REVIEW ARTICLE

Emerging Role of Human Organoids in Drug Discovery and Development: Current Advances and Challenges

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Abstract

Human tissue-derived organoid technologies have emerged as advanced platforms for drug discovery and development by providing physiologically relevant alternatives to conventional 2D cell cultures and animal models. Organoids closely mimic the structural, genetic, and functional characteristics of native organs, enabling improved investigation of disease mechanisms, drug responses, and toxicity. This review summarizes recent advances in organoid technology derived from pluripotent and adult stem cells for pharmaceutical and biomedical applications. Studies involving cancer, neurodegenerative, infectious, and rare genetic disease models were analyzed with emphasis on drug screening, personalized medicine, and translational research applications. Organoids demonstrated superior physiological relevance and improved prediction of pharmacodynamic and pharmacokinetic responses compared with traditional models. Patient-derived tumor organoids showed strong predictive accuracy for chemotherapy and immunotherapy outcomes. Organoids also enabled investigation of disease progression and individualized treatment responses. Despite significant progress, limitations including lack of vascularization, absence of immune and stromal interactions, batch variability, scalability challenges, and ethical concerns remain barriers to clinical translation. Continued development of standardized culture systems and multicellular organoid platforms may improve reproducibility and regulatory acceptance. Overall, organoid technology represents a promising approach for precision medicine, personalized therapy, and next-generation drug development.

Key words: Human organoids, drug discovery, precision medicine, disease modeling

INTRODUCTION

Human organoids have emerged as powerful tools in biomedical research and are transforming drug discovery and therapy development. These three-dimensional cellular structures, derived from pluripotent or adult stem cells (ASCs), closely mimic the architecture, function, and genetics of human organs.[1-4] Organoids bridge the gap between conventional *in vitro* cultures and *in vivo* human biology, enabling more physiologically relevant studies of disease mechanisms, drug responses, and toxicity. Since the pioneering work of Hans Clevers in 2009 demonstrating long-term intestinal organoid culture from Lgr5+ stem cells, organoid technology has expanded rapidly to include brain, liver, kidney, pancreatic, lung, retinal, cardiac, and tumor organoids.[5]

Organoids provide major advantages over traditional two-dimensional cell cultures because they preserve tissue architecture, cell-cell interactions, and metabolic gradients.[6] Patient-derived organoids (PDOs) are especially valuable for personalized medicine, as they retain donor-specific genetic and phenotypic characteristics and can predict individual drug responses. These models have been successfully applied in cancer research, infectious diseases, and genetic disorders.

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Integration with gene editing, organoid-on-chip systems, advanced imaging, and high-throughput screening has further improved their analytical potential.[7]

Despite their promise, organoids still face challenges such as batch variability, limited vascularization, lack of immune integration, high production costs, and difficulties in large-scale standardization.[8] Advances in biomaterials, microfluidics, and engineered multicellular systems are helping overcome these limitations.[9,10] Overall, organoid technology has significant potential to reduce animal testing, accelerate drug development, and support precision medicine by providing highly predictive human-relevant disease models [Figure 1].[11]

EVOLUTION OF ORGANOID TECHNOLOGY AND ITS SIGNIFICANCE IN DRUG RESEARCH

The development of organoid technology represents a major advancement in biomedical research, enabling detailed investigation of human physiology and disease mechanisms. Early tissue culture studies in the early 1900s demonstrated that cells could survive outside the body under controlled conditions, laying the foundation for organoid research. Significant progress occurred with advances in stem cell biology and three-dimensional culture engineering, which enabled the formation of self-organizing structures closely resembling real organs.[12-15] The discovery of induced pluripotent stem cells (iPSCs) and the use of extracellular matrices such as Matrigel allowed cells to grow in three dimensions rather than as flat monolayers.[16] PDOs retain tumor heterogeneity and accurately reflect drug responses, making them valuable tools for personalized medicine. Integration with *CRISPR* gene editing and multi-omic technologies has further enhanced disease modeling, biomarker discovery, and therapeutic evaluation in modern drug development.[17-19]

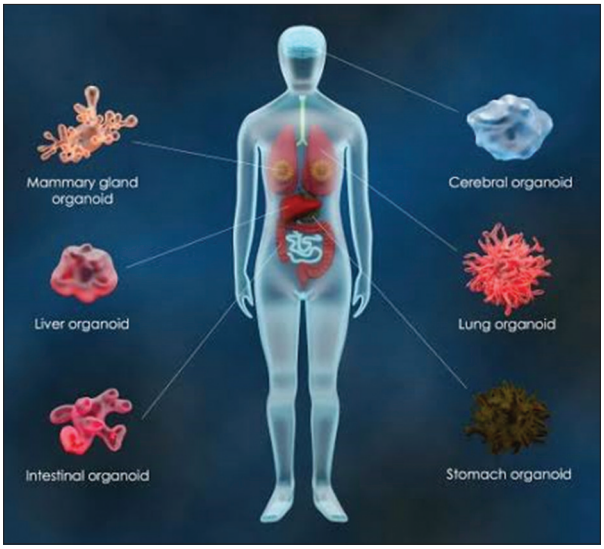

Figure 1: Reliable organoid models for human-relevant drug discovery[11]

In toxicology research, organoids are highly effective at demonstrating how different organs respond to chemicals. They enable us to predict how these chemicals may affect the liver, heart, kidneys, and brain. As technology advances, it is transforming scientific and industrial practices.[20] Pharmaceutical companies are beginning to use organoid models in the early stages of drug testing. The development of automated systems for growing organoids and specialized materials to support them is enabling consistent results and large-scale production. This is making organoids more like industrial products, which is a significant development for organoid models.[21]

SOURCES OF ORGANOID TECHNOLOGY AND DERIVATIVES

One aspect of organoid technology is that organoids can be derived from many different sources. The origin of an organoid influences its developmental potential, maturity, stability, genetic identity, and suitability for research or pharmaceutical applications. Two types of stem cells are used to generate organoids: Pluripotent stem cells (PSCs) and ASCs. Organoid technology employs both pluripotent and ASCs to create organoids. In addition, an increasing number of organoids are being generated from tumor tissues and primary cells collected from biopsies. These derivation platforms provide considerable flexibility for understanding development, human physiology, disease mechanisms, and drug effects. We use these derivation platforms to study development, physiology, pathology, and drug responses.

PSC-DERIVED ORGANOIDS

Stem cells or iPSCs are the source of organoids generated from PSCs. The ability of these PSCs to differentiate into any kind of cell in the body makes them unique. By following a set of procedures similar to what occurs as a baby develops inside its mother, we can transform these cells into organoids. This aids in the cells' self-organization into organoids, which resemble developing babies in terms of their many cell types and components.[22] Using stem cells, organoids of the brain, eyes, heart, liver, kidneys, lungs, and intestines have previously been created. All of these kinds of organoids can be produced by PSCs. Modeling congenital illnesses and early human development is where they are most useful. For example, research on neurodevelopmental disorders such as microcephaly, autism spectrum illnesses, and neurotropic viral infections has benefited greatly from the use of cerebral organoids.[23]

IPSC-DERIVED ORGANOIDS

Because they enable us to create organoids from reprogrammed adult cells, iPSCs are extremely significant. This eliminates the issues associated with employing embryonic stem cells, allowing researchers to examine a patient's traits. These iPSCs are used to create organoids, which are frequently underdeveloped and resemble the tissues of a fetus rather than the fully developed tissues of an adult.[24] By integrating blood vessels and employing unique techniques to develop cells together, people are still working on creating things. In addition, they are attempting to maintain the cells alive for a while and strengthen them through movement. This involves assisting the body's cells in becoming more like themselves [Figure 2]. The maturation patterns of the cells are being improved by vascularization, co-culture, mechanical stimulation, and long-term culture systems.[25]

ASCs-DERIVED ORGANOIDS

These organoids are really good for studying how organs work. They were first used to study the intestines. ASCs are found in tissues in our body that can make cells and turn into the type of cell that is needed for that organ. When we make organoids from these ASCs, they still look like the tissue they came from. This makes them really useful for studying things like how tissues heal, how cancer works, and how drugs affect organs.[27] These organoids also have the structure of the real tissue, which makes them really good for learning about how the body works. When it comes to cancer research, ASCs are really helpful.[28,29]

PDOs

PDOs are a kind of tool that doctors use to see how patients will react to different medicines. They make these organoids from tissue samples that they get from patients during surgery or from biopsies. PDOs are really important for learning about cancer, cystic fibrosis, and metabolic diseases. They are helpful because they have the genetic mistakes and structure of the patient's real tissue. This means doctors can use PDOs to test which treatments will work best for each patient.[30] This means that these organoids are like models of the patients and can help doctors make decisions about the treatment for cystic fibrosis and how to make it work better for each patient with cystic fibrosis.[31]

PRIMARY DIFFERENTIATED CELL-DERIVED ORGANOIDS

When we look at the sources, we also see that organoids are being made more and more from primary differentiated cells. This way of doing things is not as popular as others. The models that are made from cells do not have the ability to renew themselves for a long time, and they do not come together to form complete organ-like structures.[32] These kinds of integrations are really important for understanding how our immune system works and things like scarring, the growth of blood vessels, and how tumors talk to the tissue around them which is called tumor-stroma communication.[33]

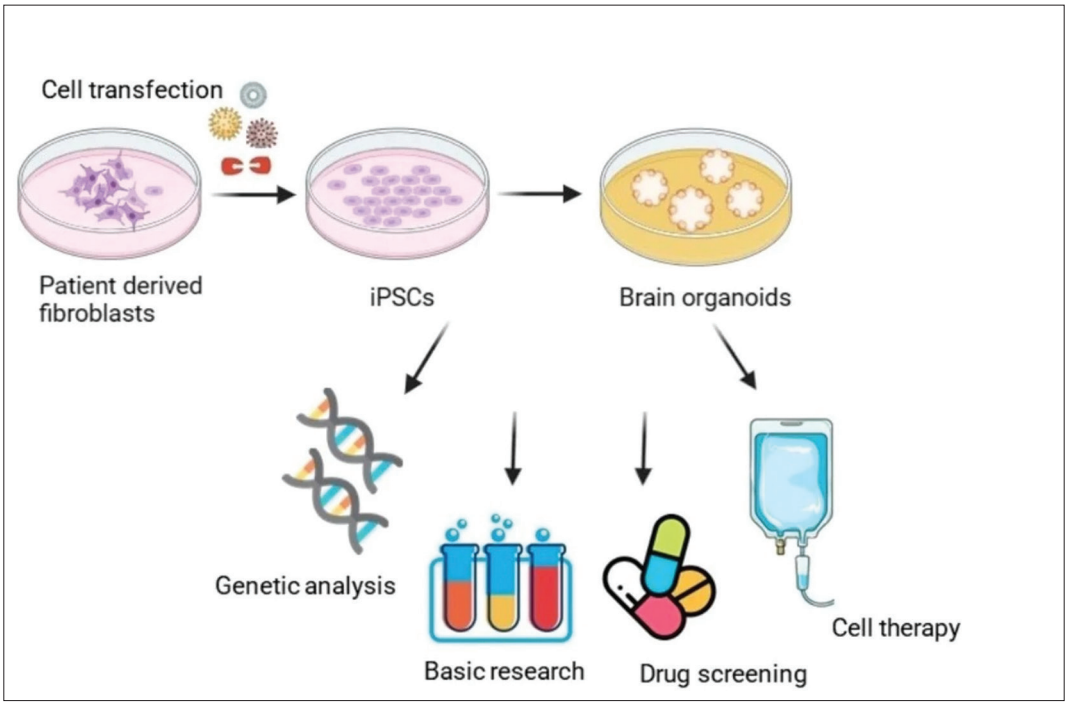

Figure 2: Induced pluripotent stem cells and organoids in advancing neuropathology research and therapies[26]

TUMOR-DERIVED ORGANOIDS

Tumor-derived organoids form another important category. They are typically obtained from resected tumors or circulating tumor cells. These cancer organoids retain intratumoral heterogeneity, purify dominant oncogenic pathways, and preserve microenvironmental traits when co-cultured with stromal cells. They are very useful for preclinical anti-cancer drug testing because their response to targeted therapy closely resembles clinical outcomes. Immune cells are being incorporated into tumor organoids in an attempt to better mimic immune-oncology responses, especially when evaluating immunotherapy.[34,35]

HOW HUMAN ORGANOIDS ARE MANUFACTURED

Human organoid generation is based on innovative bioengineering and stem cell technologies that significantly enhance experimental predictiveness. The making of organoids involves PSCs or ASCs that are differentiated following precise differentiation protocols. These cells self-organize when they are cultured in supportive matrices such as Matrigel or synthetic hydrogels that mimic the extracellular matrix (ECM). The ECM provides biochemical signals for cell proliferation, polarity establishment, and morphogenesis.[36,37]

CELL SOURCING AND PREPARATION

PSCs, whether induced or embryonic, are generally the most common choice since they can differentiate into any cell lineage. ASCs from tissue biopsies could be considered as an alternative for epithelial organoids such as intestinal, gastric, liver, and pancreatic ones. In PDOs, small pieces of tissue obtained by endoscopy, surgery, or needle biopsy are enzymatically dissociated to retrieve viable stem or progenitor cells. PSCs are kept under feeder-free conditions in chemically defined media to maintain their pluripotency while ASCs are briefly expanded in niche-supportive media to ensure viability before induction of organoids.[38]

DIRECTED DIFFERENTIATION OR NICHE-SPECIFIC INDUCTION

Stepwise induction with bio-growth factors, small molecules, and temporal signaling mimics embryogenesis. These stages create organ-specific progenitors like definitive endoderm for gut organoids, neural ectoderm for cerebral organoids, or mesodermal precursors for kidney and cardiac organoids. For ASC-derived organoids, the process is about delivering the right environmental signals from the tissue niche. Medium formulations contain R-spondin, Noggin, epidermal growth factor, and other niche factors that maintain stemness and initiate self-organization without going through all the steps of developmental induction.[39]

THREE DIMENSIONAL EMBEDDING AND AGGREGATION

A critical step in the production of organoids is the embedding of cells within an ECM matrix material. Cells may be suspended in ECM droplets or perform spheroids created by self-aggregation before embedding. The ECM matrix material provides structural support, polarity cues, and other signals that are required for morphogenesis. Cells in 3D culture will, by intrinsic development programs, spontaneously organize themselves into organ-specific domains.[40]

ORGANOID EXPANSION AND MATURATION

After embedding, cells are placed in culture media that contain signaling modulators that support the growth of organoids. These formulations depend on the organ; for instance, intestinal organoids need Wnt and R-spondin while liver organoids need hepatocyte growth factor and fibroblast growth factors to grow. The organoid expands from days to weeks, forming hollow or solid structures with increasing architectural complexity.[41]

EVALUATION OF QUALITY STABILIZATION

Organoids go through quality control evaluations, such as morphological assessment, viability assays, marker expression profiling, and occasionally genomic analysis, to confirm stability before being used for drug testing. After reaching maturity, organoids can be genetically altered, cryopreserved, or expanded for use in subsequent research.[42]

These include bioreactors, automated culture platforms, and microfluidic devices that pave the way for more scalable and reproducible organoid production. Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 allow researchers to introduce specific mutations or correct genetic variations linked to diseases. This method allows for the creation of organoids that are genetically tailored, which can then be used to study how they work or to test potential treatments.[43,44]

SIGNIFICANCE OF HUMAN ORGANOIDS IN DRUG RESEARCH AND DEVELOPMENT [TABLE 1]

Predictive platforms for early drug screening

Organoids are highly valuable tools for drug testing because they closely mimic the structure and function of real human tissues. Many compounds initially appear promising in traditional models but later fail in animal or human studies because they do not perform well in realistic biological environments. Organoids address this limitation by simulating complex tissue architecture, genetic diversity, and dynamic cellular behavior.[45,46] They also help identify which patient groups are more likely to respond to specific treatments, supporting precision medicine approaches. Advanced systems capable of growing multiple micro-organoids simultaneously allow researchers to monitor cellular growth, proliferation, and death using imaging and automated analysis tools.[47] In addition, organoids improve toxicity prediction

Table 1: Major current advances in organoid (human organoid) technologies used in drug research and development over the last decade[65-70]

Sl. No.	Name of the organoid and year	Model	Source	Application	Market status
1	Crown Bioscience organoid models 2019 (PDXO launch)	Tumor	Patient-derived/ PDXO	Oncology drug screening and translational models	Commercial service platform
2	HUB organoids 2019 (HUB adoption)	Tumor and normal tissues	Patient biopsies	Personalized cancer drug response and disease modeling	Commercialized via CROs
3	InSphero 3D Liver Organoids (3D InSight™) 2015–2017 (emergence of 3D liver models)	Liver	Stem cell-derived/ primary	Hepatic disease, toxicity and metabolism studies	Research platform
4	TrueCardium® cardiac organoid platform 2023–2024	Heart	iPSC-derived	Cardiac drug testing and disease modeling Research and screening	Research and screening
5	STEMCELL technologies organoid kits 2018	Neural, hepatic, intestinal	PSC/ASC kits	Culture and disease study	Commercial kits available
6	Cellesce standardized organoids 2022	Intestine/ various	ASCs	Scalable drug screening models	Commercial reagent and service
7	Defini GEN hepatic organoids 2021	Liver	Stem cell-derived	Metabolic disease and drug studies	Research models
8	MIMETAS organo plate systems 2013	Kidney, liver, colon	ASC and microfluidics	High-throughput drug screening	Commercial plate platform
9	Organovo 3D bioprinted organoids 2021	Skin, liver, kidney	Bioprinting	Toxicology and drug response	Research tissues and contract services
10	Horizon discovery organoid models 2018	Tumor/ genetic disease	Gene-edited organoids	Target validation and drug discovery	Research models
11	ATCC organoid repository 2019	Multiple organs	Biobanked PSC/ ASC	Model sharing and drug R&D	Available research repository
12	Dnamics brain and liver organoids 2021	Brain, liver	iPSC/primary	Disease modeling and drug efficacy	Commercial models
13	BioIVT PDO models 2020	Tumor/tissue types	Patient-derived organoids	Personalized therapy and toxicity	Offered via contract services
14	QGel 3D organoid matrices 2019	Multi-organ culture	ECM materials	Organoid culture support	Research-grade consumables
15	Corning organoid culture Tools 2017	Multiple organs	Matrices and plates	Organoid development and drug testing Widely used consumables	Widely used consumables

ECM: Extracellular matrix, PSC: Pluripotent stem cells, ASC: Adult stem cells, iPSC: Induced pluripotent stem cells

by preserving differentiated cell types and functional tissue properties. Tissue-specific organoids can be used to evaluate hepatotoxicity, nephrotoxicity, and gastrointestinal toxicity, enabling early detection of adverse drug effects and reducing the risk of late-stage clinical failure.[48]

Disease modeling for target identification

Organoids are an excellent tool for understanding the mechanisms behind human diseases. They enable us to examine bodily processes in a manner that is strikingly analogous to how they occur in actual tissues. Because organoids have a large number of cells that cooperate like those in the body, they are superior to cell cultures. This implies that we can utilize them to observe the effects of an illness. Organoids can help us understand what goes wrong when a person becomes ill and discover effective treatments for illnesses.[49] Organoids are excellent for determining what is wrong with the body and how to fix it. The ability to display a patient's genetic and physical characteristics is one advantage of organoid-based illness models.[50] For instance, we may modify the genes in organoids using a technique known as CRISPR. This enables us to observe the effects of genetic modifications and comprehend their mechanisms.[51,52] Organoids can also be used to investigate the effects of infections with bacteria, viruses, or parasites. Understanding how tumors evolve and change is greatly aided by organoid models.[53] A characteristic of cancer organoids is that they share the same genetic variations among various cell types and structures as the original tumors. This implies that scientists can observe how cancer cells proliferate, alter in response to treatment, and develop resistance to therapy.

Organoids for toxicity assessment, drug safety evaluation, and modeling

Human organoids are a great tool for evaluating a drug's toxicity to humans and its effects on the body. They are an alternative to the traditional methods of utilizing animals in experiments or cultivating cells on a flat layer. Human organoids function similarly to genuine organs because they retain the tissue's structure and contain a variety of cell types. This implies that we can gain insight into how a medication will function in humans, particularly when it comes to issues that impact certain organs and do not manifest until much later in the drug development process.[53,54] The human heart's rhythm and function can be accurately replicated by the heart organoids. This allows us to determine whether a novel medication is harmful to the heart. These systems can display things such as heartbeats, calcium issues, and potential drug-induced muscle abnormalities. Before we even give the medications to people, we can use this method to check for negative reactions. These heart organoids are helpful in forecasting potential outcomes since we know that they respond to medications that are harmful to the heart.[55,56]

PDOs in precision and personalized medicine

PDOs, for short, are fundamentally altering medicine, particularly with regard to individualized treatment. Made from real samples of a patient's tumor or healthy tissue, these PDOs resemble human bodies. PDOs can therefore be used to test medications and determine which ones will be most effective for a given patient.[57] In addition, it assists us in avoiding the use of medications that may be too dangerous or ineffective.[58] PDOs play a significant part in this process by assisting us in understanding medication sensitivity and resistance, which allows us to select the patient's course of treatment.[59] PDOs are quite useful in figuring out why some therapies don't work. They preserve the tumor's complexity so that we may observe the areas of the tumor that are resistant to treatment or how the tumor changes and adapts in response to treatment. They are also employed in the research of genetic disorders, hereditary diseases, and issues related to how our bodies digest food. We can create a unique model that closely resembles the body of a person with a condition using a sample from them.[60] This model aids in the testing of novel approaches to treating illnesses, such as employing RNA to solve issues, as well as special medications that target particular genes.

Organoids as tools for preclinical validation of novel therapeutics and their role in reducing animal use

To test treatments before they are applied to humans, human organoids are crucial. Human organoids can replicate the structure and function of human tissues. They are therefore extremely helpful in determining whether a novel treatment will be effective. Organoids have the advantage of preserving a person's unique genetic characteristics and disease-related traits. In addition, they can demonstrate how cells communicate with one another, something that conventional cell lines are unable to achieve.[61] Combining organoid cultures with high-throughput screening, researchers may eliminate ineffective molecules early on, cutting down on the time and resources needed to advance inappropriate substances.[62] When we are first starting out and attempting to understand how things work, organoids are a better approach to conduct some types of experiments. Because they are similar to people, organoids can demonstrate how the human body functions, something that animals are not always adept at. This implies that organoids provide accurate results and reduce the number of incorrect replies due to species differences. Organoids are excellent in illustrating bodily processes, which is what we truly need to understand.[63] This shift is further supported by organoid-on-chip technologies and multi-organ organoid systems, which mimic restricted natural circulation and tissue-to-tissue exchanges [Figure 3].

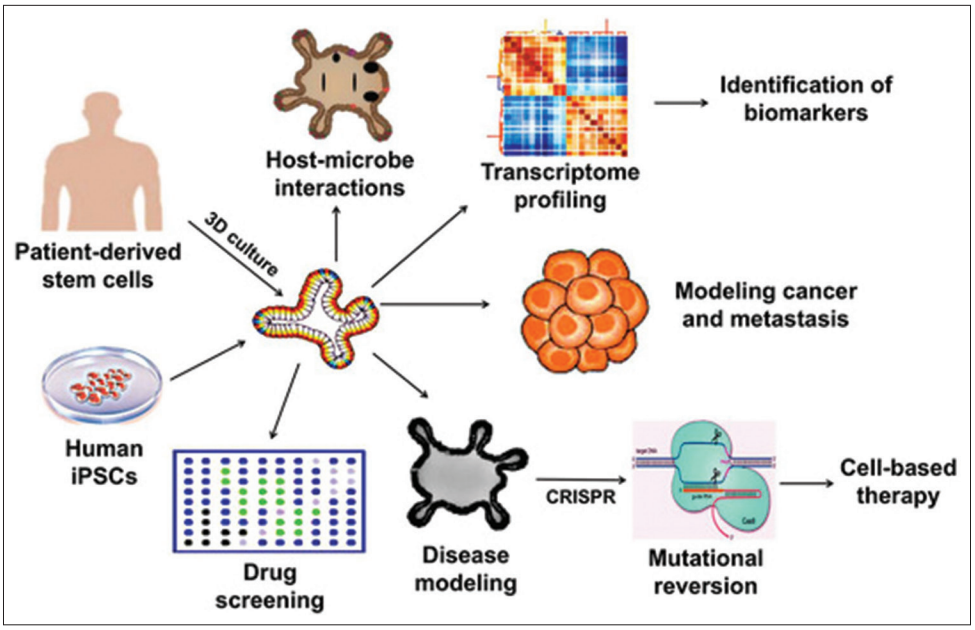

Figure 3: Applications of 3D organoids in therapeutic and pharmaceutical testing[64]

CHALLENGES IN THE APPLICATION AND THE SCALE OF HUMAN ORGANOIDS FOR DRUG DISCOVERY AND DEVELOPMENT

Although human organoids have great potential in drug discovery, several challenges limit their widespread application. One major issue is variability in organoid growth caused by differences in donor tissues, stem cell quality, laboratory handling, and culture conditions such as oxygen and nutrient supply. Even small variations can significantly affect organoid development and drug responses, making reproducibility difficult across laboratories. This variability reduces reliability in pharmaceutical research, where consistent outcomes are essential. Batch inconsistency is another major limitation. Organoids derived from different patient samples or stem cell batches may mature at different rates, develop varying structures, and respond differently to drugs. Such inconsistencies weaken predictive accuracy and limit high-throughput drug screening. In addition, organoid production and maintenance are expensive because they require specialized growth factors, proteins, culture materials, and advanced laboratory equipment. PDOs further increase costs due to tissue collection, processing, and storage requirements. Another challenge is the dependence on biological matrices such as Matrigel, which is derived from mouse tumor extracts. These matrices show batch variability, limited mechanical customization, and poor suitability for clinical translation due to xenogeneic components. Although synthetic matrices are being developed, many still lack the biological complexity needed for proper tissue communication. Therefore, improving standardization, scalability, reproducibility, and cost-effectiveness remain essential for broader application of organoid technology in drug discovery.[71]

FUTURE PERSPECTIVES: INTERCONNECTED ORGANOID NETWORKS, VASCULARISATION AND COMPUTATIONAL MODELLING FOR WHOLE-BODY DRUG SIMULATION

The future of organoid technology in drug discovery lies in developing interconnected multi-organ networks that better replicate whole-body physiology. Conventional organoids usually model a single tissue, limiting understanding of how drugs interact across multiple organs. By connecting liver, kidney, heart, intestine, and other organ models using microfluidic platforms, researchers can study drug absorption, metabolism, distribution, and toxicity more accurately. These systems improve prediction of systemic drug responses and organ-to-organ interactions.

Vascularization is another critical advancement. Most organoids rely on passive diffusion for oxygen and nutrients, which restricts maturation and functionality. Emerging approaches such as microfluidic perfusion, endothelial cell bioprinting, and self-assembled vasculature aim to create vascularized organoids that better mimic human tissues and enable investigation of vascular toxicity, thrombosis, and inflammation.[71,72]

Immune integration is equally important, particularly for vaccines, biologics, and immunotherapies. Incorporating immune cells such as macrophages, dendritic cells, and lymphocytes into organoid systems enables evaluation of immune responses, host–pathogen interactions, and immunotoxicity. Combined with computational modeling and artificial intelligence, these advanced organoid platforms may improve dose prediction, accelerate drug development,

and enhance translational accuracy while reducing reliance on animal models.

REGULATORY PERSPECTIVES FOR ORGANOIDS

The rapid advancement of organoid technology has generated significant interest among regulatory agencies because organoids provide physiologically relevant models for disease research, drug screening, toxicity testing, and personalized medicine. However, the regulatory framework for organoid-based applications remains in an evolving stage. Agencies such as the U.S. Food and Drug Administration, European Medicines Agency, and International Council for Harmonization recognize the potential of advanced *in vitro* models to complement or partially replace animal studies, particularly in preclinical drug development. For pharmaceutical applications, organoids must demonstrate reproducibility, standardization, scalability, and predictive validity before they can be accepted as regulatory decision-making tools. Critical considerations include donor-to-donor variability, genetic stability, batch consistency, culture conditions, and quality control procedures. Regulatory agencies also require evidence that organoid models accurately predict human responses to drug efficacy, toxicity, and pharmacokinetics.

CONCLUSION

Human organoids are transforming drug discovery by providing three-dimensional models that closely resemble human organs in structure and function. They are valuable for studying drug efficacy, safety, metabolism, and mechanisms of action in diseases such as cancer, diabetes, and infections. PDOs are particularly important for personalized medicine because they help predict individual drug responses and guide treatment selection. Despite their advantages, organoid technology faces challenges including variability in culture conditions, batch inconsistency, dependence on specialized matrices such as Matrigel, high production costs, and difficulties in large-scale manufacturing. Ethical concerns related to patient-derived tissues also remain important.

Future developments aim to establish standardized culture methods, synthetic extracellular matrices, automated production systems, and multicellular organoid models with vascular and immune components. Integration with artificial intelligence and machine learning may further accelerate drug development and improve prediction of clinical outcomes. Overall, human organoids represent a promising platform for translational research, personalized therapy, and reduction of animal testing in pharmaceutical development.

AUTHOR CONTRIBUTIONS

Shaik Meharaj: Conceptualization, study design, methodology development. Badri Sireesha: Supervision. Data interpretation, manuscript drafting, and final review. Saravanan Ravindran: Experimental work, chromatographic analysis, data collection, validation studies, and manuscript preparation. All authors reviewed, revised, and approved the final version of the manuscript.

AI USE STATEMENT

The authors used Grammarly and OpenAI for grammar checking, language refinement, sentence restructuring, and improving the clarity of scientific writing. BioRender software was used for figure improvement and drawing. The authors carefully reviewed, edited, and validated all generated content and take full responsibility for the final manuscript.

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