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REVIEW

Research insights and clinical opportunities of functional organoid-based platforms

Yueyu Huang[1] · Wenhui Shen[1] · Kehan Li[2] · Yutian Zhang[1] · Qiaoli Lv[3] · Changchun Wang[4] · Weimin Mao[3,4] · An Zhao[1,3]

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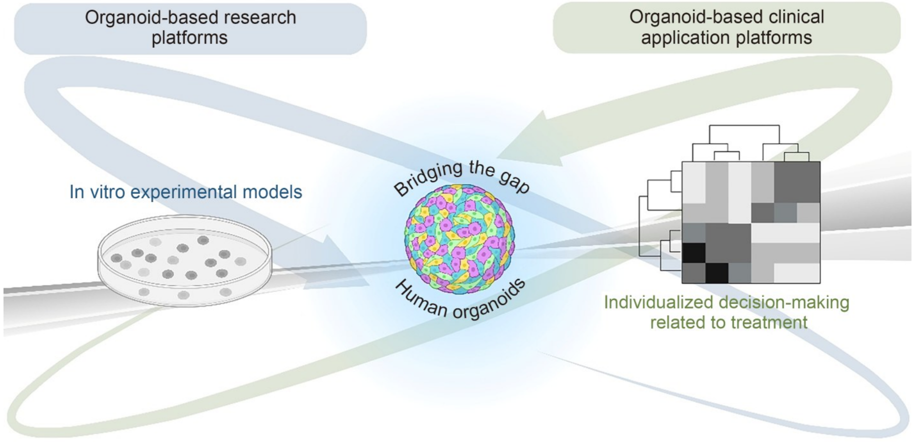
Abstract

Stem cell- or tissue-derived three-dimensional organ-like formations, known as organoids, are emerging as effective tools in biomedicine. Since they may be useful in developing customized therapeutic solutions and efficient drug screening protocols, organoids can deepen our understanding of novel disease mechanisms. In doing so, they can facilitate advancements in drug discovery platforms, pharmacological safety, and clinical trials. This review explores various biomedical applications of organoids, including drug development and disease modeling, and highlights specific tools and analytical techniques that can be employed to investigate organoids and their microenvironments. Finally, we review recent clinical trials and patents related to organoids that show great promise for future clinical translation.

Graphical abstract



Keywords Organoids · In vitro research models · Clinical trials · Functional and engineered design

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Yueyu Huang, Wenhui Shen, and Kehan Li have contributed equally to this work.

✉ Weimin Mao
maowm@zjcc.org.cn

✉ An Zhao
zhaoan@zjcc.org.cn

[1] Zhejiang Cancer Institute, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou 310011, China

[2] School of Mechanical Engineering, The University of Hong Kong, Hong Kong 999077, China

[3] Thoracic Oncology Laboratory, Jiangxi Cancer Hospital, Nanchang Medical College, Nanchang 330029, China

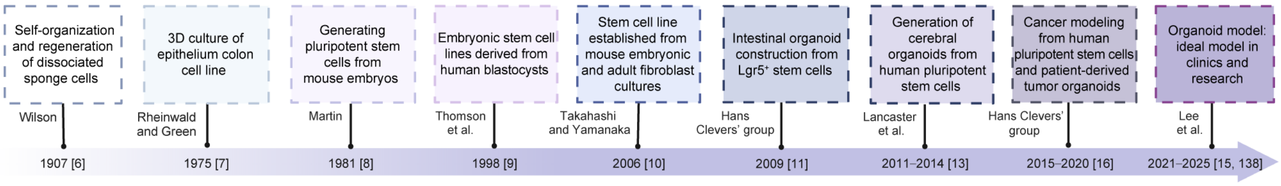
[4] Department of Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou 310011, China

1 Introduction

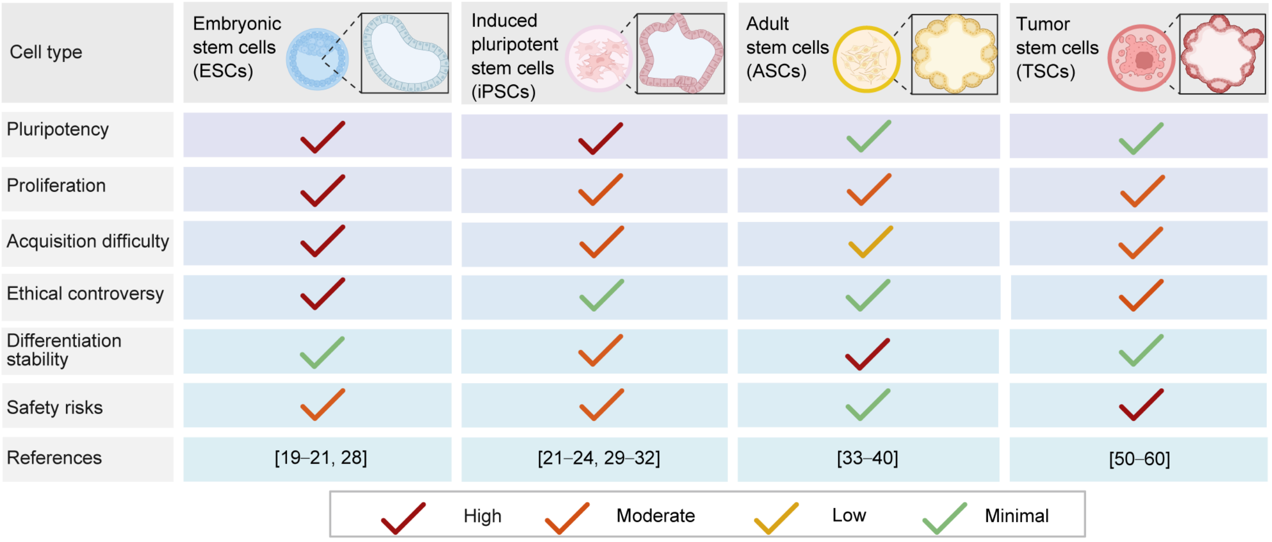
In biomedical research, traditional two-dimensional (2D) cell culture and animal model systems have been widely used to explore biological processes and develop new drugs [1, 2]. In general, model systems can help us understand signaling processes within cells, identify key molecules or genes that can be used as therapeutic targets, guide the design and optimization of candidate drugs, and further investigate the molecular evolution of cancers. However, 2D cell cultures also have important limitations. For example, as culture time in a 2D environment increases, cultured cells gradually lose their three-dimensional (3D) shape, causing them to flatten and divide abnormally under adherent conditions. This affects the phenotype of differentiated cells, the interactions between cells, and the interactions between cells and the extracellular matrix (ECM). Two-dimensional cultures can also lead to a gradual loss of cell heterogeneity, making it challenging to reflect the actual state of cells in vivo [3–5]. In addition, animal models face challenges in clinical translational research, especially regarding differences in immune systems among species.

Understanding the causal relationship between human genetic variation and disease processes is essential for developing personalized therapeutic strategies. However, the development of such strategies depends on using experimental systems that more closely approximate human physiological and pathological states. Since the late 20th century, organoid research has focused on exploring the self-organizing abilities of stem cells and their potential for generating complex tissue structures (Fig. 1a). In 1907, Wilson cultivated mechanically separated sponge cells to construct functioning organisms in vitro, marking the beginning of organoid research [6]. As induced pluripotent stem cell (iPSC) technology has advanced, it has become a versatile research tool that has profoundly impacted studies of stem cells and organoids. In 1975, the first long-term cell culture experiment was performed; in this study, primary human keratinocytes were co-cultured with 3T3 fibroblasts to successfully generate a multilayered squamous epithelial colony that showed characteristics similar to those of the human epidermis [7]. This advancement ushered in other new breakthroughs. For example, in 1981, scientists cultured pluripotent stem cells (PSCs) from mouse embryos [8], and by 1998, culturing of established human embryonic stem cells (ESCs) was possible [9]. In 2006, Takahashi and Yamanaka successfully reprogrammed fibroblasts into a pluripotent state by transfecting the key transcription factors Oct4, Sox2, Klf4, and c-Myc, thereby marking a major turning point in organoid development that completely changed the

(a) The historical evolution of organoids



(b) The origins and characteristics of organoids



Cell type	Embryonic stem cells (ESCs)	Induced pluripotent stem cells (iPSCs)	Adult stem cells (ASCs)	Tumor stem cells (TSCs)
Pluripotency	✓	✓	✓	✓
Proliferation	✓	✓	✓	✓
Acquisition difficulty	✓	✓	✓	✓
Ethical controversy	✓	✓	✓	✓
Differentiation stability	✓	✓	✓	✓
Safety risks	✓	✓	✓	✓
References	[19–21, 28]	[21–24, 29–32]	[33–40]	[50–60]

✓ High ✓ Moderate ✓ Low ✓ Minimal

Fig. 1 Organoid development and functional classification. (a) Chronology of organoid development. (b) Origins and characteristics of organoids direction of research within this field [10]. Moreover, the continuous advancement of iPSC technology has since provided a versatile tool, which has had a profound impact on stem cell-based organoid research.

In 2009, Clevers' group first reported the use of intestinal stem cells overexpressing leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5) to construct the first intestinal organs in vitro that showed a highly reduced tissue structure [11]. In a similar study, Clevers and Bender coined the term "organoid" to describe these in vitro culture models, promoting organoid technology's rapid development [12]. The unique value of organoids involves both their ability to reproduce the 3D structures of organs and their ability to approximate the cellular ecosystem, specific organ functions, and complex cell arrangements of real organs [11, 12]. More recently, in vitro cultures of organoids from different tissues and organs have been reported, including brain, retina, lung, stomach, liver, bile duct, pancreas, kidney, and tumor organoids (Fig. 1b) [13, 14].

Finally, recent advances in organoid technology have made it possible to construct models that closely resemble both physiological and pathophysiological states. This breakthrough has provided new possibilities for studying disease mechanisms, screening drug candidates, and developing personalized treatment strategies [15–18]. This review summarizes primary organoid cell sources and technical differences in contemporary organoid construction, examines potential clinical applications related to organoid construction, and discusses future research prospects and limitations of biomedical studies involving organoids.

2 Cellular origins of organoids

Numerous organoids have been established in vitro using multiple types of stem cells, including ESCs, iPSCs, adult stem cells (ASCs), and tumor stem cells (TSCs) (Fig. 1b).

2.1 Pluripotent stem cell-based organoids

PSCs mainly include iPSCs and ESCs [19, 20]. iPSCs are obtained by reprogramming differentiated cells by integrating transcription factors, whereas ESCs can be isolated and cultured from blastocysts [21]. PSCs can differentiate into various cell types by manipulating their microenvironment to provide specific conditions required during different stages of cellular differentiation [22–24]. In one groundbreaking study, Sasai et al. explored whether in vitro organoid models based on PSCs could simulate real developmental processes within the body. To do so they developed methods for culturing brain, retinal, and pituitary structures in a "petri dish" [25–27]. Furthermore, Gong et al. derived human ESC-derived spheroids in vitro, which they intended to use to induce neural lineage differentiation and reconstruct neural tube structures [28]. Subsequently, Sasai et al. reported brain organoid-like spheres derived from PSCs. To date, researchers have cultivated a wide range of organoid types from PSCs, building upon the pioneering work of Yoshiki Sasai and others [29–32].

Progress in producing PSC-derived organoids has established the feasibility of in vitro experiments for genetic disease and developmental studies. However, the inevitable differentiation of cells during culture and the requirement for repeated passaging remain the primary limitations of this system. Furthermore, ESCs are derived from the inner cell mass of the blastocyst stage. This means that they can differentiate into any cell type, which poses new ethical questions regarding stem cell sources and the extent of in vitro cultures.

2.2 Adult tissue cell-based organoids

ASCs are another primary source of developing organoids. ASCs exist in nearly all types of tissue and are crucial for tissue maintenance and regeneration following damage. ASCs can only be isolated from regenerated tissues and show better potential than ESCs and iPSCs for the reconstruction of mature tissues and functional structures [33].

By supplementing culture medium with specific stem cell niche factors that precisely modulated cell developmental signaling, Clevers et al. were the first to successfully produce in vitro cultures of $Lgr5^+$ stem cells derived from mesenchymal stem cells without a mesenchymal niche. Using this method, they were thus able to construct crypt-villus structures [11,34]. ASCs have subsequently been reported as expanding in vivo by supporting stem cell niche factors [35, 36]. Overall, the Wnt pathway has emerged as a major driver of epithelial stem cells. Lgr5, a secreted Wnt-enhanced R-spondins receptor that is encoded by a Wnt target gene, marks active stem cells present in many epithelia. Wnt activators (e.g., Wnt3A, R-spondins, and the small molecule GSK3 inhibitor CHIR) are therefore key components of most ASC organoid protocols [37, 38]. Although ASC-based organoids can repair and regenerate tissue, they are mainly composed of epithelial cells and lack other cell types, which limits the integrity of their physiological functions [36, 39, 40]. In addition, researchers have devised novel methodologies to generate various PSC- and ASC-derived structures and tissues in vitro. However, understanding which tissue culture media are required to culture specific ASC-derived organoids remains a limiting factor. Thus, differences in the culture medium required by ASCs sourced from different tissues limit the widespread application of organoids.

Three-dimensional structures produced by cells taken from healthy tissues are known as normal tissue-derived organoids. Such organoids can effectively simulate the physiological characteristics and functions of specific organs. Moreover, because they are structurally and functionally closer to real organs, 3D cultures can provide more in-depth insight into pathways related to organ development, homeostasis, and pathogenesis. For example, d'Aldebert et al. constructed organoids from normal and inflammatory bowel disease colon tissues to compare mechanisms related to drug absorption caused by differences in disease-associated gut microbes [41]. In another study, Lee et al. constructed a multicellular liver organoid model that comprised hepatocytes, Kupffer-like cells, and hepatic stellate cells [42]. This in vitro model was shown to have reasonable tissue specificity, and was therefore capable of helping scientists to better understand drug metabolism, toxic effects, and possible side effects on the liver. Moreover, the development of pancreatic organoids derived from endocrine or exocrine cells can accurately mimic the pancreatic microenvironment and deepen our mechanistic understanding of interactions between insulin secretion and pancreatic cells [43]. In addition to being used to study both physiological and pathological respiratory diseases, lung organoid models have been effectively used to study the mechanisms involved in respiratory virus (including SARS-CoV-2, the virus responsible for COVID-19) infection and related drug screenings [44, 45]. In addition, thymus organoids have been established from both adult humans and from thymus tissue extracted from fetuses or newborns to simulate key thymus functions [46–49].

2.3 Tumor cell-based organoids

Inspired by studies in which ASCs were used to construct organoids, tumor-derived cells and tumor-associated stem cells have been used to generate ordered 3D structures in vitro under special culture conditions. The resulting tissue structures are called tumoral organoids or "tumoroids." Since Hwang et al. first reported a pancreatic tumor organoid model in 2015 [50], new tumoroids have been developed for many common and rare tumors, including those associated with esophageal cancer [51], lung cancer [52], breast cancer [53], osteosarcoma [54], and thymoma [55]. Furthermore, gene sequencing studies have shown that the observed target gene mutations in tumors and their original tissues are highly similar [56, 57]. Moreover, compared to traditional 2D cell cultures, tumoroids are relatively inexpensive to construct and can preserve patients' histology, genetics, and other characteristics, thus fully recreating tumor heterogeneity. For example, a patient-derived xenograft (PDX) model only generates malignant tumor cells in vivo, while tumoroids can grow in vitro with different degrees of malignant cells [16]. Moreover, it is much easier to edit genes in vitro than in vivo for PDX or patient-derived tumor cell (PDC) models, and researchers can use clustered regularly interspaced short palindromic repeat (CRISPR) and other gene-editing tools to perform experimental studies on tumoroids using a simple one-step protocol.

In immuno-oncology, it can be difficult to evaluate the effect of various immunotherapy treatments on PDX or PDC in immunodeficient mice. However, recent studies have shown that tumors can be co-cultured with T cells in vitro, thus providing novel possibilities for experimental tumor therapies based on immune monoclonal antibodies and immune cells [58–60].

3 Organoid-based basic research platforms

3.1 Organoid-based in vitro disease models

Organoids can mirror the key features of organs in vitro, including their tissue structure and metabolic characteristics. Organoids can also be used as induced disease or direct disease models, thereby providing an in vitro experimental platform for studying mechanisms of disease.

3.1.1 Genetic disease models

The first human disease modeled using organoid tissue was cystic fibrosis (CF), a common recessive genetic disease that was successfully recapitulated in a 3D intestinal organoid tissue [61]. Moreover, CF is a multisystem disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The CFTR protein is found on the membranes of various epithelial cells and is mainly responsible for transporting chloride ions [62, 63]. Dekkers et al. cultivated organoids from the colon tissue of a CF patient in the Netherlands and ultimately obtained a cure. Thus, research has confirmed that organoids can be used as a tool for personalized medicine [61]. Moreover, using organoid models, rapid detection methods for CFTR function have been developed. This is significant because it helps achieve diagnostic and drug screening of CF, thereby helping to develop personalized medicine and related functional research. Moreover, organoid technologies have been applied to functional studies related to Fabry disease and retinal genetic disease [64, 65]. Furthermore, the most common congenital disease in humans, i.e., left heart hypoplasia syndrome, has been modeled using organoids [66]. In another study, a heart organoid model was developed to study congenital heart defect diseases by knocking out the expression of the NK2 Homeobox 5 and heart and neural crest derivatives expressed 1 genes [67]. Brain organoids have been used to assess the genetic properties of the brain and have provided a framework to study novel approaches for treating neurodevelopmental genetic disorders, including

Down syndrome and microcephaly [13, 68]. Other brain organoids have been used to model neurological disorders such as Alzheimer's disease [69] and Parkinson's disease [70].

3.1.2 Individualized tumor models

Organoid technology now provides a platform that is more precise than traditional 2D cell cultivation or animal models for modeling tumor characteristics, including their 3D structure, the DNA mutations involved, and the interactions between cells. This is because organoids are able to realistically mirror the heterogeneity of the tumor microenvironment. Consequently, organoids have emerged as an ideal model for investigating tumor generation, development, metastasis, and subsequent responses to drug treatments. In 2011, Clevers' group established the first tumor organoids, thus pioneering the novel use of organoids in oncology [36]. The research team initially cultivated micro-intestinal organoids using ASCs derived from mouse intestines. However, the team subsequently expanded their research to include the cultivation of organoids derived from colonic adenomas, adenocarcinomas, and Barrett's esophagus. In 2015, Boj et al. from the same laboratory successfully established the first human pancreatic cancer organoid model using pancreatic cancer cells from Kirsten ratsarcoma viral oncogene homolog (Kras) mutant mice [71]. This step constituted a unique and highly valuable foundation for studying the mechanisms responsible for pancreatic cancer and facilitating the development of novel therapeutic strategies. Subsequently, in 2017, Pauli et al. established 56 patient-derived organoid cultures for 769 patients that were subsequently employed in high-throughput drug screening. This was the first trial of lung cancer organoids and laid the foundation for personalized therapies for lung cancer [72]. Later, Sachs et al. established a living biobank of over 100 primary and metastatic breast cancer-like organoid lineages to be used for future molecular analysis [53]. Analysis of these lineages has shown that these organoids generally mirror the heterogeneity observed in breast cancer patients and may be employed to assess the efficacy of disparate treatment modalities [73]. The development of organoid models is also driven by the fact that there is a significant contrast between the tumor microenvironment (TME) in existing tumor models and the TME in cancer patients in vivo [74]. Neal et al. developed a novel air–liquid interface (ALI) approach that enabled a more comprehensive recapitulation of patient tumor immune microenvironments when culturing tumor-derived organoids [75]. This method maintained the complex tissue structure within the TME while simulating immune cells within the tumor, thereby revealing interactions between immune and tumor cells. The use of organoid technology enables researchers to reproduce the genetic signatures of patient-specific tumors more accurately.

3.1.3 Infectious disease models

Organoid technology also has broad application potential for the study of infectious diseases, especially for providing a robust in vitro platform for studying interactions between viruses, bacteria, protozoan parasites, and their hosts. For example, an in vitro culture model using gastric organoids infected by *Helicobacter pylori* has provided novel data regarding the molecular mechanisms of specific pathogenic factors [76]. In another study, the rapid construction of 173 alveolar, airway, and bronchial organoids designed to mimic SARS-CoV-2 infection of lung tissue considerably accelerated our understanding of the pathophysiology and pathology of SARS-CoV-2 in vivo [77–80]. Moreover, microinjection of *Cryptosporidium parvum* into human intestinal and lung organoids allowed the parasite to reproduce and undergo its complex life cycle entirely within the organoid, a life cycle that is not feasible in conventional 2D culture systems [81].

Furthermore, viral infections have a high probability of manifesting in central nervous system disease, resulting in pathologies such as encephalitis, meningitis, myelitis, and seizures. In 2016, researchers employed brain organoids to investigate the Zika virus (ZIKV) and discovered that ZIKV infection reduced the volume of the neural precursor cell (NPC) and neuronal layers of brain organoid tissue. This was caused by the inhibition of NPC proliferation and a concomitant increase in cell death in both infected NPCs and uninfected neurons [82]. Taken together, these findings represent a significant advance in our understanding of the impact of ZIKV infection on fetal brain development. The recent pandemic of 2019 coronavirus disease (COVID-19) was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a virus that is associated with both neurological symptoms and potentially fatal respiratory symptoms. However, the exact mechanism by which these neurological complications emerge remains unclear. In 2020, Pellegrini et al. used human pluripotent stem cell-derived brain-like organoids to investigate the neurophilicity of SARS-CoV-2. They found that SARS-CoV-2 infection results in damage to the choroid plexus epithelium, leading to disruption of its barrier function [83]. In healthy subjects, this barrier prevents pathogens, immune cells, and cytokines from entering the cerebrospinal fluid and brain, and its disruption may be a significant contributing factor to the development of neurological symptoms. In addition, congenital infection with human cytomegalovirus (HCMV) represents a significant etiological factor in neurodevelopmental defects. However, the precise neuropathogenic mechanisms involved remain incompletely understood. In one study, Sun et al. used human iPSC-derived brain-like organoids to reproduce microcephaly associated with HCMV infection. They discovered that neutralizing antibodies specific to the HCMV pentameric complex could prevent HCMV-induced impairment of brain-like organ development [84]. This research demonstrates that HCMV can significantly impair the development and function of the human brain and also reveals the potential value of neutralizing antibodies for alleviating brain defects caused by HCMV infection. More generally, these results demonstrate how brain organoids can play an essential role in exploring the mechanistic basis of neuroleptic viral infection, while at the same time providing a valuable tool for testing antiviral drugs in physiologically relevant 3D models.

3.2 Organoids bridge disease modeling and drug discovery research

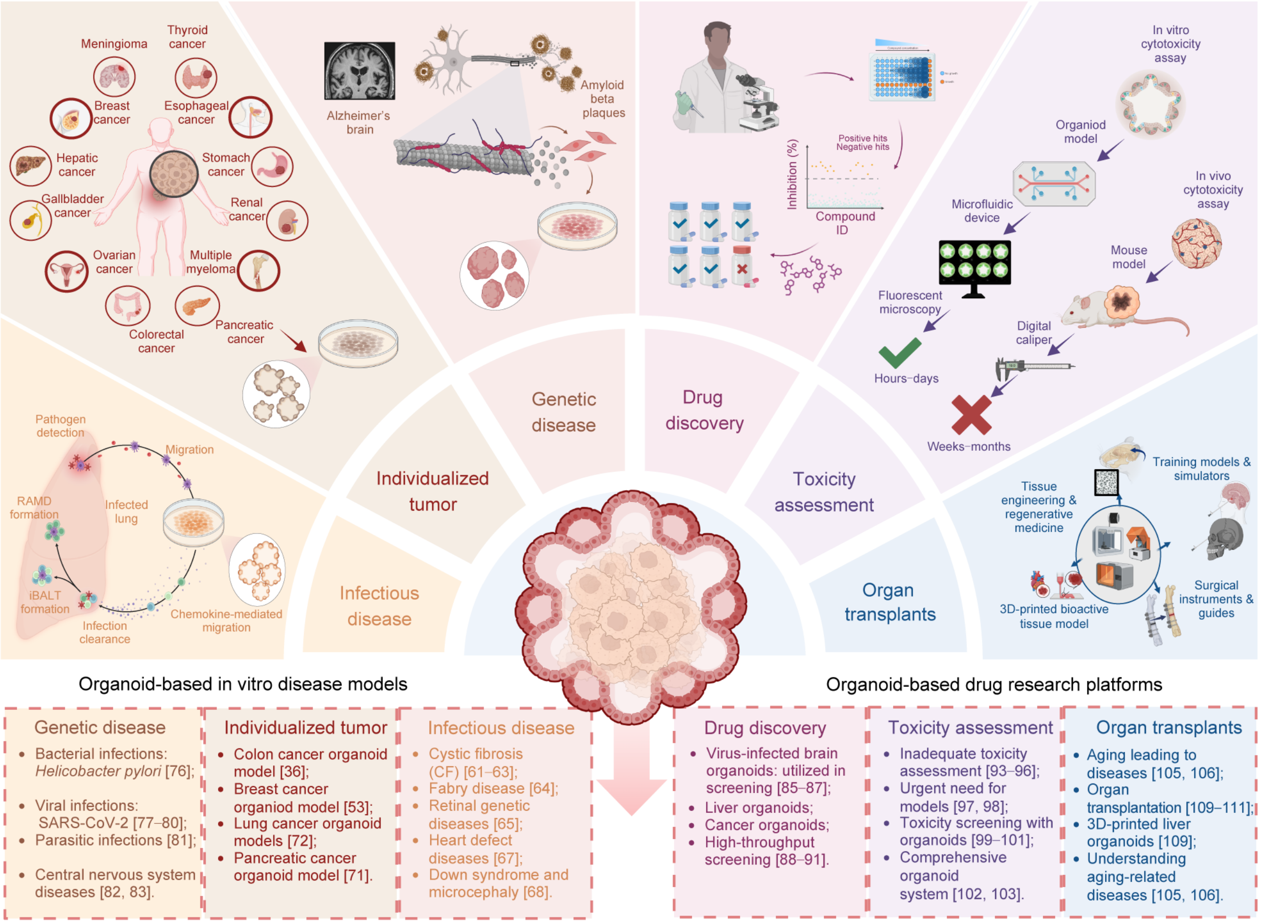
Organoid survival and functional maturity are key aspects that have been significantly improved in the recent past, with a diverse library of models now covering cancer, genetic diseases, and infectious diseases. Overall, organoid disease models not only lay the foundation for studying etiological mechanisms, but are also highly useful during drug screening. Using organoid model systems, researchers can analyze disease mechanisms, identify those related to immune escape within the tumor microenvironment, and apply these findings to improve precision medicine [85–87]. In addition, the combination of organoids and biomaterials provides new innovative opportunities for regenerative medicine and promotes new avenues for drug development (Fig. 2).

3.3 Organoid-based drug research platforms

Quickly generating accurate in vitro experimental models for various diseases and tumors is a unique advantage of organoids. This not only provides an individualized experimental platform for evaluating targeted drugs but also shortens the efficacy and safety evaluation cycles of new drugs.

3.3.1 Drug discovery

Disease-specific 3D organoids have significant potential for large-scale drug screening, thus creating new opportunities



Genetic disease

- Bacterial infections: *Helicobacter pylori* [76];
- Viral infections: SARS-CoV-2 [77–80];
- Parasitic infections [81];
- Central nervous system diseases [82, 83].

Individualized tumor

- Colon cancer organoid model [36];
- Breast cancer organoid model [53];
- Lung cancer organoid models [72];
- Pancreatic cancer organoid model [71].

Infectious disease

- Cystic fibrosis (CF) [61–63];
- Fabry disease [64];
- Retinal genetic diseases [65];
- Heart defect diseases [67];
- Down syndrome and microcephaly [68].

Drug discovery

- Virus-infected brain organoids: utilized in screening [85–87];
- Liver organoids;
- Cancer organoids;
- High-throughput screening [88–91].

Toxicity assessment

- Inadequate toxicity assessment [93–96];
- Urgent need for models [97, 98];
- Toxicity screening with organoids [99–101];
- Comprehensive organoid system [102, 103].

Organ transplants

- Aging leading to diseases [105, 106];
- Organ transplantation [109–111];
- 3D-printed liver organoids [109];
- Understanding aging-related diseases [105, 106].

Fig. 2 Organoid-based platforms for basic research and drug development. Shown are the primary applications of organoids, including the development of disease models, drug discovery, toxicity assessment, and organ transplants. RAMD: repair-associated memory depot; iBALT: inducible bronchus-associated lymphoid tissue for drug discovery. For example, virus-infected brain organoids have been used to screen for validated antiviral candidates including puromycin, ivermectin, and azithromycin [88, 89]. Similarly, brequinar and homoharringtonine have been confirmed as effective antihepatitis E virus (HEV) drugs using liver organoids [90]. Furthermore, an extracellular signal-regulated kinase inhibitor discovered by Broutier et al. has been shown to possess putative therapeutic effects using a human primary cancer organoid model system [91]. Organoids have excelled as models for high-throughput drug screening, as they permit efficient identification of the most potent molecules present in extensive compound libraries. For example, to find potentially functional drugs, Kozuka et al. cultured tiny colon organoids on 96-well plates and screened more than 2000 chemical substances [92]. In a similar study, Mao et al. constructed colorectal cancer organoids to screen 335 drugs, identifying 34 that possessed significant anti-cancer activity [86].

3.3.2 Toxicity assessment

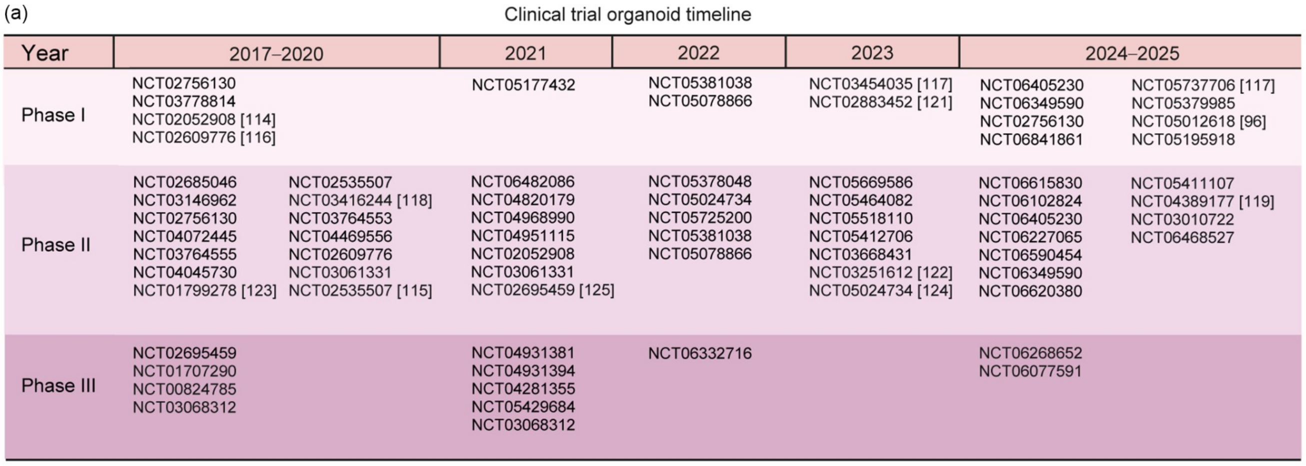
The failure of many drugs during clinical trials is partly due to inadequate assessments of drug toxicity during the preclinical phase [93–96]. Overall, the leading causes of drug clinical trial failure are hepatotoxicity, cardiotoxicity, and nephrotoxicity. Therefore, at present there is an urgent need for reliable toxicity screening models that accurately represent the physiological characteristics of real body systems [97, 98]. Organoids are ideally suited for this purpose, since they retain the original genetic information and matrix environment of focal tissues and are therefore more likely to mimic environmental factors related to drug sensitivity and resistance. Screenings involving organoids are therefore highly likely to efficiently determine optimal and most effective doses of novel drugs; in cancer systems this would mean eradicating tumor cells while causing minimal harm to healthy tissue. For example, Mekky et al. employed human liver organoids to evaluate the toxicity of valproic acid and aspartate-coated magnesium oxide nanoparticles [99]. Their findings showed that the nanoparticle drugs reduced the viability of hepatocytes, since the drug caused increased reactive oxygen species levels in hepatocytes while their adenosine triphosphate (ATP) levels were reduced. Similarly, cardiac organoids have been used to show that the cardiotoxicity of doxorubicin may be exacerbated by hypoxic cardiac injury [100, 101]. In other studies, iPSC-derived kidney organoids were used to screen for nephrotoxicity [102], while cardiac embryoid bodies established from mouse cardiac stem cell organoids or human iPSC organoids have been used for a variety of toxicity assessments [103]. In another study, Skardal et al. established a comprehensive organoid system comprising heart, lung, and liver organoid units within a unified perfusion cycle by making use of a shared medium [104]. Overall, we anticipate that organoid technology will increasingly be employed in toxicity research.

3.4 Organoid-based organ transplants

The function of human organs gradually declines with age, and over time organs show structural and functional changes. The aging process can lead to a variety of diseases, including cardiovascular disease, diabetes, and neurodegenerative disorders [105, 106]. Despite considerable progress made in organ transplantation, in which damaged or non-functional tissues are replaced with alternatives from healthy donors, limitations persist due to an insufficient number of viable donor organs, coupled with inherent risks associated with tissue rejection. These limitations underscore the necessity of finding alternative sources of tissue [107, 108]. However, organoids implanted in animals have been shown to restore function in damaged organs. For example, in one study immunodeficient mice with tyrosinemia type I and liver failure achieved phenotypic restoration of liver function following transplantation of 3D-printed engineered liver organoids [109]. Post-transplantation, these organoids successfully formed a functional vascular system, thereby facilitating liver function recovery. In another study, pancreatic islet organoids formed from islet cells supported by biological scaffolds were able to restore insulin secretion and reduce blood glucose levels following transplantation into type 1 diabetic mice [110]. In addition, Sampaziotis et al. provided a new protocol for bile duct repair using 3D organoids cultured with human bile duct epithelial cells; in doing so they were able to effectively replace damaged bile duct tissue [111].

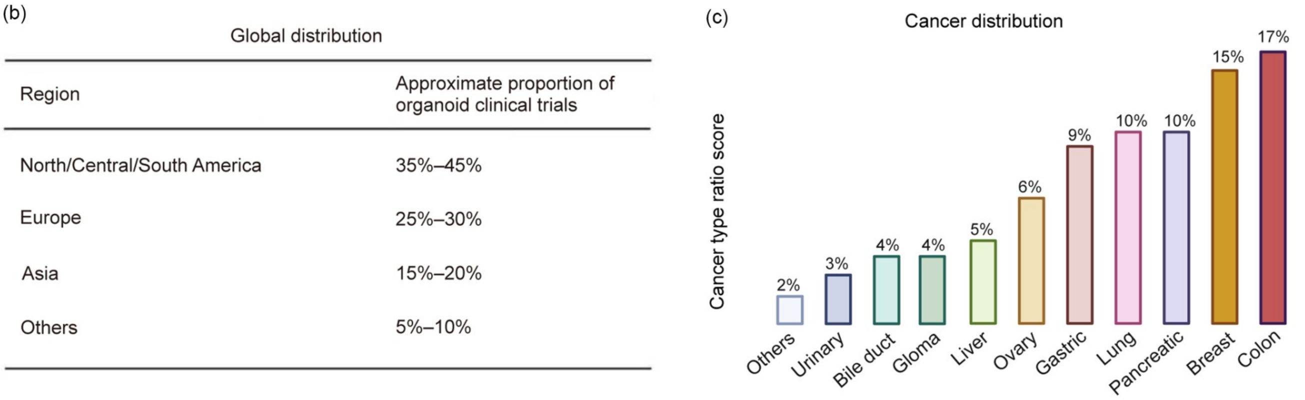
4 Organoid-based clinical application platforms

The use of organoids in clinical research has increased significantly each year since 2017 (Fig. 3). A comprehensive search of ClinicalTrials.gov (https://clinicaltrials.gov/; accessed in October 2024), a repository of clinical trial information, identified many clinical trials using PDOs that have shown significant promise. The initial search generated a list of 202 registered clinical trials, and after screening, the most studied disease was cancer, with colorectal cancer, breast cancer, and pancreatic cancer being the top three most-studied diseases. Currently, organoid clinical trials are focused on the following research areas: 1) To identify the molecular characteristics of tissue-derived tissues in vitro for the further investigation of pathogenic mechanisms; 2) Integration of in vitro drug assays with clinical data and the development of companion diagnostic biomarkers; 3) To



(a) Clinical trial organoid timeline

Year	2017–2020		2021	2022	2023	2024–2025	
Phase I	NCT02756130 NCT03778814 NCT02052908 [114] NCT02609776 [116]		NCT05177432	NCT05381038 NCT05078866	NCT03454035 [117] NCT02883452 [121]	NCT06405230 NCT06349590 NCT02756130 NCT06841861	NCT05737706 [117] NCT05379985 NCT05012618 [96] NCT05195918
Phase II	NCT02685046 NCT03146962 NCT02756130 NCT04072445 NCT03764555 NCT04045730 NCT01799278 [123]	NCT02535507 NCT03416244 [118] NCT03764553 NCT04469556 NCT02609776 NCT03061331 NCT02535507 [115]	NCT06482086 NCT04820179 NCT04968990 NCT04951115 NCT02052908 NCT03061331 NCT02695459 [125]	NCT05378048 NCT05024734 NCT05725200 NCT05381038 NCT05078866	NCT05669586 NCT05464082 NCT05518110 NCT05412706 NCT03668431 NCT03251612 [122] NCT05024734 [124]	NCT06615830 NCT06102824 NCT06405230 NCT06227065 NCT06590454 NCT06349590 NCT06620380	NCT05411107 NCT04389177 [119] NCT03010722 NCT06468527
Phase III	NCT02695459 NCT01707290 NCT00824785 NCT03068312		NCT04931381 NCT04931394 NCT04281355 NCT05429684 NCT03068312	NCT06332716		NCT06268652 NCT06077591	



(b) Global distribution

Region	Approximate proportion of organoid clinical trials
North/Central/South America	35%–45%
Europe	25%–30%
Asia	15%–20%
Others	5%–10%

(c) Cancer distribution

Fig. 3 Scope of organoids currently in clinical trials. (a) Clinical trials involving organoids are primarily in phases I–III, with a notable concentration in phase II. (b) Proportion of organoid clinical trials in different world regions. Trials are predominantly sponsored by institutions or individuals from China and the United States. (c) Proportion of cancer types associated with tumor organoids used in clinical trials. Most trials target colon cancer, breast cancer, pancreatic cancer, ovarian cancer, and/or gastric cancer

construct an organoid biobank based on a specific disease model. Overall, clinical translational applications such as generating individualized treatments using functional organoids are a major goal of this research.

4.1 Organoids in clinical trials

Ideal personalized treatments involve the selection of targeted treatment programs via in-depth consideration of disease pharmacogenomics and molecular characteristics [112]. Moreover, in vitro organoid cultures based on tumor cell biopsies can provide key information for patient treatment decisions with advanced but unresectable and/or unknown primary tumors. Given this significant potential application value, organoids have become a key research topic for clinical trials related to tumor treatments [113–117]. Listed clinical trials include those involving thyroid tumoroids (NCT06482086), lung tumoroids (NCT03979170, NCT02535507 [115], and NCT02609776 [116]), esophageal tumoroids (NCT03416244 [118] and NCT04389177 [119]), gastric tumoroids (NCT06196554), breast tumoroids (NCT06102824), colorectal tumoroids (NCT05832398, NCT02052908 [114], NCT03668431 [120], NCT02883452 [121], and NCT03251612 [122]), osteosarcoma tumoroids (NCT06064682), prostate tumoroids (NCT01799278 [123]), bladder tumoroids (NCT05024734 [124]), neuroendocrine tumoroids (NCT02695459 [125]), and other solid tumoroids (NCT05737706, NCT05379985, NCT05012618 [96], and NCT03454035 [117]).

In one study, Yao et al. constructed an organoid platform for patients with locally advanced rectal cancer and found that testing on organoids could accurately predict patient responses to neoadjuvant chemoradiotherapy [126]. In addition, Ganesh et al. confirmed the existence of a close correlation between tumor responses to treatment and those of locally advanced rectal cancer PDOs [127]. Furthermore, in a phase II study of 47 patients with locally advanced resectable esophageal squamous cell carcinoma (ESCC) [119], Shang and colleagues combined an in vitro organoid model and an external cancer dataset to find that a combination of pembrolizumab and chemotherapy was both well-tolerated and demonstrated favorable efficacy and safety profiles in patients with resectable phase III ESCC. Increases in T cell receptor gamma constant 2+ natural killer T cells have also been proposed as potential biomarkers for forecasting therapeutic efficacy, facilitating the development of novel clinical treatments. In another study, Liu et al. conducted a multicenter, double-blind, randomized, placebo-controlled clinical trial of patients with cirrhosis to assess the clinical, experimental, and pathophysiological impact of a device called Yaq-001 [128]. A study of 28 patients demonstrated that Yaq-001 significantly reduced organoid intestinal permeability and positively affected the composition and metabolism of the microbiome. As a regulated medical device, Yaq-001 successfully met its primary safety and tolerability endpoints in clinical trials, with the underlying organoid model system having provided a robust safety assessment platform for the potential clinical translation of Yaq-001 in cirrhosis patients (NCT03202498). Concurrently, Hedayat et al. emulated patient microenvironments by using circulating microRNAs in ex vivo co-cultures coupled with single-cell RNA sequencing of organoid PDOs established before and after treatment [129]. This study identified MIR652-3p as a key biomarker and driver of responses to regorafenib resistance mechanisms in chemotherapy-refractory metastatic colorectal cancer patients (NCT03010722). Taken together, this study and others like it report the identification of crucial biomarkers that can help unravel mechanisms of drug resistance across diverse cancers and can inform the optimization of therapeutic strategies.

4.2 Organoid-based clinical applications

Successful in vitro culturing of organoids provides a new system for characterizing real-time disease states before and after treatment. At present, frozen surgical tissue samples are the main samples retained by specimen banks, but the establishment of a spatiotemporal personalized organoid specimen bank can provide a new research model for researching disease etiology and informing precise treatment (Fig. 4a). Organoid technology can also enhance drug efficacy evaluation by more accurately simulating the tumor microenvironment [130–132]. In addition, researchers can rapidly prepare 3D organoids of tumor cells using 3D printing. This ease of preparation can help to generate a sufficient number of models required for the simultaneous evaluation of different chemotherapy and targeted drugs [133]. Thus, organoids combined with next-generation omics technologies and/or gene editing can provide new information for making treatment decisions. This information can

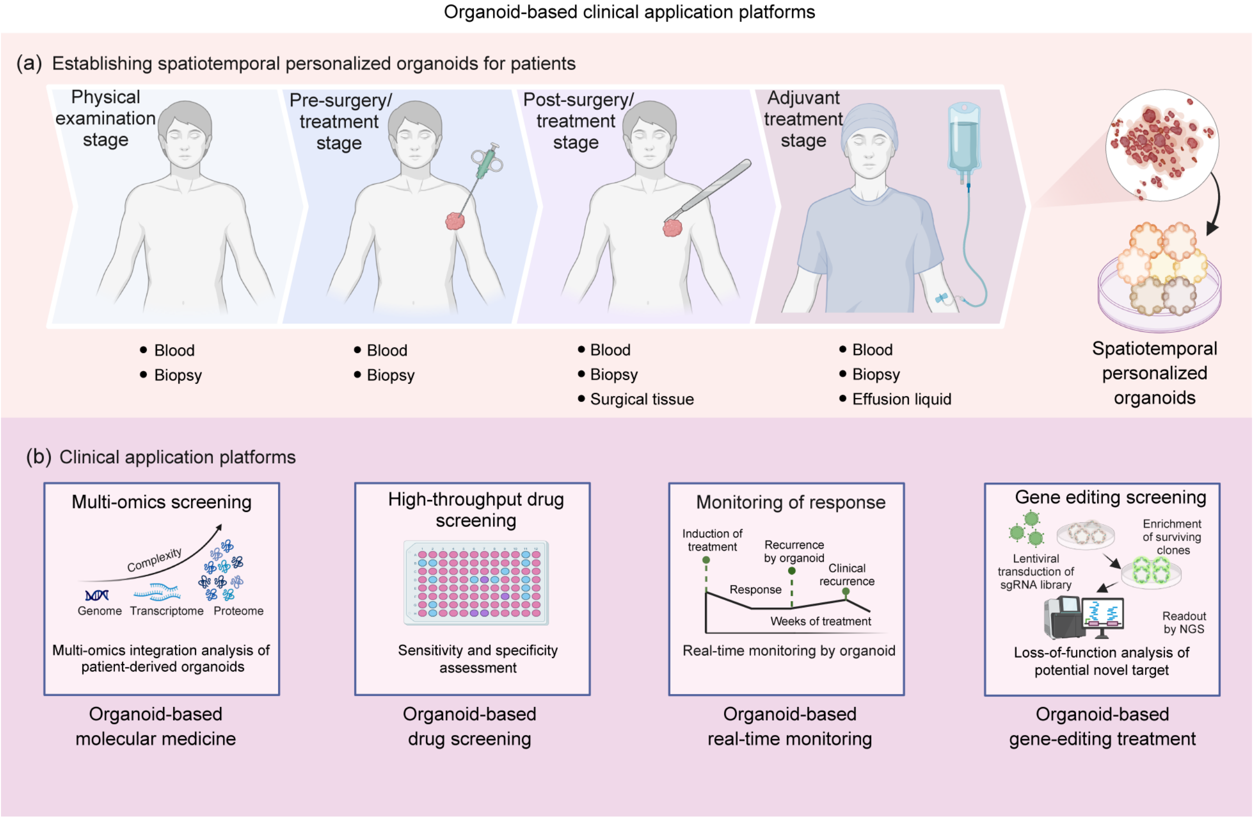


Fig. 4 Organoid-based clinical application platforms. (a) Platform for developing spatiotemporal personalized organoids for patients. (b) Clinical application platforms for organoids. Shown are: organoid-based molecular medicine, organoid-based drug screening, organoid-based real-time monitoring, and organoid-based gene-editing treatment. NGS: next-generation sequencing

involve detailed exploration of dose-response relationships, real-time monitoring of treatment responses, or novel therapeutic targets (Fig. 4b).

The natural healing ability of tumor cells can make treatment challenging, especially when chemotherapy and radiotherapy are the primary treatments used [73, 134]. In one recent study, Park et al. evaluated the activity, metabolism, and toxicity of docetaxel using stem cell-derived mouse small intestine and liver organoids [135]. They demonstrated that modification of gene expression and drug metabolism assessment can be performed using organoids in lieu of tissue analysis. Studies like this provide new perspectives regarding specific mechanisms of drug action and show the potential of organoid models for enhancing research into drug discovery and safety assessment. In another study, Li et al. developed a novel and quantitative high-throughput imaging analysis protocol that exploits the scalability of organoid cultures [136]. This method is designed to capture specific changes that occur during organoid growth, and involves measuring multiple whole-porous organoids. As a result, the authors were able to identify different reactions that occurred when the organoids were treated with drugs. This technology demonstrated the feasibility of high-throughput drug screening on an organoid platform and provided evidence for its potential in personalized tumor therapy. In a different study, Martin et al. established an organoid biobank from 65 patients with primary, metastatic, or recurrent rectal cancer (RC) [137]. After implantation of human rectal cancer organoids into the rectal mucosa of mice, invasive RCs were successfully generated in mice, and these further metastasized to the lungs and liver. Notably, tumors transplanted into the mice showed heterogeneous sensitivity to chemotherapy, which resembles related clinical observations. Thus, organoid-based ex vivo platforms can be used in conjunction with animal-based in vivo intraluminal propagation to efficiently study the biology and drug sensitivity of clinical RC isolates.

Drug sensitivity testing using organoids was also performed by Lee et al., who evaluated drug sensitivity testing using a cancer organoid diagnostic response prediction index developed using high-throughput screening of PDOs sourced from eight patients [138]. Their findings may facilitate improved predictive analysis of the efficacy of anticancer drugs in lung cancer patients, constituting a novel precision medical platform. Furthermore, sequencing-based molecular diagnostics of epidermal growth factor receptor (EGFR) mutations have been commonly used for selecting anti-lung cancer drugs. In another approach, Zhang et al. proposed a method that combined EGFR mutation detection with organoid-based drug response testing to guide personalized lung cancer drug therapy in individual patients [139]. Their proposed approach constitutes a significant advancement in the field of personalized medicine, thereby facilitating the development of increasingly precise and effective treatment plans for specific patients.

5 Challenges in organoid applications

Organoid technology shows great potential for disease modeling and for designing regenerative medicine treatments [140–142]. However, its translation into clinical applications faces several significant challenges [143–145]. Below we discuss several issues in turn.

5.1 Technical challenges

Achieving reproducibility is crucial because variability in cell sources can lead to differences in organoid growth rates and differentiation, both of which complicate research and practical applications. Environmental factors such as the composition of culture media, oxygen and carbon dioxide levels, and ambient temperature, can all significantly influence organoid development, with minor fluctuations potentially causing large variations in outcome. Furthermore, organoid preparation and culturing processes involve multiple steps that all require high precision. For example, prolonged culturing can introduce genetic mutations and lead to aging, incomplete differentiation, and cell type imbalances, all of which ultimately affect organoid stability and reproducibility. The complexity of organoids necessitates rigorous experimental standardization, thereby posing additional challenges for researchers.

Achieving stability and reproducibility in organoids is vital for clinical application purposes, since organoids used for patient treatments and/or research purposes must be consistent and behave similarly. However, the complex nature of organoids makes them vulnerable to multiple environmental factors, including those related to manual preparation of culture conditions, as mentioned above. The influence of environmental factors presents a challenge regarding ensuring the homogeneity among batches of organoids. To address these challenges, researchers have applied techniques such as microfluidics and 3D printing to enhance the efficiency of organoid production [146]. The use of microfluidic technologies has been shown to provide a dynamic environment that is conducive to the production of organoids for both biological (i.e., nutrition) and mechanical (i.e., shear stress) reasons. Accordingly, these methods may provide more uniform production conditions with respect to critical environmental factors [147]. Microfluidics-based protocols enable precise fluid manipulation through microchannels, thereby facilitating the precise manufacturing of organoids. In one study, Jiang et al. proposed a novel automated organoid platform that combines microfluidic and 3D printing techniques to achieve a manufacturing speed of up to 1000 organoid precursors within a 10-min timeframe. This approach achieves a significant reduction in manufacturing time, and has the potential to reduce the current 4–6 week organoid growth period to a more efficient 5–7 day period [148]. Moreover, combining novel techniques indicates the potential of new approaches for substantial enhancement of organoid technologies, including the development of efficient, standardized manufacturing procedures and protocols [149]. Although a detailed discussion regarding the future development of organoid production is required, advanced organoid protocols hold considerable promise for the design of new clinical applications.

5.2 Cost issues

Organoid cultivation and maintenance require specialized media and equipment, and can therefore lead to relatively high production costs that can restrict their widespread application. In addition, the development and optimization of organoids demand significant time and human resources, further increasing the associated expense. The importance of minimizing organoid-associated costs also emphasizes the importance of developing a standardized manufacturing protocol regarding culture media and experimental procedures. Once a suitable protocol has been established, integrating automated high-throughput devices into the manufacturing process can be undertaken, which in turn may stimulate interest among industrial-scale organoid production.

5.3 Ethical and regulatory considerations

Ethical discussions are inevitable since tumor organoids are constructed using patient tissues [150–152]. For example, one significant goal of organoid ethics, commercialization, and clinical applications is to provide a suitable informed consent model for tissue donors in organoid research [153]. Some researchers believe that “dynamic consent” protocols for different stages of organoid use should be considered, while others prefer a “governance consent” model that donors can use to track organoid use. In either case, by including patients in the ongoing governance process, organoid-specific consent models enable patients to influence organoid development and participate as stakeholders rather than passive tissue donors.

As organoid technology continues to advance, transparency and public participation both become particularly important. To ensure compliance with ethical standards, research teams should actively and regularly communicate with patients and their families to provide up-to-date information on research progress and potential applications [150]. Open communication not only helps build trust but can also promote the active participation of patients in research, thereby improving ethical standing and social acceptance of organoid research.

Finally, the informed consent of patients during the collection of tissue samples for organoid construction can be considered during the research planning discussions of hospitals or research organizations. For example, these organizations should consider the informed consent of patients to complete organoid collection at the time of surgery. However, this approach requires cooperation from a suitable specimen bank or research institution.

5.4 Diversity and complexity

Variations among tissue types and disease states, as well as among patients, can impact organoid performance, posing challenges for the broad applicability of organoid studies. In addition, differences between organoid microenvironments and in vivo conditions necessitate further research to accurately recreate complex cell-to-cell interactions that occur within the body in related model systems.

6 Future opportunities

By solving the key problems described here, we anticipate that advances in organoid technology can facilitate significant progress in disease modeling and in the development of efficient and precise regenerative medicinal treatments. These consequences will not only help improve patient outcomes but can also promote the progress of medical research as a whole. Key strategies include standardizing organoid preparation and culture techniques to enhance reproducibility and stability, exploring cost reduction strategies to streamline production processes, and establishing clear ethical guidelines and regulatory standards to ensure compliance and promote responsible research. In addition, increased investment in clinical trials is vital to further validate the use of organoids in real-world applications, while further studies designed to focus on the organoid microenvironment and on cell interactions may contribute to technological advancements and novel applications in the future.

7 Conclusions

Organoids represent a groundbreaking advance that continues to transform the landscape of biomedical research and related disciplines. By integrating insights from developmental biology, bioengineering, materials science, and computational modeling, the study of organoids provides a novel and versatile platform for studying human diseases in more physiologically relevant contexts. Furthermore, navigating the complexities of new automation technologies, ethical considerations, and architectural challenges will benefit from collaboration among diverse fields. Such a collaborative approach will not only enhance the functionality and scalability of organoid systems but also address critical ethical concerns related to organoid research.

Moreover, leveraging recent advances in high-throughput screening and artificial intelligence may allow researchers to enhance the predictive power of organoid-based experiments related to drug discovery and personalized medicine. In this way, further integration of different technological fields can enable efficient identification of therapeutic targets and the development of treatment strategies tailored to the needs of individual patients.

Ultimately, improvements in organoid technology can facilitate future advances in our understanding of specific disease mechanisms and in the improvement of clinical outcomes. By embracing an interdisciplinary framework, we can ensure that organoids are effectively used in future medical research, thus paving the way for innovative solutions to some of the most pressing health challenges of our time.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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