WPI News

Organoids in Biomedical Research: Opportunities and Challenges

By Adrienne L. Watson, PhD (Chief Scientific Officer, WPI)

Organoids are three-dimensional, miniature models of organs and tissues that are grown *in vitro* from stem cells or other progenitor cells with the ability to differentiate into a cell type found in a given organ or tissue. They closely mimic the structure and function of human organs, making them valuable tools for studying human development, disease modeling, drug discovery, and personalized medicine.

Applications of Organoids

Organoids have a wide range of applications in biomedical research and drug development:

Disease Modeling: Organoids have been successfully used in combination with gene-editing and derived from patients to model diseases such as cancer, cystic fibrosis, and neurodegenerative disorders, providing valuable insights into disease progression and treatment response. These disease-model organoids have allowed researchers to study the mechanisms underlying diseases in a more physiologically relevant model. Better preclinical disease models can lead to a better understanding of disease progression and the development of personalized treatment strategies, giving organoids an advantage over less complex biological models.

Drug Screening: Organoids provide a platform for drug screening and testing that more closely resembles human physiology compared to traditional two-dimensional cell cultures. Organoids are unique in that they are often more physiologically relevant than other cell culture models, yet less complex and challenging to study than animal models. The ability to screen through large numbers of organoids in the laboratory can be leveraged to effectively identify potential therapeutic agents, assess toxicity and efficacy, and predict drug responses in a more accurate and efficient manner.

Developmental Biology: Organoids can be used to study the processes of organ growth, tissue generation, and other critical biological processes during development. By manipulating the culture conditions, researchers can investigate how specific cell types interact and differentiate to form complex structures, providing insights into normal development and potential regenerative medicine approaches.

Precision Medicine: Organoids have the potential to advance personalized medicine by enabling the testing of drug responses and treatment options on patient-specific organoid models. By isolating patient-specific cells or using gene-editing to make genetic changes associated with various diseases or phenotypes, organoids can be leveraged to identify the most effective therapies for individual patients based on their unique genetic makeup and disease characteristics.

Disease Mechanisms and Pathophysiology: Organoids offer a platform to study the molecular and cellular mechanisms underlying disease pathogenesis. By analyzing organoid models, researchers can gain insights into disease progression, identify key signaling pathways, and discover potential therapeutic targets for intervention.

Evolution of Organoids

Organoids were enabled in the 2000s, when methods for growing organ-specific structures from stem cells were first developed. Since then, the field has expanded rapidly, with advancements and improvements in technology enabling the generation of more complex and functional organoids. Key technology supporting the development of specialized culture media, 3D scaffolds, and microfluidic systems to support the growth and maturation of organoids has advanced the ability of researchers to perform biological and pathological modeling using organoids. Further, technologies to analyze organoids have enabled this platform to be used for understanding disease mechanisms and, importantly, perform therapeutic screening and drug discovery.

Advantages of Organoids in Research

Organoids offer several advantages over other research and preclinical models, but there are also limitations:

Standard Cell Culture

Organoids provide a more physiologically relevant model compared to traditional 2D cell culture. Organoids replicate the complexity and architecture of real organs, allowing for more accurate representation of tissue structure and function. They can also better recapitulate disease phenotypes and responses to drugs. However, organoids can be more challenging to establish and maintain compared to standard cell cultures, requiring specialized protocols and expertise. The protocols available for organoids are nowhere near as established as standard cell culture leading to problems with standardization and the need for significant resources for establishing these models.

3D Cell Culture

While both organoids and 3D cell cultures involve the growth of cells in three dimensions, organoids are more complex structures that closely mimic the organization and function of real organs. Organoids contain multiple cell types and exhibit tissue-specific functions, making them more suitable for modeling organ development, disease, and drug responses. In contrast, 3D cell cultures typically focus on the growth of one cell type or a simple multicellular structure. Organoids can be more challenging to establish, as the development of complex structures often requires complex growth and development conditions with specific organization that is often challenging to mimic in culture. This makes organoids expensive and difficult to establish and experiment with.

Organ-on-Chip Systems

Organoids and organ-on-chip technologies can be complementary approaches for modeling human physiology and disease. While organoids often physically combine different cell types, organ-on-chip systems use microfluidics and barriers to mimic the dynamic interaction between cells. Organ-on-chip systems offer precise control over the microenvironment and interactions between many different cells and fluids. While organoids generally mimic a single tissue or organ, organ-on-chip devices can model many different tissues and organs and how they interact together.

Animal Models

Organoids offer an ethical and lower cost alternative to animal models for studying human biology and disease. Organoids can be derived from human cells, allowing researchers to investigate disease mechanisms and drug responses in a patient-specific context. However, organoids may not fully recapitulate the systemic interactions and complexity of whole organisms, limiting their utility for certain research questions. Animal models remain valuable for studying complex physiological processes, whole-body responses, and *in vivo* drug testing. Further, animals provide a platform for understanding drug delivery and dosing, and allow for clinical imaging, surgeries, and other procedures that cannot be replicated with *in vitro* systems.

Emerging Organoid Market

The market for organoids is expected to grow significantly in the coming years as this technology becomes more widespread and accessible. Several companies and research institutions are actively involved in the development and commercialization of organoid-based products and services. The global organoids market is projected to reach $1.6 billion by 2025, driven by the increasing demand for personalized medicine and the need for more predictive preclinical models.

World Precision Instruments (WPI) offers products and technologies to support organoid research today, in the same way that WPI supports the development and evaluation of other preclinical models, from standard cell culture models to organ-on-chip and animal models. Organoids offer a preclinical platform that WPI currently supports by offering lab supplies and consumables for cell culture experiments, standard microscopy and live cell imaging equipment to visualize organoids, and microfluidic technology that supports the growth, maintenance, and analysis of organoids. Organoids often lack certain cell types and are unable to represent the interactions of multiple tissues and organs. Further, the inability to model the vascular and lymphatic system is another limitation of organoids. By combining organoids with microfluidic devices like organ-on-chip and other micro-physiological systems, researchers can create more physiologically relevant models that incorporate aspects of both technologies and improve the accuracy of drug testing and disease modeling using organoids. WPI is committed to supporting technologies that advance and synergize with organoids, including organ-on-a-chip systems, microfluidics, and genome editing.

One of WPI's foundational technologies, transepithelial electrical resistance (TEER) measurements has been integrated into organoid research and enabled researchers to overcome some of today's limitations with organoid research. TEER has been performed on the cells that are used for organoids prior to generation of the organoids for functional validation and quality control, ultimately reducing the heterogeneity that organoids often exhibit and improving reproducibility. By qualifying cells prior to the generation of organoids, researchers can standardize their starting material and protocols to reduce variability and generate more meaningful data. Organoids can be challenging to functionally assess, with microscopy being the main tool used, however, TEER offers a non-invasive method to measure barrier integrity and provide a and functional readout of organoids. In the last two years, there have been several publications demonstrating the utility of TEER measurements in organoid research:

- Varani et al., Cell-Matrix Interactions Contribute to Barrier Function in Human Colon Organoids. , 2019.
- WPI's EVOM technology enabled TEER measurements to evaluate the interaction between cells and the basement membrane in human colon organoids, demonstrating that the cell-matrix interactions significantly contributed to barrier integrity in the colon.
- Hori et al. Trophoblast stem cell-based organoid models of the human placental barrier, 2024.
- TEER measurements enabled by WPI's EVOM instrumentation was able to demonstrate the barrier integrity and maturation level of the human placenta organoid model derived from trophoblast stem cells, providing an ideal model of understanding how to facilitate drug development for enabling or avoiding compounds crossing the placental barrier.
- Varani et al., A multi-mineral intervention to counter pro-inflammatory activity and to improve the barrier in human colon organoids, 2023.
- TEER was measured using WPI's EVOM™ technology to demonstrate the effect of various compounds on the barrier integrity of the inflamed human colon, modeled using human colonic organoids.
- Warschkau et al., From 3D to 2D: Harmonization of Protocols for Two-dimensional Cultures on Cell Culture Inserts of Intestinal Organoids from Various Species, 2022.
- WPI's manufactured Millicel ERS-2 was used to optimize organoid development from 2D cultures to mimic the tissue barrier function and develop electrophysiological tight junctions in functional organoid cultures.
- Salari et al. Human Colonoid-Myofibroblast Coculture for Study of Apical Na+/H+ Exchangers of the Lower Cryptal Neck Region, 2023.
- WPI's EVOM™ TEER measurements were used to quantify the functionality of paracellular transport of cocultured myofibroblast-colonic epithelial cells compared to monoculture cells, demonstrating the spatially organized functionality of the colonic crypts is better modeled in an organoid system.
- Deleu et al., High Acetate Concentration Protects Intestinal Barrier and Exerts Anti-Inflammatory Effects in Organoid-Derived Epithelial Monolayer Cultures from Patients with Ulcerative Colitis, 2023.

EVOM™ measured TEER was utilized to preclinically assess the effects of high acetate concentrations on inflammation and barrier integrity in organoid-based monolayer cultures from ulcerative colitis patients.

In summary, organoids have emerged as a powerful tool for advancing biomedical research and drug development, offering unique advantages over standard cell culture, 3D cell culture, organ-on-a-chip systems, and animal models. WPI supports organoid research platforms and WPI's TEER technology has been instrumental in functionally assessing organoids for barrier integrity and drug discovery and development. WPI continues to develop and integrate additional technology that is key to overcoming the existing limitations of organoids, paving the path to widespread adoption of this technology in different laboratories studying a variety of diseases. By leveraging the strengths of multiple *in vitro* and preclinical models and addressing their respective limitations, researchers can develop more predictive and translational models for studying human biology and disease.

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