylated iRGD-targeted tumor-penetrating nanocomplexes (TPNs). Using high-resolution optical imaging, the authors monitored the distribution and extent of penetration of the nanoparticles throughout the PDAC organoids. The study revealed that TPNs formulated with a scrambled iRGD peptide predominantly adhered to the outer edges of the organoids and lacked the ability to penetrate deeper. In contrast, the siRNA enclosed within the TPNs could deeply infiltrate large primary human organoids with a diameter greater than 200 μm, achieving penetration depths of several hundred microns. Subsequent

in vivo experiments involving human and mouse organoid cultures further confirmed the robust tumor penetration of siRNA by TPNs. These findings showed that the tumor-penetrating dynamics observed in organoid models are similar to those observed in living organisms, indicating that there could be a high potential for in vivo application.[69]

Capitalizing on organoids' ability to mimic tumor hypoxia, Vidhi M Shah et al explored liposomal vinblastine-N-oxide (CPD100Li) in PDAC organoids. Hypoxia-inducible factor 1 alpha (HIF1A) expression-based criteria were used to select PDOs. Free CPD100 and CPD100Li were used to treat these organoids and determine their cell inhibition response. These results suggest that high expression of HIF1A in an organoid is most effective when it is treated with CPD100Li. The study was more comprehensive, including organoid models in addition to conventional cell lines and PDX models, than previous assessments performed on CPD100Li.[70]

Beyond single-cell-type models, recent advances have leveraged organoids' unique capacity to reconstruct tumor-stroma crosstalk. A potential therapy for pancreatic cancer called CEACAM6-EBET (carcinoembryonic antigen-related cell adhesion molecule 6-bromodomain and extra-terminal protein degrader) was developed by Youya Nakazawa et al. The authors used organoid models of PDAC and PDX stromal cell coculture systems in this study to determine the efficiency of CEACAM6-EBET. These systems are designed to mimic how complexly different types of cells within a tumor interact with each other and the surrounding environment. In this study, the PDAC organoid model allows researchers to understand what happens between cancer cells and stromal components within the tumor microenvironment. This work also shows that cocultures consisting of organoids can be an important platform for testing new anticancer drugs. These findings indicate that the organoid models can significantly improve PDAC treatment approaches toward more effective approaches against such aggressive forms of cancer.[71]

Breast Cancer Organoids

Among women, breast cancer is the most prevalent malignancy and the second most frequent cause of cancer-related mortality.[72] Traditional breast cancer treatments include surgical excision, radiation therapy, and chemotherapy. Several nanomedicines have been approved and used in clinics, including Doxil™ (doxorubicin liposome), Myocet™ (doxorubicin liposome), Lipusu™ (paclitaxel liposome), and Genexol-PM™ (paclitaxel polymeric micelle), demonstrating reduced off-target effects through improved drug delivery mechanisms.[73] Despite the evident clinical advantages of nanomedicine, the current options are still very limited. As nanotechnology has advanced, researchers have developed new classes of nanoscale treatment paradigms, such as dendritic polymers, nanocrystals, inorganic nanoparticles, and nanocarriers that respond to the tumor microenvironment.[74,75] However, the progress of nanomedicine development for breast cancer treatment has been slow, with most anticancer nanomedicines failing to demonstrate enhanced clinical outcomes.[76] This translational gap principally originates from breast cancer being highly heterogeneous in terms of genetic background, histology, degree of differentiation, and molecular subtypes.[77] It is composed of heterogeneous cell subsets within the same tumor, which leads to significant differences in clinical prognosis and patient response and is the main reason for drug resistance or treatment failure.[78,79]

Breast cancer organoids represent a paradigm shift in tumor modeling by recapitulating critical pathophysiological features of native malignancies.[80,81] The development of comprehensive biobanks housing organoids derived from diverse clinical stages, including primary and metastatic lesions, enables systematic investigation of intertumoral heterogeneity while maintaining genetic fidelity through serial culture expansions.[82] This platform successfully models rare histological variants, such as giant papillary breast cancer, which have been reported. By embodying both molecular complexity and phenotypic adaptability, organoid technology establishes a new standard for precision oncology research that transcends conventional model limitations.

Breast cancer organoids have been used as in vitro models for assessing patient-specific drug sensitivity. Breast cancer organoids have been used in the testing of chemotherapy drugs, inhibitors, and combination therapies and have shown consistency in terms of clinical study outcomes, which proves their good application prospects.[83] According to genetic tests, organoids have been shown to simulate the effects of targeted drugs (eg, afatinib, gefitinib, everolimus, and AZD8055) and PARP inhibitors (eg, olaparib), along with other drugs, such as those that act through the HER signaling pathway.[82,84,85] The integration with tumor-on-chip technology enhances predictive capabilities by recapitulating critical tumor microenvironment dynamics, enabling real-time analysis of drug permeation through vascularized tumor-stroma

interfaces under pathologically relevant biomechanical conditions.[86] This functional synergy between molecular characterization and microenvironmental fidelity addresses fundamental challenges in therapeutic resistance prediction, ultimately informing personalized treatment strategies through mechanistically grounded preclinical validation.[83,87] These models further accelerate therapeutic innovation by serving as high-content screening platforms for novel drug candidates, particularly enabling nanomedicine optimization through simultaneous evaluation of targeting efficiency, biocompatibility, and tumor penetration kinetics.[88]

Recent breakthroughs in organoid-enabled immunotherapy development demonstrate the platform's translational capacity. Huang et al pioneered an in situ dendritic cell (DC) vaccine (HELA-Exos) for breast cancer treatment. The effects of the vaccine on restraining tumor growth and activating immune responses were studied in both immunocompetent mice and triple-negative breast cancer (TNBC) PDOs. Researchers have investigated the activation effects of HELA-Exos on the activation of human T cells in PDOs cocultured with peripheral blood mononuclear cells (PBMCs). The results indicated that HELA-Exos activated DCs effectively in situ and improved the antitumor $CD8^+$ T-cell response within the organoid coculture system. Furthermore, HELA-Exo treatment resulted in a significant inhibition of organoid growth, which is consistent with observations in immunocompetent mice. This study highlights the usefulness of organoids for assessing the immune-activating effects of nanoparticles.[89]

Beyond predicting therapeutic responses, breast cancer organoids are now instrumental in validating nanomedicine delivery mechanisms critical for metastasis suppression. This translational potential was exemplified in Zihao Liu's study, where a nanoparticle loaded with membrane-associated phosphatidylinositol-transfer protein three inhibitors (NP-C8018-7840). After a 10-day incubation period, the presence of CD206-positive cells within the PDOs was observed. The results revealed that NP-C8018-7840 significantly decreased vimentin expression and increased CDH1 expression, which indicated similar trends in 2D cell line studies. The nanoparticles caused notable inhibition of breast cancer metastasis in animal models in mice, such as xenografts or organoids, thus showing their possible use as therapies against metastatic breast cancers.[90]

Recent advances in organoid-based drug delivery validation have revealed critical limitations in conventional nanoparticle tumor penetration. Addressing this challenge, Bozhao Li and colleagues conducted a study utilizing organoids derived from primary estrogen receptor (ER)-positive breast cancer tissues to evaluate the effectiveness of a nanoparticle system called PPFA-cRGD (poly(ethylene glycol) (PEG)-poly(β-amino ester)-arginylglycylaspartic acid nanoparticle loaded with fulvestrant and abemaciclib) in vitro. These findings demonstrated that the drug sensitivity detected in these organoids was similar to the responses seen in in vivo models. The authors characterized CK8, ER, and Ki67 expression in organoids as indicators of breast cancer through confocal laser scanning microscopy and Western blot analysis. Additionally, this research evaluated how these organoids take up PPFA-cRGD. The results showed that, compared with chemotherapy alone, PPFA-cRGD caused more cells to die in the organoids, suggesting a personalized approach in which this nanoparticle system kills breast cancer cells more effectively depending on individual needs.[91]

The evolution of aptamer-based targeting has entered a new phase with multimodal recognition strategies. In proof-of-concept research using pathologically validated organoids, Simona Camorani et al investigated the therapeutic potential of Iren-AuSiO2-Aptamer nanoparticles. These organoids were generated from human surgical samples and fully analyzed at the pathological and molecular levels. To increase the efficiency of photodynamic therapy and photothermal therapy, the nanoparticles were formulated with two RNA aptamers that targeted different sites via a dual-aptamer strategy. Research has shown that dual aptamer-modified particles were distributed more evenly than single-aptamer-modified nanoparticles were. They were also found to have a greater ability to penetrate three-dimensional tissue models, which is necessary for better cancer treatment methods.[92]

Breast cancer organoids are unlocking new dimensions in treatment evaluation by modelling tumor-microenvironment interactions that 2D cultures fail to replicate. This unique capability was highlighted in nanoparticle delivery studies, where a study led by Ting Jiang assessed the anticancer effects of PTX@MOF/siDDIT4-AS1 on breast cancer PDOs. This study revealed that the application of PTX@MOF/siDDIT4-AS1 significantly decreased the number and size of breast cancer organoids. Furthermore, four different types of organoids lost their viability, suggesting that this treatment could effectively target cancer cells.[93]

Bridging the gap between diagnostic precision and therapeutic efficacy, organoid platforms enable real-time tracking of drug delivery dynamics in patient-specific contexts. Scialabba's team formulated carbon nanodots loaded with irinotecan that binds to biotin (CDs-PEG-BT@IT), demonstrating 3-fold greater efficacy in select breast cancer organoids compared to conventional therapies, while revealing patient-specific drug response variability undetectable in 2D and xenograft models. These organoids successfully predicted the metastasis-inhibiting capacity of nanoformulations, establishing a clinically actionable framework for personalized nanotherapy optimization.[94]

Advancing beyond conventional phototherapy evaluation models, tumor organoids are emerging as critical platforms for assessing microenvironment-specific therapeutic interactions. Roscigno et al demonstrated this through sulfur-doped carbon nanodots (CD). The efficacy and working mechanisms were studied in patient-derived tumor organoids. This study revealed that the organoid model could enhance transformation and provide a clinically relevant platform for evaluating therapeutic effects by reflecting the physiology of cancerous tissues.[95]

Colorectal Cancer Organoids

As the third most common cancer worldwide and the second cause of cancer death, colorectal cancer (CRC) presents unique challenges in modeling its glandular architecture and stromal interactions.[96] To bridge this gap, researchers have developed CRC organoid biobanks that preserve individual patients' tumor features.[47,97] By maintaining the intricate 3D organization of native tumors, these organoids preserve both structural details and genetic diversity across cancer subclones that effectively mirror how tumor cells interact with surrounding stromal cells to drive progression.[98,99] These biobanks can generate clinically actionable drug response profiles within several weeks after biopsy collection, a rapid turnaround enabling real-time alignment with treatment planning cycles while supporting personalized therapeutic strategies.[100]

The clinical predictive power of CRC organoids is particularly evident in therapeutic response modeling. These models have strong potential to evaluate drug resistance in vitro drug screening studies with inhibitors,[101] drug combination therapy,[102,103] and preclinical settings.[104] Many studies confirm that the in vitro drug sensitivity and resistance profiles derived from CRC organoids align closely with the clinical responses observed in patients. The use of organoids for locally advanced rectal cancer revealed that the response of patients and organoids to chemoradiotherapy was well matched, exhibiting an accuracy of 84.43%, sensitivity of 78.01%, and specificity of 91.97%.[21,105] These organoid systems are revolutionizing drug discovery pipelines through high-throughput screening capabilities. Du et al demonstrated a scalable organoid production platform and efficiently conducted high-throughput screening of thousands of drugs, which significantly propelled organoid research and drug discovery processes.[106] Subsequently, Norkin et al developed a high-content RNA sequencing method to guide drug candidate selection in CRC organoids.[107,]

Building on the established utility of organoids in drug response assessment, Huang et al developed a delivery system utilizing exosomes derived from primary patient cells to transport small interfering RNAs (siRNAs) targeting coiled-coil domain-containing protein 80 (CCDC80). This platform successfully silenced CCDC80 expression in chemoresistant CRC organoids and patient-derived xenograft models, enhancing cancer cell sensitivity to chemotherapy. Their findings validate organoids as robust models for evaluating nanotherapeutic delivery systems, demonstrating precise siRNA targeting and restored chemotherapeutic efficacy.[108]

Complementing advances in targeted drug delivery, organoid models are proving equally vital for evaluating immune-modulating therapies. Roberto Benelli et al conjugated zoledronic acid (ZA), an aminobisphosphonate, to the anti-EGFR antibody cetuximab (Cet) to construct a Cet-ZA antibody conjugate (ADC). They investigated the efficacy of Cet-ZA ADCs against primary CRC organoids derived from 13 patients. Cet-ZA ADC treatment triggered elevated isopentenyl pyrophosphate and butyrophilin levels in organoids within 48 hours, activating Vδ2 T lymphocytes. The conjugate also enhanced Vδ2 T-cell proliferation and tumor-killing capacity in T lymphocyte co-culture systems with CRC organoids. These findings collectively demonstrate that the organoid coculture system conceivably offers a viable, cost-effective, dependable, and replicable model for customized preclinical therapeutic assessment.[109]

Recent studies highlight the growing potential of targeting tumor metabolism as a therapeutic strategy. Liu Peng's team utilized patient-derived organoids to evaluate PL-DFX, which is composed of deferasirox and hyperbranched polylysine. According to this study, organoid models outperform traditional cell lines in predicting clinical efficacy. The

results obtained from the organoid experiments led to the conclusion that interfering with iron metabolism could serve as a good treatment strategy for malignant neoplasms via PL-DFX.[110]

Building on innovations in multifunctional nanoparticle design, researchers are now leveraging organoid precision to optimize combination therapies. Shengyun Hu led a study that examined the therapeutic effectiveness of curcumin using $CaCO_3$@Cur@QTX125@HA nanoparticles in CRC PDO models. These nanoparticles are multifunctional, containing curcumin, a polyphenol capable of fighting cancer naturally, and QTX125, a histone deacetylase inhibitor. The team then modified them with hyaluronic acid (HA) to increase the capability of the particles to target cancer cells and enhance their uptake. The results showed that the $CaCO_3$@Cur@QTX125@HA particles were effectively taken into the PDO models, thereby inducing apoptosis in tumor cells. The authors hypothesized that HA coats may interact with organoids, leading to increased cellular absorption, hence enhancing their therapeutic outcome. This research showed that the in vitro application of PDO models allowed us to closely mimic complex patient tumors while evaluating the efficacy of nanoparticles in cancer treatment.[111]

Recognizing the critical role of tumor microenvironment responsiveness in drug delivery optimization, recent advancements have focused on developing stimulus-responsive nanocarriers. Huiling Song et al reported a novel pH-sensitive cetuximab (Cet)-conjugated drug delivery system. DMAKO-20/PCL-PEOz-targeted nanoparticles (DMAKO@PCL-PEOz-Cet) were constructed to enhance the efficacy of CRC treatment. The authors employed PDOs to study the ability of DMAKO@PCL-PEOz-Cet to carry therapeutic agents. This study indicated that DMAKO@PCL-PEOz-Cet had better inhibitory effects on CRC organoids than Cet alone. Cet combined with DMAKO-20 resulted in significant disruption of CRC organoids. This drug delivery system may help overcome tumor heterogeneity and drug resistance. In this study, the CRC organoid model provides valuable insights into the possibilities for nanodrug delivery systems to overcome tumor heterogeneity and drug resistance challenges.[112]

Brain Cancer Organoids

Glioblastoma (GBM) is one of the most common and aggressive adult brain cancers and has high rates of drug resistance and recurrence. GBMs exhibit diverse morphological characteristics and are complex networks composed of multiple cell types, including endothelial cells, astrocytes, and pericytes.[113] Most GBMs have increased vascularity, promoting the proliferation of endothelial cells. They are dense in cellular content and mixed with necrotic tissue, which has varying degrees of atypicality.[114]

Despite advances in surgical resection, chemotherapy, and radiation, median survival has only increased by an average of four months.[115] A nanoparticle drug delivery system is an attractive solution for treating GBM.[116] Owing to their small size, shape, and surface properties, nanoparticles can facilitate targeted drug delivery to cancer cells by overcoming the blood-brain barrier, escaping capture and clearance by the reticuloendothelial system, and actively binding to receptors on the cell surface.[117,118] A variety of nanodelivery therapies targeting brain tumors have been developed, including liposomes,[119] silica,[120] polymer micelles, dendrimers, and metal particles.[121,122]

Numerous in vivo and in vitro studies have demonstrated the efficiency and therapeutic potential of nanocarrier-based GBM therapies. However, these drug-delivery system therapies have had limited success in clinical trials and have not yet been applied to treat patients.[123] We still lack a comprehensive and systematic understanding of the interactions between nanocarriers and the blood-brain barrier (BBB), such as the potential toxicity to the BBB, the changes before and after penetration, and drug delivery efficiency.[124] Currently, the commonly used BBB models are animals. In situ high-resolution imaging of the brain of an animal model is difficult, limiting the study of the interaction mechanism between nanocarriers and the blood-brain barrier.[125]

Brain organoids are becoming cutting-edge tools in brain cancer research.[126] Several types of patient-derived organoids have been successfully established and identified in brain tumors, such as glioblastoma organoids, meningioma organoids, and neoplastic cerebral organoids.[127,128] Glioma organoids provide a powerful tool for understanding drug nanocarrier-BBB interactions and are essential for developing nanomedicines with high BBB penetration and good biocompatibility. They are potential in vitro blood-brain barrier models that can accurately replicate human pathophysiological behaviors and respond to potential drugs, improve the reliability of drug validation studies, and accelerate drug screening and nanodrug development.

Owing to the rapid establishment and precise generalization of parental tumors, many researchers are using brain cancer organoids to test the efficacy of anticancer therapies.[129,130] In an observational study, Jacob et al reported that glioblastoma organoids matched the response of patients, with 83% sensitivity and 88% specificity.[131] Glioma organoids are easy to establish and relatively economical, and several techniques, such as 3D bioprinting and the establishment of microarray chips, have been employed to speed up and scale up drug testing.[128,132–135] Claire Simonneau reported that the human BBB organoid array is a powerful, high-throughput platform for discovering novel mechanisms of receptor-mediated antibody transfer. The BBB organoid array allows each experiment to grow more than 3000 homologous organs simultaneously in a highly repeatable manner. Implementing the platform during the initial phases of drug development, the process may speed up the creation of innovative approaches for brain delivery technologies.[135] Bergmann et al outlined a novel protocol for developing BBB organoids to assess brain-permeable compounds for potential therapeutic use.[136] This work also described the application of confocal fluorescence microscopy and mass spectrometry imaging to analyze drug penetration into organoids.

Advancing beyond single-barrier models, cutting-edge organoid systems now enable precise evaluation of nanodrug trafficking across complex biological interfaces. Kathrin Kostka et al investigated the absorption, distribution, and efficacy of gold nanoparticles (AuTioDox-AF647) loaded with doxorubicin (Dox) and AlexaFluor-647-cadaverine (AF647). The authors developed normal and glioblastoma organoids by culturing different human brain cells (pericytes, the outer layer of endothelial cells, astrocytes, U87-MG cells, microglia, oligodendrocytes, and neurons). The normal and GBM organoids successfully reproduced the three-dimensional structure and essential physiological functions of the blood-brain barrier and had good BBB integrity. This pioneering organoid platform enables simultaneous tracking of nanoparticle penetration kinetics and therapeutic payload release dynamics within glioblastoma microenvironments.[137,138]

Prostate Cancer Organoids

The primary cause of clinical treatment failure and progressive malignancy in prostate cancer (PCa) is its high degree of heterogeneity. Therefore, further search for broad-spectrum drugs that can be used in different clinical stages of PCa is urgently needed. However, only seven PCa cell lines are stored in the American Type Culture Collection, which is very low in representation.

Various prostate cancer organoids have been successfully cultivated and are continually expanding. Prostate cancer organoid models have been successfully established from tumor surgical excision samples and biopsy samples, circulating tumor cells, PCa cell lines, prostate cancer PDXs, and human embryonic stem cells.[139] These models represent the well-known phenotypic diversity of castrate-resistant prostate cancers. This includes AR-driven adenocarcinomas and AR-independent neuroendocrine, positive or double-negative types. This fully reflects the heterogeneity of PCa.[140] Researchers established a prostate cancer organoid biobank using samples from 81 patients. These patient-derived models now enable efficient testing of personalized treatment options across diverse cancer cases.[141]

Organoids used in prostate cancer research and treatment enable efficient, large-scale drug development and testing.[142] They are also used for basic biological research to study early cancer, identify drug targets, and study drug resistance. Several studies have shown that the response of prostate organoids to chemotherapy drugs, hormonal drugs, and targeted drugs can predict clinical outcomes, and in vitro drug sensitivity is correlated with patient genotype and treatment response.[140,143] Research demonstrated that LuCap-derived organoids with BRCA2 mutations exhibit heightened sensitivity to olaparib, aligning with clinical observations.[143]

In addition, several studies have described protocols for analyzing and optimizing drug responses in prostate cancer organoids, providing methods for evaluating drugs that can be used to assess multiple parameters or biological endpoints simultaneously. For example, bright field imaging[144] and high-content live-cell imaging[48] have been used to study a variety of morphological changes, such as changes in organoid size, shape, and structure, during or after exposure to organoids. It is crucial to recognize that the architecture, spatial arrangement, and dimensions of organoids significantly impact drug efficacy.[144]

Bladder Cancer Organoids

Bladder cancer, one of the most common urinary system cancers, is classified into two types: nonmuscle invasive and muscle invasive: nonmuscle invasive and muscle invasive. Among all bladder cancer cases, 75% are nonmuscle invasive

bladder cancer.[145] Research has revealed that different kinds of nanoparticles can be used in bladder cancer therapy. Physical excision and drug-assisted chemotherapy are common treatments for bladder cancer. Commonly used chemotherapy nanomedicines include accelerated or dose-dense methotrexate, doxorubicin, vinblastine, cisplatin, or gemcitabine and cisplatin. In addition, chitosan nanoparticles, polymeric nanoparticles, lipid-based nanoparticles, and protein nanoparticles have also been proven effective in the laboratory.[146]

Emerging bladder cancer organoid models demonstrate remarkable fidelity in recapitulating tumor biology, offering a transformative platform for therapeutic development. These systems provide a clinically relevant alternative to high-risk human trials for evaluating novel nanoparticle therapies. Organoid technology has significantly advanced drug evaluation protocols, yet its implementation in bladder cancer studies still lags. This gap is most apparent in targeted drug delivery optimization, where the intricate tumor microenvironment necessitates models that better replicate human physiology.

Complementing existing drug delivery strategies with biological vectors, recent work has leveraged exosomes' natural trafficking capabilities to enhance therapeutic precision. In a paper published by Wenqing Li et al, human bladder cancer organoids were used to investigate the molecular mechanisms underlying bladder cancer progression and the potential therapeutic effects of miR-3960. miR-3960 was encapsulated in exosomes generated from HEK293T cells. This study revealed that exosome-loaded miR-3960 significantly decreased dexamethasone-induced protein expression and reduced organoid growth.[147]

Challenges in Organoid Model Applications

Organoid models have transformed preclinical cancer research, yet several limitations must be overcome to maximize their utility for nanoparticle drug development. A primary challenge lies in their incomplete replication of tumor ecosystems, particularly regarding immune cell populations and vascular networks. The concept of assembloids, inspired by the co-culture technique, shows promise by combining organoids with stromal/immune cells to address these issues.[148] A study indicated that long-term cultured bladder organoids lack the key components of the normal bladder. They subsequently modified the model by creating assembloids and confirmed that they successfully restored the missing microenvironmental.[149]

While organoid models offer valuable insights into nanoparticle accumulation and penetration within tumor microenvironments, they cannot fully capture systemic pharmacokinetic processes such as hepatic metabolism or renal clearance. This inherent limitation creates important discrepancies between in vitro observations and in vivo drug behavior, underscoring the continued need for complementary animal studies to validate active targeting strategies.

Reproducing organoid models consistently across laboratories remains challenging due to significant variations in culture protocols.[150] One major obstacle is the choice of extracellular matrix. Matrigel offers biological relevance but lacks consistency, whereas synthetic hydrogels provide uniformity but may not fully support organoid growth. The mechanical properties of the growth matrix also require careful tuning, with stiffness parameters ranging dramatically from soft to rigid. Oxygen tension control further complicates culture conditions, as maintaining physiologically relevant hypoxia levels proves technically demanding. Meanwhile, cost considerations also emerge, as organoid cultures remain more expensive than cell lines, despite being cheaper than PDX models.

Therefore, further research is needed to fully explore the capabilities of tumor organoids in the context of nanoparticle drug development and to assess their impact on the overall effectiveness of nanomedicine-based cancer treatments. Additionally, the repeatability and reliability of some organoid research results merit further scrutiny, and the long-term stability and sustainability of organoid models require more in-depth investigation.

Discussion and Future Perspectives

Organoid models are reshaping how nanoparticle therapeutics move from bench to bedside.[151] These models capture critical aspects of human tissue complexity that traditional cell cultures miss, providing more clinically relevant data on drug delivery and response. Their ability to maintain patient-specific characteristics while allowing controlled experimentation makes them particularly valuable for optimizing nanocarrier design and dosing strategies. The integration of organoid models represents more than just another experimental tool. It reflects an important shift toward more human-

relevant preclinical testing.[152] While not replacing all animal studies, these systems are becoming an essential bridge between traditional cell culture and clinical trials, particularly for targeted nanotherapies where species differences often complicate translation. Their continued refinement and standardization will play a key role in accelerating the development of safer, more effective nanomedicines. As the technology matures, it could substantially reduce late-stage clinical attrition by identifying promising candidates and eliminating poor performers earlier in development.

In the future, as technological advancements persist, the development and cultivation of organoid models are expected to improve, enabling them to simulate tumor characteristics more accurately. More comprehensive studies across cancer types may be needed to find more universally applicable treatment strategies. The fusion of organoid research with artificial intelligence and big data analysis will usher in a new era of in-depth data mining and analysis. These findings will help to provide more accurate guidance for cancer treatment and further reveal the complex interactions among nanoparticles, tumor microenvironment, and organoid models to promote the wide application of nanomedicine in cancer treatment. Organoid models are expected to play a significant role in tailoring cancer treatments to the unique needs of individual patients.

The advent of organoid technology has heralded a new era in cancer research, particularly in nanoparticle drug development. Organoids offer a more accurate and biologically relevant model than traditional cell lines or animal models, as they retain the histopathological, genomic, and molecular features of the original tumors. Organoids can help overcome the challenges of developing cancer nanomedicines by providing a more precise representation of the tumor microenvironment. The ability to simulate key genetic, physical, and mechanical cues of the tumor microenvironment allows for a more accurate prediction of drug responses, which is crucial for the success of nanoparticle-based treatments.

Integrating organoid technology with nanoparticle drug development is a significant step in cancer therapy. Organoids not only serve as models for drug screening but also offer insights into the complex interactions between nanoparticles and the tumor microenvironment. This approach has the potential to accelerate the translational application process of nanoparticle drugs from the laboratory to the clinic. Establishing biobanks containing large collections of patient-derived organoids (PDOs) enables high-throughput preclinical optimization and evaluation of novel nanoparticle drug delivery systems, which is a major advantage over traditional models.

Meanwhile, organoid intelligence represents a paradigm shift in in vitro modeling, offering transformative potential for biomedical research and therapeutic discovery.[153,154] Advanced image analysis techniques have allowed automated, high-throughput assessment of nanoparticle behavior in organoid models, including distribution patterns, penetration efficiency, and stromal barrier interactions. Machine learning approaches have been applied to electron microscopy data to enable quantitative morphological characterization of nanoparticles, facilitating large-scale statistical analysis in nanomedicine research.[155] The integration of organoid intelligence with multi-omics profiling and microphysiological systems promises to generate clinically actionable insights that could fundamentally bridge the gap between benchtop discoveries and patient outcomes in the future.

Conclusion

The tumor organoid model has advantages in simulating the tumor microenvironment, reflecting tumor characteristics, predicting drug response, etc, and is of great value in drug development and evaluation. Organoid models have revolutionized preclinical cancer research. This method overcomes the main limitations of traditional in vitro and in vivo methods. Compared with cell lines, they can more accurately represent the tumor status of patients, mimic the cell diversity of tumors, the relationships between cells and the matrix of cells, etc. However, current organoid models still face limitations in replicating complete organ architecture and immune microenvironment components. As the technology continues to evolve, the integration of organoids and nanomedicine is paving the way for transformative cancer treatments. By refining culture protocols, incorporating immune components, and standardizing methodologies, this approach holds tremendous potential to bridge the gap between preclinical research and clinical translation, ultimately enabling truly personalized cancer therapy.

Funding

This research was supported by the Zhejiang Provincial Natural Science Foundation of China under Grant No. ZCLTGY24C1001.

Disclosure

The authors report there are no competing interests to declare.

References

1. Gavas S, Quazi S, Karpiński TM. Nanoparticles for cancer therapy: current progress and challenges. *Nanoscale Res Lett*. 2021;16(1):173. doi:10.1186/s11671-021-03628-6
2. Peng S, Xiao F, Chen M, Gao H. Tumor-microenvironment-responsive nanomedicine for enhanced cancer immunotherapy. *Adv Sci*. 2022;9(1): e2103836. doi:10.1002/advs.202103836
3. Poornima K, Francis AP, Hoda M, et al. Implications of three-dimensional cell culture in cancer therapeutic research. *Front Oncol*. 2022;12:891673. doi:10.3389/fonc.2022.891673
4. Fröhlich E. Issues with cancer spheroid models in therapeutic drug screening. *Curr Pharm Des*. 2020;26(18):2137–2148. doi:10.2174/1381612826666200218094200
5. Sato K, Zhang W, Safarikia S, et al. Organoids and spheroids as models for studying cholestatic liver injury and cholangiocarcinoma. *Hepatology*. 2021;74(1):491–502. doi:10.1002/hep.31653
6. Zhou B, Feng Z, Xu J, Xie J. Organoids: approaches and utility in cancer research. *Chin Med J*. 2023;136(15):1783–1793. doi:10.1097/CM9.0000000000002477
7. Gasco S, Muñoz-Fernández M. A review on the current knowledge on ZIKV Infection and the interest of organoids and nanotechnology on development of effective therapies against zika infection. *Int J Mol Sci*. 2020;22(1):35. doi:10.3390/ijms22010035
8. Park G, Rim YA, Sohn Y, Nam Y, Ju JH. Replacing animal testing with stem cell-organoids: advantages and limitations. *Stem Cell Rev Rep*. 2024;20(6):1375–1386. doi:10.1007/s12015-024-10723-5
9. Ma AE-S, Troulis MJ, Pan CX, Rao RA. Unlocking the potential of organoids in cancer treatment and translational research: an application of cytologic techniques. *Cancer Cytopathol*. 2024;132(2):96–102. doi:10.1002/cncy.22769
10. Sun G, Wu Y, Li J, et al. Quercetin liposomes conjugated with hyaluronidase: an efficient drug delivery system to block pancreatic cancer. *J Control Release*. 2025;382:113642. doi:10.1016/j.jconrel.2025.113642
11. Ye X, Chen S, Xiong W, et al. Magnetic-guided delivery of antisense oligonucleotides for targeted transduction in multiple retinal explant and organoid models. *Adv Sci*. 2025;12(22):e2417363. doi:10.1002/advs.202417363
12. Uner B, Akyildiz EO, Kolci K, Reis R. Nanoparticle formulations for intracellular delivery in colorectal cancer therapy. *AAPS Pharm Sci Tech*. 2025;26(3):81. doi:10.1208/s12249-025-03069-9
13. Lee S, Kim K, Jeong HJ, et al. Combining multiplexed CRISPR/Cas9-nickase and PARP inhibitors efficiently and precisely targets cancer cells. *Cancer Res*. 2025. doi:10.1158/0008-5472.CAN-24-2938
14. Zeng G, Yu Y, Wang M, et al. Advancing cancer research through organoid technology. *J Transl Med*. 2024;22(1):1007. doi:10.1186/s12967-024-05824-1
15. Kretzschmar K. Cancer research using organoid technology. *J Mol Med*. 2021;99(4):501–515. doi:10.1007/s00109-020-01990-z
16. Qu S, Xu R, Yi G, et al. Patient-derived organoids in human cancer: a platform for fundamental research and precision medicine. *Mol Biomed*. 2024;5(1):6. doi:10.1186/s43556-023-00165-9
17. Wilson SS, Mayo M, Melim T, et al. Optimized culture conditions for improved growth and functional differentiation of mouse and human colon organoids. *Front Immunol*. 2020;11:547102. doi:10.3389/fimmu.2020.547102
18. Zhang M, Zhang B. Extracellular matrix stiffness: mechanisms in tumor progression and therapeutic potential in cancer. *Exp Hematol Oncol*. 2025;14(1):54. doi:10.1186/s40164-025-00647-2
19. Kalli M, Stylianopoulos T. Defining the role of solid stress and matrix stiffness in cancer cell proliferation and metastasis. *Front Oncol*. 2018;8:55. doi:10.3389/fonc.2018.00055
20. Li L, Zhang Y, Zhou Y, et al. Quaternary nanoparticles enable sustained release of bortezomib for hepatocellular carcinoma. *Hepatology*. 2022;76(6):1660–1672. doi:10.1002/hep.32584
21. Yao Y, Xu X, Yang L, et al. Patient-derived organoids predict chemoradiation responses of locally advanced rectal cancer. *Cell Stem Cell*. 2020;26(1):17–26.e16. doi:10.1016/j.stem.2019.10.010
22. Nam C, Ziman B, Sheth M, Zhao H, Lin DC. Genomic and epigenomic characterization of tumor organoid models. *Cancers*. 2022;14(17):4090. doi:10.3390/cancers14174090
23. Sato T, Stange DE, Ferrante M, et al. Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. *Gastroenterology*. 2011;141(5):1762–1772. doi:10.1053/j.gastro.2011.07.050
24. Wood LD, Ewald AJ. Organoids in cancer research: a review for pathologist-scientists. *J Pathol*. 2021;254(4):395–404. doi:10.1002/path.5684
25. Chen K, Ma Y, Zhong X, et al. Single-cell transcriptome profiling of primary tumors and paired organoids of pancreatobiliary cancer. *Cancer Lett*. 2024;582:216586. doi:10.1016/j.canlet.2023.216586
26. Liu T, Li X, Li H, et al. Intestinal organoid modeling: bridging the gap from experimental model to clinical translation. *Front Oncol*. 2024;14:1334631. doi:10.3389/fonc.2024.1334631
27. Veninga V, Voest EE. Tumor organoids: opportunities and challenges to guide precision medicine. *Cancer Cell*. 2021;39(9):1190–1201. doi:10.1016/j.ccell.2021.07.020
28. Driehuis E, Kretzschmar K, Clevers H. Establishment of patient-derived cancer organoids for drug-screening applications. *Nat Protoc*. 2020;15(10):3380–3409. doi:10.1038/s41596-020-0379-4
29. Clevers H. Modeling development and disease with organoids. *Cell*. 2016;165(7):1586–1597. doi:10.1016/j.cell.2016.05.082
30. Genta S, Coburn B, Cescon DW, Spreafico A. Patient-derived cancer models: valuable platforms for anticancer drug testing. *Front Oncol*. 2022;12:976065. doi:10.3389/fonc.2022.976065
31. Pasch CA, Favreau PF, Yueh AE, et al. Patient-derived cancer organoid cultures to predict sensitivity to chemotherapy and radiation. *Clin Cancer Res*. 2019;25(17):5376–5387. doi:10.1158/1078-0432.CCR-18-3590

32. Li Z, Li Q, Zhou C, et al. Organoid-on-a-chip: current challenges, trends, and future scope toward medicine. *Biomicrofluidics*. 2023;17(5):051505. doi:10.1063/5.0171350
33. Du Y, Wang YR, Bao QY, et al. Personalized vascularized tumor organoid-on-a-chip for tumor metastasis and therapeutic targeting assessment. *Adv Mater*. 2025;37(6):e2412815. doi:10.1002/adma.202412815
34. Quintard C, Tubbs E, Jonsson G, et al. A microfluidic platform integrating functional vascularized organoids-on-chip. *Nat Commun*. 2024;15(1):1452. doi:10.1038/s41467-024-45710-4
35. Park SE, Georgescu A, Huh D. Organoids-on-a-chip. *Science*. 2019;364(6444):960–965. doi:10.1126/science.aaw7894
36. Hofer M, Lutolf MP. Engineering organoids. *Nat Rev Mater*. 2021;6(5):402–420. doi:10.1038/s41578-021-00279-y
37. Wang H, Ning X, Zhao F, Zhao H, Li D. Human organoids-on-chips for biomedical research and applications. *Theranostics*. 2024;14(2):788–818. doi:10.7150/thno.90492
38. Rothbauer M, Ertl P. Emerging biosensor trends in organ-on-a-chip. *Adv Biochem Eng Biotechnol*. 2022;179:343–354. doi:10.1007/10_2020_129
39. Trivedi P, Liu R, Bi H, Xu C, Rosenholm JM, Åkerfelt M. 3D modeling of epithelial tumors-the synergy between materials engineering, 3D bioprinting, high-content imaging, and nanotechnology. *Int J Mol Sci*. 2021;22(12):6225. doi:10.3390/ijms22126225
40. Kumari R, Xu X, Li HQ. Translational and clinical relevance of PDX-derived organoid models in oncology drug discovery and development. *Curr Protoc*. 2022;2(7):e431. doi:10.1002/cpz1.431
41. Yoshida GJ. Applications of patient-derived tumor xenograft models and tumor organoids. *J Hematol Oncol*. 2020;13(1):4. doi:10.1186/s13045-019-0829-z
42. Xu X, Shang L, Wang P, et al. Creating matched in vivo/in vitro patient-derived model pairs of PDX and PDX-derived organoids for cancer pharmacology research. *J Vis Exp*. 2021; 171. doi:10.3791/61382
43. Xu X, Kumari R, Zhou J, et al. A living biobank of matched pairs of patient-derived xenografts and organoids for cancer pharmacology. *PLoS One*. 2023;18(1):e0279821. doi:10.1371/journal.pone.0279821
44. Guillen KP, Fujita M, Butterfield AJ, et al. A human breast cancer-derived xenograft and organoid platform for drug discovery and precision oncology. *Nat Cancer*. 2022;3(2):232–250. doi:10.1038/s43018-022-00337-6
45. Huang L, Holtzinger A, Jagan I, et al. Ductal pancreatic cancer modeling and drug screening using human pluripotent stem cell- and patient-derived tumor organoids. *Nat Med*. 2015;21(11):1364–1371. doi:10.1038/nm.3973
46. Yu YY, Zhu YJ, Xiao ZZ, et al. The pivotal application of patient-derived organoid biobanks for personalized treatment of gastrointestinal cancers. *Biomark Res*. 2022;10(1):73. doi:10.1186/s40364-022-00421-0
47. Kim SC, Park JW, Seo HY, et al. Multifocal organoid capturing of colon cancer reveals pervasive intratumoral heterogenous drug responses. *Adv Sci*. 2022;9(5):e2103360. doi:10.1002/advs.202103360
48. Van Hemelryk A, Erkens-Schulze S, Lim L, et al. Viability analysis and high-content live-cell imaging for drug testing in prostate cancer xenograft-derived organoids. *Cells*. 2023;12(10):1377. doi:10.3390/cells12101377
49. Calandrini C, Schutgens F, Oka R, et al. An organoid biobank for childhood kidney cancers that captures disease and tissue heterogeneity. *Nat Commun*. 2020;11(1):1310. doi:10.1038/s41467-020-15155-6
50. Xie X, Li X, Song W. Tumor organoid biobank-new platform for medical research. *Sci Rep*. 2023;13(1):1819. doi:10.1038/s41598-023-29065-2
51. Amreddy N, Babu A, Muralidharan R, et al. Recent advances in nanoparticle-based cancer drug and gene delivery. *Adv Cancer Res*. 2018;137:115–170.
52. Hoshyar N, Gray S, Han H, Bao G. The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. *Nanomedicine*. 2016;11(6):673–692. doi:10.2217/nnm.16.5
53. Yu Z, Shen X, Yu H, Tu H, Chittasupho C, Zhao Y. Smart polymeric nanoparticles in cancer immunotherapy. *Pharmaceutics*. 2023;15(3):775. doi:10.3390/pharmaceutics15030775
54. Millard M, Yakavets I, Zorin V, Kulmukhamedova A, Marchal S, Bezdetnaya L. Drug delivery to solid tumors: the predictive value of the multicellular tumor spheroid model for nanomedicine screening. *Int J Nanomed*. 2017;12:7993–8007. doi:10.2147/IJN.S146927
55. Monteduro AG, Rizzato S, Caragnano G, Trapani A, Giannelli G, Maruccio G. Organs-on-chips technologies - A guide from disease models to opportunities for drug development. *Biosens Bioelectron*. 2023;231:115271. doi:10.1016/j.bios.2023.115271
56. Liu C, Qin T, Huang Y, Li Y, Chen G, Sun C. Drug screening model meets cancer organoid technology. *Transl Oncol*. 2020;13(11):100840. doi:10.1016/j.tranon.2020.100840
57. Zhang S, Gao H, Bao G. Physical principles of nanoparticle cellular endocytosis. *ACS Nano*. 2015;9(9):8655–8671. doi:10.1021/acsnano.5b03184
58. Li K, He Y, Jin X, Jin K, Qian J. Reproducible extracellular matrices for tumor organoid culture: challenges and opportunities. *J Transl Med*. 2025;23(1):497. doi:10.1186/s12967-025-06349-x
59. Zinger A, Koren L, Adir O, et al. Collagenase nanoparticles enhance the penetration of drugs into pancreatic tumors. *ACS Nano*. 2019;13(10):11008–11021. doi:10.1021/acsnano.9b02395
60. Schuth S, Le Blanc S, Krieger TG, et al. Patient-specific modeling of stroma-mediated chemoresistance of pancreatic cancer using a three-dimensional organoid-fibroblast co-culture system. *J Exp Clin Cancer Res*. 2022;41(1):312. doi:10.1186/s13046-022-02519-7
61. Astashkina AI, Jones CF, Thiagarajan G, et al. Nanoparticle toxicity assessment using an in vitro 3-D kidney organoid culture model. *Biomaterials*. 2014;35(24):6323–6331. doi:10.1016/j.biomaterials.2014.04.060
62. Kokkinos J, Sharbeen G, Haghighi KS, et al. Ex vivo culture of intact human patient derived pancreatic tumour tissue. *Sci Rep*. 2021;11(1):1944. doi:10.1038/s41598-021-81299-0
63. D'Agosto S, Andreani S, Scarpa A, Corbo V. Preclinical Modelling of PDA: is organoid the new black? *Int J Mol Sci*. 2019;20(11):2766. doi:10.3390/ijms20112766
64. Boj SF, Hwang CI, Baker LA, et al. Organoid models of human and mouse ductal pancreatic cancer. *Cell*. 2015;160(1–2):324–338. doi:10.1016/j.cell.2014.12.021
65. Tiriac H, Plenker D, Baker LA, Tuveson DA. Organoid models for translational pancreatic cancer research. *Curr Opin Genet Dev*. 2019;54:7–11. doi:10.1016/j.gde.2019.02.003

66. Choi D, Gonzalez-Suarez AM, Dumbrava MG, et al. Microfluidic organoid cultures derived from pancreatic cancer biopsies for personalized testing of chemotherapy and immunotherapy. *Adv Sci*. 2024;11(5):e2303088. doi:10.1002/advs.202303088
67. Palzer J, Mues B, Goerg R, et al. Magnetic fluid hyperthermia as treatment option for pancreatic cancer cells and pancreatic cancer organoids. *Int J Nanomed*. 2021;16:2965–2981. doi:10.2147/IJN.S288379
68. Lei F, Xi X, Rachagani S, et al. Nanoscale platform for delivery of active IRINOX to combat pancreatic cancer. *J Control Release*. 2021;330:1229–1243. doi:10.1016/j.jconrel.2020.11.029
69. Lo JH, Hao L, Muzumdar MD, et al. iRGD-guided tumor-penetrating nanocomplexes for therapeutic siRNA delivery to pancreatic cancer. *Mol Cancer Ther*. 2018;17(11):2377–2388. doi:10.1158/1535-7163.MCT-17-1090
70. Shah VM, Dorrell C, Al-Fatease A, et al. Microfluidics formulated liposomes of hypoxia activated prodrug for treatment of pancreatic cancer. *Pharmaceutics*. 2022;14(4):713. doi:10.3390/pharmaceutics14040713
71. Nakazawa Y, Miyano M, Tsukamoto S, et al. Delivery of a BET protein degrader via a CEACAM6-targeted antibody-drug conjugate inhibits tumour growth in pancreatic cancer models. *Nat Commun*. 2024;15(1):2192. doi:10.1038/s41467-024-46167-1
72. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12–49. doi:10.3322/caac.21820
73. Gawali P, Saraswat A, Bhide S, Gupta S, Patel K. Human solid tumors and clinical relevance of the enhanced permeation and retention effect: a 'golden gate' for nanomedicine in preclinical studies? *Nanomedicine*. 2023;18(2):169–190. doi:10.2217/nnm-2022-0257
74. Zhou Q, Dong C, Fan W, et al. Tumor extravasation and infiltration as barriers of nanomedicine for high efficacy: the current status and transcytosis strategy. *Biomaterials*. 2020;240:119902. doi:10.1016/j.biomaterials.2020.119902
75. Moti LAA, Hussain Z, Thu HE, Khan S, Sohail M, Sarfraz RM. Multi-functionalization, a promising adaptation to overcome challenges to clinical translation of nanomedicines as nano-diagnostics and nano-therapeutics for breast cancer. *Curr Pharm Des*. 2021;27(43):4356–4375. doi:10.2174/1381612827666210830092539
76. Boix-Montesinos P, Soriano-Teruel PM, Armiñán A, Orzáez M, Vicent MJ. The past, present, and future of breast cancer models for nanomedicine development. *Adv Drug Deliv Rev*. 2021;173:306–330.
77. Zou T, Lu W, Mezhuev Y, et al. A review of nanoparticle drug delivery systems responsive to endogenous breast cancer microenvironment. *Eur J Pharm Biopharm*. 2021;166:30–43. doi:10.1016/j.ejpb.2021.05.029
78. de Oliveira JV, Oliveira da Rocha MC, de Sousa-Junior AA, et al. Tumor vascular heterogeneity and the impact of subtumoral nanoemulsion biodistribution. *Nanomedicine*. 2022;17(27):2073–2088. doi:10.2217/nnm-2022-0176
79. Wang L, Sheth V, Liu K, et al. Primary human breast cancer-associated endothelial cells favor interactions with nanomedicines. *Adv Mater*. 2024;36(28):e2403986. doi:10.1002/adma.202403986
80. Dekkers JF, van Vliet EJ, Sachs N, et al. Long-term culture, genetic manipulation and xenotransplantation of human normal and breast cancer organoids. *Nat Protoc*. 2021;16(4):1936–1965. doi:10.1038/s41596-020-00474-1
81. Yang L, Liu B, Chen H, et al. Progress in the application of organoids to breast cancer research. *J Cell Mol Med*. 2020;24(10):5420–5427. doi:10.1111/jcmm.15216
82. Sachs N, de Ligt J, Kopper O, et al. A living biobank of breast cancer organoids captures disease heterogeneity. *Cell*. 2018;172(1–2):373–386. e310. doi:10.1016/j.cell.2017.11.010
83. Chen P, Zhang X, Ding R, et al. Patient-derived organoids can guide personalized-therapies for patients with advanced breast cancer. *Adv Sci*. 2021;8(22):e2101176. doi:10.1002/advs.202101176
84. Duarte AA, Gogola E, Sachs N, et al. BRCA-deficient mouse mammary tumor organoids to study cancer-drug resistance. *Nat Methods*. 2018;15 (2):134–140. doi:10.1038/nmeth.4535
85. Campaner E, Zannini A, Santorsola M, et al. Breast cancer organoids model patient-specific response to drug treatment. *Cancers*. 2020;12 (12):3869. doi:10.3390/cancers12123869
86. Dornhof J, Kieninger J, Muralidharan H, Maurer J, Urban GA, Weltin A. Microfluidic organ-on-chip system for multi-analyte monitoring of metabolites in 3D cell cultures. *Lab Chip*. 2022;22(2):225–239. doi:10.1039/D1LC00689D
87. Wu H, Wang W, Zhang Y, et al. Establishment of patient-derived organoids for guiding personalized therapies in breast cancer patients. *Int J Cancer*. 2024;155(2):324–338. doi:10.1002/ijc.34931
88. Luan X, Yuan H, Song Y, et al. Reappraisal of anticancer nanomedicine design criteria in three types of preclinical cancer models for better clinical translation. *Biomaterials*. 2021;275:120910. doi:10.1016/j.biomaterials.2021.120910
89. Huang L, Rong Y, Tang X, et al. Engineered exosomes as an in situ DC-primed vaccine to boost antitumor immunity in breast cancer. *Mol Cancer*. 2022;21(1):45. doi:10.1186/s12943-022-01515-x
90. Liu Z, Shi Y, Lv L, et al. Small molecular inhibitors reverse cancer metastasis by blockading oncogenic PITPNM3. *Adv Sci*. 2022;9(35): e2204649. doi:10.1002/advs.202204649
91. Li B, Qi F, Zhu F, et al. Nanoparticle-based combination therapy enhances fulvestrant efficacy and overcomes tumor resistance in ER-positive breast cancer. *Cancer Res*. 2023;83(17):2924–2937. doi:10.1158/0008-5472.CAN-22-3559
92. Camorani S, Caliendo A, Morrone E, et al. Bispecific aptamer-decorated and light-triggered nanoparticles targeting tumor and stromal cells in breast cancer derived organoids: implications for precision phototherapies. *J Exp Clin Cancer Res*. 2024;43(1):92. doi:10.1186/s13046-024-03014-x
93. Jiang T, Zhu J, Jiang S, et al. Targeting lncRNA DDIT4-AS1 sensitizes triple negative breast cancer to chemotherapy via suppressing of autophagy. *Adv Sci*. 2023;10(17):e2207257. doi:10.1002/advs.202207257
94. Scialabba C, Sciortino A, Messina F, et al. Highly homogeneous biotinylated carbon nanodots: red-emitting nanoheaters as theranostic agents toward precision cancer medicine. *ACS Appl Mater Interfaces*. 2019;11(22):19854–19866. doi:10.1021/acsami.9b04925
95. Roscigno G, Affinito A, Quintavalle C, et al. Ultrasmall carbon nanodots as theranostic nanoheaters for precision breast cancer phototherapy: establishing the translational potential in tumor-in-a-dish models. *ACS Biomater Sci Eng*. 2024;10(7):4269–4278. doi:10.1021/acsbiomaterials.4c00209
96. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
97. van de Wetering M, Francies HE, Francis JM, et al. Prospective derivation of a living organoid biobank of colorectal cancer patients. *Cell*. 2015;161(4):933–945. doi:10.1016/j.cell.2015.03.053

98. Li J, Liu J, Xia W, Yang H, Sha W, Chen H. Deciphering the tumor microenvironment of colorectal cancer and guiding clinical treatment with patient-derived organoid technology: progress and challenges. *Technol Cancer Res Treat*. 2024;23:15330338231221856. doi:10.1177/15330338231221856
99. Li H, Dai W, Xia X, et al. Modeling tumor development and metastasis using paired organoids derived from patients with colorectal cancer liver metastases. *J Hematol Oncol*. 2020;13(1):119. doi:10.1186/s13045-020-00957-4
100. Vlachogiannis G, Hedayat S, Vatsiou A, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science*. 2018;359(6378):920–926. doi:10.1126/science.aao2774
101. Shen X, Zhang Y, Xu Z, et al. KLF5 inhibition overcomes oxaliplatin resistance in patient-derived colorectal cancer organoids by restoring apoptotic response. *Cell Death Dis*. 2022;13(4):303. doi:10.1038/s41419-022-04773-1
102. Benboubker V, Ramzy GM, Jacobs S, Nowak-Sliwinska P. Challenges in validation of combination treatment strategies for CRC using patient-derived organoids. *J Exp Clin Cancer Res*. 2024;43(1):259. doi:10.1186/s13046-024-03173-x
103. Smabers LP, Wensink E, Verissimo CS, et al. Organoids as a biomarker for personalized treatment in metastatic colorectal cancer: drug screen optimization and correlation with patient response. *J Exp Clin Cancer Res*. 2024;43(1):61. doi:10.1186/s13046-024-02980-6
104. Gonzalez-Exposito R, Semiannikova M, Griffiths B, et al. CEA expression heterogeneity and plasticity confer resistance to the CEA-targeting bispecific immunotherapy antibody cibisatamab (CEA-TCB) in patient-derived colorectal cancer organoids. *J Immunother Cancer*. 2019;7(1):101. doi:10.1186/s40425-019-0575-3
105. Luo L, Ma Y, Zheng Y, Su J, Huang G. Application progress of organoids in colorectal cancer. *Front Cell Dev Biol*. 2022;10:815067. doi:10.3389/fcell.2022.815067
106. Du Y, Li X, Niu Q, et al. Development of a miniaturized 3D organoid culture platform for ultra-high-throughput screening. *J Mol Cell Biol*. 2020;12(8):630–643. doi:10.1093/jmcb/mjaa036
107. Norkin M, Ordóñez-Morán P and Huelsken J. High-content, targeted RNA-seq screening in organoids for drug discovery in colorectal cancer. *Cell Reports*. 2021;35(3):109026. doi:10.1016/j.celrep.2021.109026
108. Huang C, Zhou Y, Feng X, Wang J, Li Y, Yao X. Delivery of engineered primary tumor-derived exosomes effectively suppressed the colorectal cancer chemoresistance and liver metastasis. *ACS Nano*. 2023;17(11):10313–10326. doi:10.1021/acsnano.3c00668
109. Benelli R, Costa D, Salvini L, et al. Targeting of colorectal cancer organoids with zoledronic acid conjugated to the anti-EGFR antibody cetuximab. *J Immunother Cancer*. 2022;10(12):e005660. doi:10.1136/jitc-2022-005660
110. Liu P, Wang Q, Li K, et al. A DFX-based iron nanochelator for cancer therapy. *Front Bioeng Biotechnol*. 2022;10:1078137. doi:10.3389/fbioe.2022.1078137
111. Hu S, Xia K, Huang X, et al. Multifunctional CaCO(3)@Cur@QTX125@HA nanoparticles for effectively inhibiting growth of colorectal cancer cells. *J Nanobiotechnol*. 2023;21(1):353. doi:10.1186/s12951-023-02104-w
112. Song H, Li H, Shen X, et al. A pH-responsive cetuximab-conjugated DMAKO-20 nano-delivery system for overcoming K-ras mutations and drug resistance in colorectal carcinoma. *Acta Biomater*. 2024;177:456–471. doi:10.1016/j.actbio.2024.01.047
113. Gonzales-Aloy E, Ahmed-Cox A, Tsoli M, Ziegler DS, Kavallaris M. From cells to organoids: the evolution of blood-brain barrier technology for modelling drug delivery in brain cancer. *Adv Drug Deliv Rev*. 2023;196:114777. doi:10.1016/j.addr.2023.114777
114. Nowogrodzki J. How cerebral organoids are guiding brain-cancer research and therapies. *Nature*. 2018;561(7724):S48–s49. doi:10.1038/d41586-018-06708-3
115. Witthayanuwat S, Pesee M, Supaadirek C, Supakalin N, Thamronganantasakul K, Krusun S. Survival analysis of glioblastoma multiforme. *Asian Pac J Cancer Prev*. 2018;19(9):2613–2617. doi:10.22034/APJCP.2018.19.9.2613
116. Wiwatchaitawee K, Quarterman JC, Geary SM, Salem AK. Enhancement of therapies for glioblastoma (GBM) using nanoparticle-based delivery systems. *AAPS Pharm Sci Tech*. 2021;22(2):71. doi:10.1208/s12249-021-01928-9
117. Zhang C, Nance EA, Mastorakos P, et al. Convection enhanced delivery of cisplatin-loaded brain penetrating nanoparticles cures malignant glioma in rats. *J Control Release*. 2017;263:112–119. doi:10.1016/j.jconrel.2017.03.007
118. Song P, Zhao X, Xiao S. Application prospect of peptide-modified nano targeting drug delivery system combined with PD-1/PD-L1 based immune checkpoint blockade in glioblastoma. *Int J Pharm*. 2020;589:119865. doi:10.1016/j.ijpharm.2020.119865
119. Gaillard PJ, Appeldoorn CC, Dorland R, et al. Pharmacokinetics, brain delivery, and efficacy in brain tumor-bearing mice of glutathione pegylated liposomal doxorubicin (2B3-101). *PLoS One*. 2014;9(1):e82331. doi:10.1371/journal.pone.0082331
120. Sun R, Liu M, Lu J, et al. Bacteria loaded with glucose polymer and photosensitive ICG silicon-nanoparticles for glioblastoma photothermal immunotherapy. *Nat Commun*. 2022;13(1):5127. doi:10.1038/s41467-022-32837-5
121. Banks WA. From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery. *Nat Rev Drug Discov*. 2016;15(4):275–292. doi:10.1038/nrd.2015.21
122. Xie J, Shen Z, Anraku Y, Kataoka K, Chen X. Nanomaterial-based blood-brain-barrier (BBB) crossing strategies. *Biomaterials*. 2019;224:119491. doi:10.1016/j.biomaterials.2019.119491
123. Ananda S, Nowak AK, Cher L, et al. Phase 2 trial of temozolomide and pegylated liposomal doxorubicin in the treatment of patients with glioblastoma multiforme following concurrent radiotherapy and chemotherapy. *J Clin Neurosci*. 2011;18(11):1444–1448. doi:10.1016/j.jocn.2011.02.026
124. Teixeira MI, Lopes CM, Amaral MH, Costa PC. Navigating neurotoxicity and safety assessment of nanocarriers for brain delivery: strategies and insights. *Acta Biomater*. 2024;189:25–56. doi:10.1016/j.actbio.2024.09.027
125. Fan Y, Xu C, Deng N, et al. Understanding drug nanocarrier and blood-brain barrier interaction based on a microfluidic microphysiological model. *Lab Chip*. 2023;23(7):1935–1944. doi:10.1039/D2LC01077A
126. Andreatta F, Beccaceci G, Fortuna N, et al. The organoid era permits the development of new applications to study glioblastoma. *Cancers*. 2020;12(11):3303. doi:10.3390/cancers12113303
127. Yamazaki S, Ohka F, Hirano M, et al. Newly established patient-derived organoid model of intracranial meningioma. *Neuro Oncol*. 2021;23(11):1936–1948. doi:10.1093/neuonc/noab155
128. Rybin MJ, Ivan ME, Ayad NG, Zeier Z. Organoid models of glioblastoma and their role in drug discovery. *Front Cell Neurosci*. 2021;15:605255. doi:10.3389/fncel.2021.605255

129. Darrigues E, Zhao EH, De Loose A, et al. Biobanked glioblastoma patient-derived organoids as a precision medicine model to study inhibition of invasion. *Int J Mol Sci*. 2021;22(19):10720. doi:10.3390/ijms221910720
130. Lenin S, Ponthier E, Scheer KG, et al. A drug screening pipeline using 2D and 3D patient-derived in vitro models for pre-clinical analysis of therapy response in glioblastoma. *Int J Mol Sci*. 2021;22(9):4322. doi:10.3390/ijms22094322
131. Jacob F, Salinas RD, Zhang DY, et al. A patient- derived glioblastoma organoid model and biobank recapitulates inter- and intra-tumoral heterogeneity. *Cell*. 2020;180:188–204. doi:10.1016/j.cell.2019.11.036
132. Yi HG, Jeong YH, Kim Y, et al. A bioprinted human-glioblastoma-on-a-chip for the identification of patient-specific responses to chemoradiotherapy. *Nat Biomed Eng*. 2019;3(7):509–519. doi:10.1038/s41551-019-0363-x
133. Chadwick M, Yang C, Liu L, et al. Rapid processing and drug evaluation in glioblastoma patient-derived organoid models with 4D bioprinted arrays. *iScience*. 2020;23(8):101365. doi:10.1016/j.isci.2020.101365
134. Linkous A, Balamatsias D, Snuderl M, et al. Modeling patient-derived glioblastoma with cerebral organoids. *Cell Rep*. 2019;26(12):3203–3211. e3205. doi:10.1016/j.celrep.2019.02.063
135. Simonneau C, Duschmalé M, Gavrilov A, et al. Investigating receptor-mediated antibody transcytosis using blood-brain barrier organoid arrays. *Fluids Barriers CNS*. 2021;18(1):43. doi:10.1186/s12987-021-00276-x
136. Bergmann S, Lawler SE, Qu Y, et al. Blood-brain-barrier organoids for investigating the permeability of CNS therapeutics. *Nat Protoc*. 2018;13 (12):2827–2843. doi:10.1038/s41596-018-0066-x
137. Kostka K, Sokolova V, El-Taibany A, et al. The application of ultrasmall gold nanoparticles (2 nm) functionalized with doxorubicin in three-dimensional normal and glioblastoma organoid models of the blood-brain barrier. *Molecules*. 2024;29(11):2469. doi:10.3390/molecules29112469
138. Balyasnikova IV, Zannikou M, Wang G, et al. Indocarbocyanine nanoparticles extravasate and distribute better than liposomes in brain tumors. *J Control Release*. 2022;349:413–424. doi:10.1016/j.jconrel.2022.07.008
139. Zhou L, Zhang C, Zhang Y, Shi C. Application of organoid models in prostate cancer research. *Front Oncol*. 2021;11:736431. doi:10.3389/fonc.2021.736431
140. Karkampouna S, La Manna F, Benjak A, et al. Patient-derived xenografts and organoids model therapy response in prostate cancer. *Nat Commun*. 2021;12(1):1117. doi:10.1038/s41467-021-21300-6
141. Servant R, Garioni M, Vlajnic T, et al. Prostate cancer patient-derived organoids: detailed outcome from a prospective cohort of 81 clinical specimens. *J Pathol*. 2021;254(5):543–555. doi:10.1002/path.5698
142. Puca L, Bareja R, Prandi D, et al. Patient derived organoids to model rare prostate cancer phenotypes. *Nat Commun*. 2018;9(1):2404. doi:10.1038/s41467-018-04495-z
143. Beshiri ML, Tice CM, Tran C, et al. A PDX/organoid biobank of advanced prostate cancers captures genomic and phenotypic heterogeneity for disease modeling and therapeutic screening. *Clin Cancer Res*. 2018;24(17):4332–4345. doi:10.1158/1078-0432.CCR-18-0409
144. Van Hemelryk A, Mout L, Erkens-Schulze S, French PJ, van Weerden WM, van Royen ME. Modeling prostate cancer treatment responses in the organoid era: 3D environment impacts drug testing. *Biomolecules*. 2021;11(11):1572. doi:10.3390/biom11111572
145. Minoli M, Cantore T, Hanhart D, et al. Bladder cancer organoids as a functional system to model different disease stages and therapy response. *Nat Commun*. 2023;14(1):2214. doi:10.1038/s41467-023-37696-2
146. Winnicka A, Brzeszczyńska J, Saluk J, Wigner-Jeziorska P. Nanomedicine in bladder cancer therapy. *Int J Mol Sci*. 2024;25(19):10388. doi:10.3390/ijms251910388
147. Li W, Wang Z, Jiang Z, et al. MiR-3960 inhibits bladder cancer progression via targeting of DEXI. *Biochem Biophys Res Commun*. 2023;668:8–18. doi:10.1016/j.bbrc.2023.05.055
148. Kaps L, Schuppan D. Targeting cancer associated fibroblasts in liver fibrosis and liver cancer using nanocarriers. *Cells*. 2020;9(9):2027. doi:10.3390/cells9092027
149. Kim E, Choi S, Kang B, et al. Creation of bladder assembloids mimicking tissue regeneration and cancer. *Nature*. 2020;588(7839):664–669. doi:10.1038/s41586-020-3034-x
150. Wang Q, Yuan F, Zuo X, Li M. Breakthroughs and challenges of organoid models for assessing cancer immunotherapy: a cutting-edge tool for advancing personalised treatments. *Cell Death Discov*. 2025;11(1):222. doi:10.1038/s41420-025-02505-w
151. Tao B, Li X, Hao M, et al. Organoid-guided precision medicine: from bench to bedside. *MedComm*. 2025;6(5):e70195. doi:10.1002/mco2.70195
152. Chen B, Du C, Wang M, Guo J, Liu X. Organoids as preclinical models of human disease: progress and applications. *Med Rev*. 2024;4 (2):129–153. doi:10.1515/mr-2023-0047
153. Shi H, Kowalczewski A, Vu D, et al. Organoid intelligence: integration of organoid technology and artificial intelligence in the new era of in vitro models. *Med Nov Technol Devices*. 2024;21:100276.
154. Deng S, Li C, Cao J, et al. Organ-on-a-chip meets artificial intelligence in drug evaluation. *Theranostics*. 2023;13(13):4526–4558. doi:10.7150/thno.87266
155. Bai L, Wu Y, Li G, Zhang W, Zhang H, Su J. AI-enabled organoids: construction, analysis, and application. *Bioact Mater*. 2024;31:525–548. doi:10.1016/j.bioactmat.2023.09.005