Narrative Review Article

Advancing Alzheimer's Disease Research Using Brain Organoids and Organ-on-Chip Technologies

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ABSTRACT

Alzheimer's disease ranks as one of the gravest health threats facing humanity today. This disease progressively impairs memory, cognition, and neuronal integrity in millions worldwide and inflicts severe personal and social loss. Its profound impact, notably, has elevated it to a top priority in biomedical research. However, established models, including animal studies and two-dimensional cell cultures, often fall short and are unable to replicate the human brain's complexity in both structure and function. Consequently, clinical trial failure rates remain high. This review examines the transformative role of emerging technologies in Alzheimer's disease research, focusing on brain organoids and organ-on-chip systems. By generating brain organoids from human pluripotent stem cells, researchers can develop pathological features in a three-dimensional context. These models reveal features such as amyloid-beta deposition, tau pathology, and synaptic dysfunction. In parallel, organ-on-chip platforms utilize microfluidic systems to simulate physiological conditions. This enables the study of cellular interactions, including those involving the blood–brain barrier. By integrating these approaches, researchers acquire more relevant human models. This combined strategy deepens mechanistic insight and enhances drug-screening accuracy. It also brings new opportunities to explore innovative treatment methods. With such tools in hand, early disease processes can be investigated—sometimes even before clinical symptoms emerge. However, challenges remain, including limited tissue complexity and enduring technical issues. Nonetheless, as progress continues steadily, these prototypes are becoming increasingly practical. Such advances bring significant potential for Alzheimer's disease research. They offer hope for earlier diagnosis, improved treatments, and more individualized care.

Keywords: Alzheimer's Disease; Brain Organoids; Organ-on-Chip; Blood–brain Barrier; Neurodegeneration; Drug Discovery; Personalized Medicine; Microphysiological Systems

INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory impairment, cognitive decline, and loss of functional independence (1). As the leading cause of dementia worldwide, it places a major burden on global health, especially among the aging population (2). Despite decades of extensive research, effective disease-modifying therapies remain limited. The complex, multifactorial nature of the disease, along with limitations of existing models, presents major barriers to advancing treatment (3, 4).

One major challenge in Alzheimer's disease research lies in the inability of standard models to accurately replicate the structural and functional complexity of the human brain. Transgenic mice are frequently

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Accepted April 16 2026
https://doi.org/10.70251/HYJR2348.42413419

used to study hallmark features, such as amyloid-beta accumulation and tau pathology. However, these models fail to fully capture critical facets of human neurodegeneration. In particular, higher-order cognitive dysfunction and progressive neuronal loss often remain inadequately modeled (5, 6).

Two-dimensional (2D) cell culture systems also fall short. While these cultures provide tightly controlled experimental conditions, they lack the three-dimensional architecture and cellular heterogeneity found in brain tissue. Without this, it becomes difficult to replicate neuronal networks and intercellular communication. In turn, a significant translational gap remains between laboratory findings and clinical outcomes (3, 7).

To address these limitations, recent advances in stem cell biology and bioengineering have enabled the development of improved models, such as brain organoids and organ-on-a-chip systems. These technologies provide human-based approaches that simulate brain structure and function. By bridging the translational gap, researchers use these models to study diseases, discover new drugs, and develop personalized treatments under controlled yet biologically relevant conditions (8, 9). This review discusses the role of brain organoids and organ-on-chip technologies in advancing Alzheimer's disease research, emphasizing their impact on disease modeling, mechanistic insights, and translational applications.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease brings about complex molecular and cellular processes that lead to neurodegeneration. Its hallmark pathological features include extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein (10). These abnormalities disrupt synaptic function, interfere with neuronal communication, and ultimately result in neuronal loss (5, 11).

Cleavage of amyloid precursor protein (APP) results in the production of amyloid-beta (Aβ) (12). When this process becomes dysregulated in Alzheimer's disease, Aβ peptides accumulate and form both soluble oligomers and insoluble plaques. Soluble Aβ oligomers, considered the most toxic form, disrupt synaptic plasticity and neuronal signaling, contributing to early cognitive dysfunction. Still, amyloid pathology alone does not fully explain disease progression, so additional mechanisms are likely involved (5, 13).

Tau pathology emerges as a critical downstream process in Alzheimer's disease. When hyperphosphorylated, tau detaches from microtubules, destabilizing and disrupting axonal transport. This disruption leads to neuronal dysfunction, which then progresses to cell death. The regional distribution of tau pathology closely tracks disease severity, reinforcing the central role of tau in neurodegeneration (11, 13).

Neuroinflammation plays a significant role in disease progression. Upon activation, microglia and astrocytes release pro-inflammatory cytokines that exacerbate neuronal damage (14). Inflammation initially serves a protective function, yet when it becomes chronic, a toxic microenvironment forms and drives ongoing neurodegeneration. Oxidative stress and mitochondrial dysfunction can further amplify these effects, producing a self-perpetuating cycle of neuronal damage (9, 15).

Alzheimer's disease also features a prolonged preclinical stage. During this period, pathological changes can occur several years before clinical symptoms appear. Early processes include synaptic dysfunction, protein misfolding, and subtle alterations in neuronal signaling. Unfortunately, conventional systems struggle to model such early events. This limits the development of effective interventions. To improve diagnosis and therapy, understanding these events is critical. Therefore, given the complexity, accurately modeling Alzheimer's disease remains especially challenging using standard experimental systems.

LIMITATIONS OF CONVENTIONAL RESEARCH MODELS IN ALZHEIMER'S DISEASE

Traditional models have played a crucial role in advancing Alzheimer's disease research; however, their limitations have become increasingly evident. Animal models, particularly genetically modified mice, are widely used to study amyloid-beta and tau pathology. Nevertheless, these models do not fully recapitulate human disease features, such as progressive neuronal loss and multifactorial cognitive impairment. Their relevance is further limited by interspecies differences in brain structure, lifespan, and gene expression (5, 6).

A major challenge in Alzheimer's disease research is the high failure rate of therapeutic candidates in clinical trials. Many drugs that effectively reduced amyloid pathology in animal models have not demonstrated clinical benefit in humans. This discrepancy highlights inherent species-specific differences and underscores the limitations of relying solely on animal-based systems for

drug development (3, 7).

Significant limitations are evident in two-dimensional (2D) cell culture systems. While these platforms provide controlled experimental conditions, the absence of three-dimensional architecture and necessary cellular interactions prevents them from replicating the human brain. Neuronal monocultures fail to form complex networks, and interaction with other cell types—such as astrocytes and microglia—is often incomplete. Thus, systems like these struggle to model disease mechanisms that rely on multicellular dynamics (4, 9).

In addition to these limitations, ethical considerations further emphasize the need for alternative models. The use of animals in long-term neurological research raises concerns related to welfare and scientific validity. Consequently, there is increasing interest in developing human-based *in vitro* systems that are both ethically acceptable and biologically relevant. Technologies such as organoids and organ-on-chip systems address these challenges by providing more representative models of human brain biology (16, 17).

STEM CELL TECHNOLOGIES IN ALZHEIMER'S DISEASE MODELING

Induced pluripotent stem cell (iPSC) technology represents a significant advancement in the study of neurodegenerative diseases. iPSCs are generated by reprogramming adult somatic cells into a pluripotent state, enabling their differentiation into various cell types, including neurons and glial cells. This approach allows the development of patient-specific models that retain the genetic characteristics associated with Alzheimer's disease (18).

iPSC-derived neuronal models have contributed significantly to the investigation of disease-related processes, including amyloid-beta production, tau pathology, and synaptic dysfunction. These models enable the study of genetic mutations and risk factors involved in disease development at the cellular level. Importantly, they capture inter-individual variability, a key feature of Alzheimer's disease that is often not represented in conventional models (13, 19).

In addition to mechanistic studies, stem cell technologies support the development of personalized therapeutic strategies. Patient-derived neurons can be used to evaluate drug responses in a controlled, patient-specific context, improving the accuracy and effectiveness of treatment approaches. This represents a step toward precision medicine, in which therapies are tailored to individual biological characteristics (18, 19).

Despite these advantages, stem cell-based models have several limitations. Variability in differentiation efficiency and the lack of standardized protocols can lead to inconsistencies in experimental outcomes. Furthermore, iPSC-derived neurons do not fully replicate the structural and functional complexity of brain tissue. These limitations have driven the development of more advanced systems, such as brain organoids and organ-on-chip platforms, which extend stem cell-based approaches to provide more physiologically relevant models of Alzheimer's disease (20).

BRAIN ORGANOIDS IN ALZHEIMER'S DISEASE RESEARCH

Brain organoids are three-dimensional cellular structures derived from human pluripotent stem cells that resemble early human brain tissue. These models have become valuable tools in Alzheimer's disease research, as they recapitulate key aspects of neuronal architecture, cellular diversity, and disease pathology that cannot be achieved in two-dimensional systems (11, 21).

One of the major advantages of brain organoids is their ability to model amyloid-beta (Aβ) pathology. Organoids derived from patient-specific iPSCs have demonstrated spontaneous aggregation of Aβ peptides, forming extracellular plaques similar to those observed in Alzheimer's disease. These aggregates disrupt synaptic transmission and induce neuronal toxicity, making organoids useful for investigating early pathogenic events (13). They also replicate key pathological features, including amyloid-beta deposition and tau-related neurodegeneration, as reported in previous studies (11).

In addition to amyloid pathology, brain organoids enable the study of tau-associated neurodegeneration. Hyperphosphorylated tau forms intracellular neurofibrillary tangles that destabilize microtubules and disrupt axonal transport, leading to neuronal dysfunction and cell death. These models also allow investigation of the interaction between amyloid and tau pathology, which is critical to disease progression (11, 13).

Brain organoids are particularly useful for studying synaptic dysfunction, a key feature associated with cognitive decline. Loss of synaptic connectivity often occurs before overt neuronal loss. Organoid systems support the formation of neuronal networks that can be monitored over time, enabling detailed analysis of synaptic activity and degeneration. This makes them valuable for identifying early biomarkers and therapeutic

targets (13, 21).

Furthermore, brain organoids facilitate the study of early disease processes that occur years before clinical symptoms appear. These models exhibit molecular changes, including protein misfolding, oxidative stress, and alterations in neuronal signaling, providing insight into the preclinical stage of Alzheimer's disease. Understanding these processes is critical for improving early diagnosis and intervention strategies (7, 13).

Despite these advantages, brain organoids have inherent limitations. They lack vascularization, which restricts nutrient and oxygen diffusion, and they do not fully represent immune components, such as microglia, in all models. These limitations can affect long-term modeling accuracy. However, ongoing advances in organoid engineering are expected to improve their physiological relevance and applicability in Alzheimer's disease research (5, 22).

ORGAN-ON-CHIP TECHNOLOGY IN ALZHEIMER'S DISEASE RESEARCH

Organ-on-chip technology represents a significant advancement in modeling complex human physiological systems by integrating living cells into microfluidic platforms that recreate *in vivo*-like conditions. Brain-on-chip models enable the study of neuronal interactions, disease mechanisms, and therapeutic responses in Alzheimer's disease within a controlled environment (9, 15).

A key feature of organ-on-chip systems is their ability to model the blood–brain barrier (BBB), a critical structure that regulates molecular transport between the brain and the bloodstream. BBB dysfunction is increasingly recognized in Alzheimer's disease, as it contributes to impaired amyloid-beta clearance and increased neuroinflammation. Brain-on-chip platforms can recreate BBB architecture using endothelial cells, astrocytes, and pericytes, allowing investigation of permeability changes and drug transport mechanisms (15, 23).

Microfluidic flow within these systems mimics blood circulation, enabling continuous nutrient supply and waste removal. This dynamic environment supports long-term neuronal viability and function. It also facilitates the study of pharmacokinetics and pharmacodynamics, allowing evaluation of therapeutic compounds under physiologically relevant conditions (9, 23).

Organ-on-chip systems are also valuable for studying neuroinflammation. Activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines that contribute to neuronal damage. These systems can incorporate immune components, enabling investigation of inflammatory responses and their role in disease progression. They also provide a controlled platform for testing anti-inflammatory therapies (9, 15).

In addition, organ-on-chip technology enables the study of neuronal network dysfunction. Integration of electrodes and imaging techniques allows real-time monitoring of electrical activity and signal transmission between neurons. This provides insight into how Alzheimer's disease disrupts neural communication and leads to cognitive impairment (15, 20).

Overall, organ-on-chip technology provides a dynamic and physiologically relevant platform for Alzheimer's disease research. These systems help bridge the gap between conventional *in vitro* models and clinical studies by offering precise environmental control with human-derived cells, thereby improving the predictive validity of preclinical research (7, 9).

ORGANOID AND ORGAN-ON-CHIP SYSTEM INTEGRATION

Organoid-on-chip platforms combine brain organoids with organ-on-chip technology, integrating the structural complexity of organoid systems with the dynamic microenvironment of microfluidic platforms. This approach overcomes several limitations of standalone organoid models, particularly in terms of nutrient delivery, waste removal, and long-term culture stability (20, 24).

In the context of Alzheimer's disease, organoid-on-chip systems enable modeling of disease progression over extended periods. Continuous nutrient and oxygen supply supports sustained neuronal activity and enables monitoring of temporal changes in pathological features, including amyloid plaque formation, tau aggregation, and synaptic loss. This is particularly important for studying a disease that develops over decades in humans (7, 20).

These integrated systems also support the inclusion of multiple cell types, such as neurons, astrocytes, endothelial cells, and immune cells, thereby providing a more comprehensive representation of the brain microenvironment. This facilitates investigation of complex cellular interactions and their role in disease processes, including neuroinflammation and blood–brain barrier (BBB) dysfunction (24). The microfluidic architecture further enables simulation of BBB function and neuroinflammatory responses, as discussed in previous studies (15).

Furthermore, organoid-on-chip platforms can be

expanded to incorporate multi-organ interfaces, such as brain–liver systems, to examine the influence of systemic factors on Alzheimer's disease progression. This systems-level approach enhances the translational relevance of experimental findings and supports the development of more effective therapeutic strategies (7, 23).

DRUG DISCOVERY AND PERSONALIZED MEDICINE APPLICATIONS

A major challenge in Alzheimer's disease drug development is the high failure rate of therapeutic candidates in clinical trials. Numerous amyloid-beta-targeting drugs have shown success in preclinical studies but have failed to demonstrate clinical efficacy. This highlights the limitations of conventional models and the need for more predictive experimental systems (3, 6).

Brain organoids and organ-on-chip technologies offer significant potential for improving drug discovery by providing human-relevant platforms for preclinical testing. These models enable assessment of drug effects on neuronal survival, protein aggregation, and synaptic activity, thereby improving the accuracy of efficacy predictions. They also help reduce the time, cost, and risk associated with clinical trials by identifying ineffective compounds at early stages of development (7, 25).

In addition to drug screening, these technologies support personalized medicine approaches. Patient-derived iPSCs can be used to generate organoids that reflect individual genetic backgrounds and disease characteristics. This allows evaluation of therapeutic responses in patient-specific models, facilitating selection of the most effective treatment strategies for individual patients (18, 19).

Furthermore, organoid-on-chip systems enable modeling of drug delivery across the blood–brain barrier, providing insights into the challenges of drug transport in Alzheimer's disease. This improves the development of therapies that can effectively target specific regions of the brain (7, 23). Overall, these platforms represent a significant advancement in Alzheimer's disease drug development by enabling more precise, efficient, and personalized evaluation of therapeutic strategies.

LIMITATIONS AND CHALLENGES

Despite their potential, organoid and organ-on-chip technologies have several limitations that must be addressed to improve their translational applicability. The complexity of the human brain remains a major challenge, as it cannot be fully replicated *in vitro*. Brain organoids lack a fully developed vascular system and may not accurately simulate higher-order brain functions that depend on long-range neuronal connectivity (5, 22).

Variability in organoid formation and differentiation can lead to inconsistencies in experimental outcomes. Standardization of protocols and quality control measures is therefore essential to ensure reproducibility. Although organ-on-chip systems are highly advanced, they require specialized equipment and technical expertise, which may limit their accessibility in certain research settings (17, 20).

Another important limitation is the incomplete representation of immune responses, which play a critical role in Alzheimer's disease progression. While efforts have been made to incorporate microglia and other immune cells, current models do not fully capture neuroinflammatory processes, highlighting the need for further development (5, 15).

FUTURE DIRECTIONS IN ALZHEIMER'S DISEASE MODELING

Future developments in Alzheimer's disease modeling are expected to focus on improving the physiological relevance and scalability of organoid and organ-on-chip systems. Efforts are underway to incorporate vascularization and more advanced immune components into brain organoids, which would enable more accurate representation of *in vivo* conditions (21, 24).

The integration of artificial intelligence and machine learning is also expected to enhance data analysis and predictive modeling. These approaches can identify complex patterns in large datasets generated from organoid and organ-on-chip experiments, facilitating the discovery of novel therapeutic targets and improving the prediction of disease progression (9, 25).

In addition, the development of multi-organ systems will allow investigation of interactions between the brain and other organs, such as the liver and immune system, providing a more comprehensive understanding of Alzheimer's disease as a systemic condition. These advances are likely to improve drug development processes and support the design of more effective and personalized therapeutic strategies (7, 24).

CONCLUSION

Brain organoid and organ-on-chip technologies represent a significant advancement in Alzheimer's disease research by enabling the development of human-

relevant models that more accurately reflect the structural and functional complexity of the brain. These systems provide important insights into key disease processes, including amyloid-beta deposition, tau pathology, synaptic dysfunction, blood–brain barrier impairment, and neuroinflammation, which are difficult to replicate using conventional models.

By addressing the limitations of traditional animal and two-dimensional cell culture systems, these technologies enhance the ability to investigate early disease mechanisms and evaluate therapeutic responses. They also offer significant potential to improve drug discovery by reducing translational failures and supporting the development of personalized treatment strategies.

Despite these advances, several challenges remain, including limited vascularization, incomplete immune representation, variability in model reproducibility, and technical complexity. Addressing these limitations through improved standardization, integration of vascular and immune components, and the application of artificial intelligence will be critical for enhancing the reliability and scalability of these platforms.

Overall, organoid and organ-on-chip technologies have the potential to bridge the gap between preclinical research and clinical application. Continued development of these systems is expected to advance early diagnosis, improve therapeutic development, and support precision medicine approaches in Alzheimer's disease.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

FUNDING

This research received no external funding.

ACKNOWLEDGEMENTS

The author sincerely thanks Dr. Devinder Singh, Retired Professor of Zoology, University of Delhi, and the author's grandfather, as well as Dr. Rup Lal, Retired Professor of Zoology, University of Delhi, for their guidance, mentorship, and careful review of this work. Their support was especially helpful in improving the secondary research, making complex biological concepts easier to understand, and guiding the reading of scientific literature. Their feedback and encouragement greatly improved the clarity and overall quality of this report.

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