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The Future of OOC on Neurological Diseases - Alzheimer's

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Abstract: ***Neurological Diseases such as Alzheimer's and Parkinsons' have been deemed incurable diseases. The complexity of the human brain is an obstacle for scientists to understand how treatments could interact with human brain microenvironments. To this date, researchers have used traditional modeling methods, such as in vitro cell culture and in vivo animal models. These methods are unable to showcase the different layers of the blood-brain barrier or accurately represent the cellular interactions within the brain. The proposed solution is a new research technology, organ on a chip, a multi-organ system connected with microfluidics. This review explores the organ on a chip, what it is made for, and how it is the future of drug development. In addition, we explore the lymphatic system and the different organ-on-a-chip models that can simulate the lymphatic system and BBB. Organ on a chip has the potential to help efficiently develop drugs and treatment, which has the potential to improve neurological disease conditions.***

I. INTRODUCTION

Organ-on-a-chip (OOC), is a tool that has been engineered throughout the decades as a new innovative way to model human organ systems and the human body's microenvironment. The Organ-On-a-chip is a microfluidic device that can replicate the structural and functional units of human organs on a miniature scale, demonstrating a physiologically relevant environment. These systems are utilized to study human diseases, drug development, and personalized medicine in a more accurate way rather than relying on animal models and other traditional methods to understand the human body. The OOC is fabricated in a way to incorporate multiple cell types and mechanical and biochemical cues, and to mimic the fluid flow in *in vivo* environments. The OOC is particularly reliant on modeling vascular diseases, such as brain diseases, simulating conditions like hemodynamics and the interaction of blood components with endothelial cells. The OOC incorporated various elements that use common materials which include polydimethylsiloxane (PDMS), and other polymers, with channels that are covered with biofunctional materials like collagen and fibronectin to enhance the biological relevance. Techniques like 3D printing and photolithography are used to create precise microfluidic channels that imitate the microarchitecture of human vasculature (Shakeri 2023). One instance of when a microfluidic model was used, is to study tumor-NK cell interaction. The 3D microfluidic model included two side channels lined with endothelial cells imitating the blood vessels. They then grew cancer cells (MCF7), creating tumor clusters that were hidden within the gel. The clusters were either placed alone or near human NK cells. Antibodies were then placed through the side channels, to observe how the antibodies impacted the NK cell's ability to kill the MCF7 cells. In this scenario, the double channel as well as the membrane microfluidic model help study how the NK cells kill cancer cells, more accurately. Most of these Ooc technology devices are filled with blue dye for visibility, which allows them to see the side channels lined with endothelial cells, tumor clusters, and antibodies surrounded by the NK cells (Ayuso 2018). This example needed OOC, to see the impact of antibodies' ability to kill MCF7 cells, which is appropriate to the human body, and it also does not pose any risks that could be detrimental to an individual's health. The OOC overall offers the ability to study a disease's mechanisms, drug responses, and cell behaviors in a controlled environment that closely resembles human physiology.

To see the effect of the OOC on the human brain, it is vital to understand the brain's mechanisms, and why OOC is needed to help researchers discover the unknown and complexities integrated into our lymphatic system and nervous system. The central organ of the nervous and lymphatic systems, compromised of various regions, is the human brain. The functions include cognition, memory, and motor control. The brain is composed of a complex network of neurons, glial cells, and blood vessels that work to maintain brain function and homeostasis. The brain regulates and controls all bodily functions which include thoughts, emotions, and memory. It processes sensory information and coordinates responses to internal and external stimuli. To model the brain's intricate environment and study neurological diseases, OOC allows researchers to study the brain's physiology, stimulate disease conditions, and test potential treatments without the limitations of traditional models. Incorporated in the blood vessels within the brain is the Blood-Brain Barrier (BBB).

The BBB is a highly selective, semi-permeable barrier formed by endothelial cells that line the blood vessels of the brain, along with supporting cells like astrocytes and pericytes. The BBB protects the brain from harmful substances in the blood while also allowing essential nutrients to pass in and out of the human body. It helps the brain maintain a stable environment and protects the central nervous system (CNS) from toxins and pathogens. It regulates the transport of molecules between the bloodstream and brain tissue, ensuring that only necessary substances reach the brain. Due to the BBB's multiplex structure and function, the BBB's tight junctions and selective permeability make it difficult to replicate *in vitro* (Wu 2023). The multiple cell types pose a challenge for studying their function and developing methods to deliver drugs across.

For diseases such as Alzheimer's disease, the OOC is a reliable method to study the complex background of the BBB and why Alzheimer's disease is still "incurable". Alzheimer's is a progressive neurodegenerative disease characterized by the accumulation of amyloid-β plaques and neurofibrillary tangles in the brain. This is what causes memory loss, cognitive decline, and changes in behavior. Alzheimer's is the most common cause of dementia which has affected millions globally. Alzheimer's is a significant public health challenge due to the aging population and the lack of effective treatments. The abnormal accumulation of amyloid-β plaques and tau protein tangles leads to the degeneration of neurons, and researchers have found genetic and environmental factors that contribute to the onset and progression of the disease. The spread of tau protein pathology across brain regions leads to neural death and brain atrophy. The complexity of the disease, the variability in symptom, and the progression among patients are the difficulties to study this neurodegenerative disease. There are multiple difficulties in studying the disease in its early stages and the challenge of replicating human brain conditions *in vitro.*

The porous membrane, made up of polymeric, flat microstructures ensures that there is communication between the two compartments, which is beneficial to the neurovascular unit (Spritz, 2021). The double-channel membrane-based models are first planted with endothelial cells into hollowed-out hydrogels to mimic blood vessels. Collecting endothelial cells enables the creation of a reduced version of functional characteristics of the human brain, immune system, skin, etc (Spritz 2021).

II. WHAT IS AN ORGAN-ON-A-CHIP AND WHAT IS THE GLYMPHATIC SYSTEM?

Organ-on-a-chip (Ooc) technology is a platform for the development of drugs and research. OOC can model the BBB because the OOC incorporates multiple human cell types such as endothelial cells, astrocytes, and pericytes, that when cultured and grown can replicate the multilayer structure of the BBB. Key considerations in OOC use include the number of channels, material type, fabrication, fluid flow, and cell types.

A niche technique to help culture and grow cells is used to replicate the complex components of the human body environment. The design of this chip plays a crucial role in how a researcher measures the permeability of the microenvironment of cells in different organ systems. Chip designs differ based on the study of the organ; However, the similarity of these designs depends on the channels and compartments that best fit the permeability physiology of the human cell environment. Single Channel, Double Channel (parallel), Double Channel (Sandwich), Multi Channel, are options for constructing OOC; however, they are commonly used to mimic the blood vessels, and the Blood-brain barrier (BBB) is a Double Channel OOC design. The BBB is typically modeled using a double channel OOC, as it allows to recreate the luminal (blood-facing) and abluminal (brain-facing) sides of the BBB, simulating the separation and flow of blood and brain interstitial fluid. To establish permeability between different cells in the same tissue, a porous membrane can connect OOC chips with two distinct channels. The porous membrane plays a crucial role in encapsulating the permeability of two different cells and ensuring communication between the two microenvironments.

Curating an OOC technology comes with different aspects that have a specific role in the performance and efficiency of how accurately the model can display a human organ environment. The most common materials used are polydimethylsiloxane (PDMS), glass, and thermoplastics; each fabrication has its own set of advantages. PDMS is a silicon-based elastomer. PDMS is the most common material for OOC, as it is cheaper to access, allows transparency and flexibility, and is oxygen permeable. However, PDMS is not hydrophobic so it may alter the efficacy of the flow and permeability rate between the two cell environments. Another alternative material is glass. With a range of types of glass to create the OOC, the glass allows transparency, hydrophilicity, and biocompatibility. It is important to note that glass is not flexible and unable to absorb gasses, leading to an inaccurate permeability flow rate. On the rise in OOC development is the material thermoplastic. What makes the material so compelling, is the low costs, and biocompatibility of its linear branched molecules, which are resistant to temperature fluctuations. The material allows gas permeability but does not match the ability of PDMS (Tajeddin 2021).

There have been significant advancements in OOC fabrication techniques; however, the methods have all derived from the two main methods of fabrication: Photolithography, and etching.

The most conventional microfabrication technique combines photolithography and etching while utilizing silicon, and silicon-based glasses. Photolithography, although costly, incorporates a 13nm light focused with mirrors. This is called the Extreme Ultraviolet Lithography (EUV). The EUV is used to create extremely precise features on the base material which processes are carried out to build the microenvironment, for example, the silicon-based glass. The 13nm light focused with mirrors creates fine features, and patterns, like nanopillars, which are used to make nanofluidics. Electron Beam Lithography (EBL) is an additional microfabrication technique that is on a beam of electrons that scans over the surface of the silicon-based glass without needing a mask. A “mask” on microfabrication is a structured template used for processes like photolithography to carry out specific designs onto the base. The EBL is a direct method that writes patterns onto the base by using an electron beam’s position and exposure time. The EBL method is specific to make precise features less than 10 nanometers, and for high-resolution patterning. Wet Etching is another technique where the silicon-based glass is immersed in a chemical solution (etchant), which removes materials from the base’s surface. Etchant is a chemical substance primarily used in microfabrication processes, to “etch” away layers of the silicon base, revealing multiple layers and creating customizable cavities and designs for specific OOCs. The heavy ions in the chemical substance carve out tracks and create porous membranes with controlled pores (Puryear III 2020).

One of the many benefits of OOC is its versatility and ability to be customized to mimic most human organ systems, including the brain and the glymphatic system. The glymphatic system's role is to regulate extracellular ion concentrations, Cerebrospinal fluid (CSF) dynamics, and clearance of metabolic waste, enabling the brain to maintain optimal conditions for neuronal functioning and synaptic connections. Each ion, CSF, and metabolic waste has a clear path from the brain. The CSF, for example, enters the subarachnoid space (SAS) from the ventricular system. An arterial pulsation drives CSF back into the brain parenchyma within periarticular spaces, so that when the CSF circulates, it mixes with the interstitial fluid (ISF), guides the delivery of fluid and interstitial solutes to the routes from the brain. Alongside the CSF, Astroglial Endfeet are extensions of astrocytes - a type of glial cell in the brain and spinal cord. This endfeet surrounds blood vessels in the brain, particularly in the perivascular spaces. The Astroglial Endfeet not only provides the foundation support for the blood-brain barrier (BBB) but also plays a crucial role in regulating water flow between blood vessels and brain tissue, due to the densely packed aqua 4 channels (AP4Q). Additionally, they facilitate the movement of CSF from the periarterial space into the brain interstitium. The Glymphatic system's main method of fluid and solute transport is the perineuronal spaces, where the CSF and ISF mixture bulk flow. This fluid and other dilutes are directed into the brain’s deep veins, basal meningeal, and cervical lymphatic vessels. Eventually, the fluid is drained to the peripheral lymph nodes and some of the fluid enters circulation. There are instances that the exchange between the CSF and the ISF mixture is less efficient, and this could have a significant impact on the glymphatic system’s ability to clear waste and deliver the right nutrients to the brain. Similarly, when the flow of the CSF is weakened, there is a sudden buildup of CSF within the brain. This increased volume and pressure can cause damage to the brain structures due to the increased intracranial pressure. The glymphatic system is for the clearing of metabolic waste and other solutes in the brain, so when the clearance system is impaired, many harmful substances accumulate over time. These harmful substances could potentially contribute to neuroinflammatory and neurodegenerative conditions, such as Alzheimer's disease (Reeves 2020). The glymphatic system is made up of a complex network of vessels, more notably the blood vessels creating the BBB which makes it hard for researchers to investigate when there is a risk of damaging cells or blood vessels. The OOC provides an ideal method for creating a simulated microsystem derived from the human brain, allowing a detailed investigation without the potential risks.

Apart from the glymphatic system, the BBB is made up of endothelial cells that line the blood vessels. The purpose of the BBB is to regulate and protect the brain from pathogens, using the junctional complexes that are surrounded by pericytes and astrocytes. The challenge of these tight junctions and selective permeability is that the BBB prevents efficient drug delivery to the brain. The existing models that we have today, fail to create the human anatomical intricacy of the blood vessel barriers, which leads to misleading results in clinical trials.

III. USE OF ORGAN-ON-A-CHIP TO MODEL THE BBB

The BBB plays a critical role within the glymphatic system, preventing neurotoxic plasma, pathogens, and blood cells from entering the brain. It regulates the transport of essential nutrients. Therefore the BBB needs selective permeability to maintain the brain microenvironment, which by default also prevents treatment and potential drugs to treat neurological diseases (Boghdeh 2022). Diseases such as Alzheimers or Parkinson's disease are deemed to be untreatable due to the competitive permeability that essentially blocks some treatments that could be crucial for brain therapy. Traditional models such as the animal model and *in vitro* systems are a method to model the complexity of the human BBB but fail to accurately depict the brain's functions, leading to false results in clinical trials. This is true due to the vast differences between animal models and the human brain function and structure, which is why researchers can’t assume results can be applied and similar to humans.

How the BBB is structured is that it is made up of tightly packed endothelial cells, pericytes, and astrocyte end-feet, that create the selectively permeable barrier. Tight junctions are made in between the endothelial cells that regulate the paracellular pathway that only allows specific ions and small molecules. The OOC offers a pathway that is a more accurate model of the BBB, which closely mimics the microenvironment and the cellular interaction precisely, such as the endothelial cells and the fluidity between the outer and inner environment of vesicles and cells. This way researchers can improve drug development and brain disease modeling. When it comes to neurodegenerative diseases such as Alzheimer's and Parkinson's, there could be a BBB dysfunction. For example, there could be an accumulation of a peptide called amyloid-beta that disrupts BBB functionality within an Alzheimer's brain (Gao 2023).

There are various methods on how to accurately model the BBB through OOC technology. Currently, a team led by Campisi, developed a novel 3-dimensional BBB microvascular network model through vasculogenesis to accurately mimic *in vivo* neurovascular organization. They used a two-fluid channel 3D microfluidic model composed of PMDS. Human-induced pluripotent stem cell-derived endothelial cells, brain pericytes, and astrocytes are seeded into the device to form the vascular BBB network. To evaluate the characterization of the BBB parameters, the researchers used confocal images to assess permeability with FiTC-dextran tracers and quantify vascular permeability coefficients. The researchers found that the model formed a selective microvascular network that had lower permeability compared to conventional *in vitro* models. There was a significant increase in tight junction protein expression and extracellular matrix proteins: laminin, and collagen IV. Gene expression of BBB-specific membrane channels and receptors was higher, and there was direct contact between Astrocytes endfeet and the surface brain vessels. Overall, the model showed reduced permeability and improved morphology of BBB anatomical structures. The researchers concluded that the 3D BBB microvascular model accurately represented the human brain BBB environment and that it is a physiologically relevant platform for drug discovery, and capable of predicting neurotherapeutic transport efficiency in the preclinical processes (Campisi 2018). The OOC can be an applicable tool that can transform our understanding of the glymphatic system, and more specifically the BBB.

Researchers identified a consistent lack of predictive models that mimic the BBB, which can hinder the development of drugs for neurodegenerative diseases like Alzheimer’s. Utilizing animal models, on the other hand, researchers are put in scientific constraints. Another set of researchers aimed to find advanced models that offer reliable data in a versatile, reproducible, and animal-free manner. The researcher's methodology was to develop a BBB Oc platform using human neurovascular cells: astrocytes, pericytes, and endothelial cells. These cells were cultured and seeded into the BBB-oC platform. Their setup included a trans-endothelial electrical resistance (TEER) measurement system that was used to monitor the exact permeability of the BBB. When fabricating the microfluidic devices, they used gold electrodes for TEER measurements positioned at micrometric distances from the endothelial barrier. The positioning of the gold electrodes ensures explicit measurement of electrical resistance across the endothelial barrier. Placing these electrodes does not obstruct cell imaging; in fact, it enables a clearer picture of the cell structure and the right junction formation. The researchers made sure to evaluate the cytotoxicity and permeability of GNR-PEG-Ang2/D1, a therapeutic nanosystem within the BBB-oc.

Once fabricating the OOC, they were able to create a neurovascular network of tight junctions in the endothelium, which was helpful when analyzing the TEER measurement and the GNR-PEG-Ang2/D1 synthesis. GNR-PEG-Ang2/D1 was synthesized and functionalized with Polyethylene Glycol, Angiopep-2 peptide (Ang2), and D1 peptide, which are helpful to enhance the stability and biocompatibility if the gold nanorods (through polyethylene glycol), establish crossing of the BBB (via angiopep-2 peptide), and avoid beta-amyloid fibrillation associated with Alzheimer’s diseases (using D1 peptide). Taking a closer look at the non-cytotoxic range determination, the GNR-PEG-Ang2/D1 was determined to be 0.05-0.4 nM. This range means that the concentration of GNR-PEG-Ang2/D1 does not cause toxic effects on the cells being tested. In terms of permeability, the experiment showcased that the GNR-PEG-Ang2/D1 was able to cross the BBB, as long as it was facilitated by the Ang2 peptide. These measurements are from the TEER values, which indicated the strengthening of the endothelial barrier over time.

The researchers concluded that the BBB-OC platform with the assistance of the integrated TEER measurement was proved to be functional and offers a strong alternative to animal experimentation. The OOC platform not only evaluates the brain permeability performance of nanotherapeutics in a physiological environment using human cells, but it also is a successful development for evaluating a nanotherapeutic agent against Alzheimer’s disease. The TEER-BBB-OC system comes in handy for assessing the portability of potential drugs that accelerate the drug screen processes for neurodegenerative diseases such as Alzheimer's and Parkinson’s (Palma-Florez 2023). This particular experiment is a contrast to the previous one as it shows the development of the BBB through OOC but using measurement tools such as TEER measurement, rather than cell imaging.

In a different application of the OOC, a group of researchers wanted to test the BBB-Oc against the Venezuelan Equine Encephalitis Virus (VEEV), which damages the integrity of BBB. The VEEV infection damages endothelial cells, which overall leads to the loss of tight junctions and increased permeability of the BBB. A direct impact of the virus can infect the BBB, cause cell death, and compromise the structure of the BBB. The traditional two-dimensional models and animal models do not accurately represent the human BBB, which is a recurring problem and hinders the attempts to find therapeutic strategies against VEEV. As animal models have different brain structures and functions to humans, it is harder to measure treatment for a long time. In this experiment, the researchers used the three-dimensional OOC model of the human BBB, specifically known as the neurovascular unit (NVU). As with the other models, this model includes the endothelial cells, astrocytes, and pericytes. To fabricate the gravity-flow NVU (gNVU), the researchers used PDMS. The gNVU allows for perfusion-based gravity flow, especially used in high-containment laboratories. The endothelial cells, pericytes, and astrocytes were all cultured and loaded into the gNVU device. To test the cultures against the VEEV virus, the researchers infected the gNVUSs with the attenuated VEEV-TC83 strain. Later, Omaveloxolone (OMA) was used to treat the infected gNVUs to evaluate its antiviral properties. Using a cytotoxicity test, the researchers found that OMA is not toxic to the gNVU cells at concentrations up to 0.5 µM. The OMA treatment resulted in a significant reduction of the virally infected cells and the OMA treatment was able to preserve the BBB structural integrity. A FITC dextran, a tool to study the permeability microcirculation of the virally infected cells, also determined that within the VEEV-TrD infected gNVUs, OMA was able to control the increase of BBB permeability. Overall, the studies demonstrated that the OOC gNVU model can help evaluate potential drugs more accurately, and in this case specifically against VEEV. This different type of approach of OOC could be a more relevant and human-like model for studying viral infections that damage the BBB, enhancing preclinical findings.

IV. ALZHEIMER'S PATHOPHYSIOLOGY USING OOC TECHNOLOGY

Alzheimer's disease (AD) is one of the most common forms of dementia, widespread among people who are 65 or older. It is predicted that by 2050, AD cases will increase to almost 152 million people. With years of research, AD is still deemed to be “untreatable”, due to the brain's complex structure; however, researchers over the years have curated a hypothesis that explains the AD pathogenesis, which is called the amyloid cascade hypothesis. The root cause of AD is the accumulation of β-amyloid peptide (Aβ), as the clumps of Aβ gradually form neurofibrillary tangles (NFTs) by hyperphosphorylated Tau protein. Specifically, the Aβ irritates from senile plaques, and with the combination of NFTs, those are the main histopathological features of AD (Sansores-Espana 2021). In their efforts to understand AD pathology, researchers have developed various models to mimic NFTs and Aβ plaques using the latest technology to aid in treatment and development. In attempts to find a therapeutic removal of AD existing amyloid plaques, PDAPp transgenic mouse, carries human amyloid precursor protein (APP) gene with a V717F mutation, which leads to the formatting of Aβ plaques. Researchers find mice that develop amyloid plaques that have a similar resemblance to human amyloid plaques in human Alzheimer patients, which explains why this approach has persisted for many years. With years of mice being a tool for modeling, researchers have identified their limitations, especially for replicating the human Alzheimer's brain. There is a lack of efficacy in aged mice, as research has shown the N-terminal antibodies that help to clear existing plaques are slowly diminishing. The PDAPP transgenic mouse model typically has strong amyloid plaque deposition, which poses a challenge to demonstrating the reduction of plaque lowering and makes it difficult to measure over time. In addition, the differences in the deposition rates of plaques in human AD patients and transgenic mice could impact the translation validity of any findings (B. Dematttos 2012).

Researchers aim to address these limitations that are found in common mice models, by using *in vitro* models, such as OOC, of neurological diseases. In this specific study, researchers used iPSC-Derived 3D models, where the iPSCs are reprogrammed from patients’ cells to create 3D neurospheroids and organoids. A part of the 3D OOC model is a LUHMES cell line, derived from human embryonic mesencephalic tissue, used to develop a 3D model for neurotoxicity studies by forming a spherical aggregated containing astrocytes, neurons, oligodendrocytes, and microglia. These organoids from human iPSCs were used to specifically study neurological diseases such as AD, and Parkinson’s disease (PD). The model was built based on a problem that the researchers were determined to uncover. In PD, they wished to investigate the role of peripheral inflammation and the genetic background of PD patients, and how that affects the degeneration of dopaminergic neurons. They explored the PD pathogenesis by adding fluidic systems to the OOC model, to mimic the BBB. In AD, the researchers wanted to examine the genetic/environmental factors that could influence AD. They were able to understand the multifactorial nature of AD, that they couldn’t before with the restriction of animal models. Post conducting the study, the researchers found that the PD 3D model showed how LUHMES cells are differentiated into mature dopaminergic neurons, forming natural ECM and undergoing rapid maturation.

This proved that 3D *in vitro* models with integrated laboratory automation technology, explained the nature of dopaminergic neurons and populations of neural cells in PD pathogenesis. Similarly in the AD model, the 3D neurospheroid model based on iPSCs from peripheral leukocytes of AD patients showed different variations in drug efficacy that are correlated to genetic backgrounds (Slanzi 2020). The results demonstrate that OOC models, particularly 3D cultures and organoids, have been the closest to replicating the human brain environment, as they demonstrate the cell interaction in blood flow. Researchers are also able to control the experimental environment more accurately while using actual human cells. Contrary to the mice models, OOC models are specific to patients, which helps researchers understand patient-specific diseases and mechanisms, and the environmental response to drug treatment.

V. POTENTIAL DRUG DEVELOPMENT FROM ORGAN-ON-A-CHIP

The pharmaceutical industry needs efficient methods for drug discovery. OOC is a promising tool for disease modeling that can lead to drug testing. OOC can help with drug development as it can emulate physiological environments and functionalities of human organs on a chip (Ma 2020). When researchers replicate the BBB microenvironment, they can use it as a trial to test drugs that could be potential treatments for neurological diseases, such as Alzheimer's and Parkinson's'.

Traditional *in vitro* 2D and *in vivo* animal models are dissatisfying for preclinical drug evaluation. Animal studies often fail to accurately predict human responses, as species differ. Currently, using traditional models, almost 40% of newly developed drugs fail in clinical trials despite successful preclinical evaluations, as the limitations of *in vivo* studies impact the prolonged drug development cycles and accelerate costs. *In vitro,* cell cultures lack the complexity of tissue microarchitecture and function. Although some challenges remain in broadly implementing OOC, the technology offers promise to reduce the need for animal testing and provide more accurate human models (Ma 2020).

VI. DISCUSSION

Organ-on-a-chip is a method of modeling different human systems to ensure a better understanding of diseases, and the physiological functions of the system, and a method to test drug effectiveness. The various features and designs of the OOC allow for the growth and culturing of human cells, emulating the cell environment and how the disease impacts cell interactions and permeability. Techniques to manufacture OOC including Photolithography and Wet etching allow researchers to customize OOC to their specific investigation needs, enabling versatility to adapt to different systems, such as the glymphatic system. Within the glymphatic system lies a selective semi-permeable membrane called the BBB, which influences the way researchers approach studies on the brain and neurodegenerative diseases. The nature of the BBB, as it regulates the transportation of essential nutrients into and out of the brain, poses a challenge for researchers to navigate the brain to test for treatments to improve Alzheimer's disease. This is why the OOC must mimic the BBB environment using endothelial cells, astrocytes, and pericytes. Measuring the permeability through the TEER measurement system, allows researchers to obtain an accurate representation of the human BBB, a basis for drug development.

Different iterations of OOC, including the BBB models and the glymphatic system model each have advantages and limitations. For example, the BBB model specifically uses a double-channel design to simulate the blood and brain interfaces, focusing on the selective permeability and tight junctions that are established by the endothelial cells. The glymphatic system model simulates cerebrospinal fluid (CSF) dynamics and waste clearing. The model is used to emphasize the fluid transport between the CSF and the interstitial fluid (ISF). Although they might differ in what system they mimic, both systems use PDMS which is a more flexible material. Both systems incorporate human cell types, such as endothelial cells, astrocytes, and pericytes. These human cell types as well as the incorporation of flow systems help mimic human conditions. Both the BBB model and the CSF model are expensive, and material limitations, such as the PDMS not being hydrophobic, can limit the application of OOC in some situations. High costs limit mass production and standardization of OOC devices across different labs. PDMS experiences thermal expansions, hydrophobicity, and swelling, which makes the material challenging to work with and limits standardization (Gaio 2018). When replicating the full complexity of human organ systems, there are difficulties in using PDMS to integrate multiple organ systems into a single chip. However, the limitations do not outweigh the benefits that come with the OOC.

Currently, researchers are working on enhancing the integration of organ-on-a-chip (OOC) systems with advanced technologies like AI, iPSCs, and multi-organ models. OOC creates microfluidic platforms and cellular interactions that improve the precision of disease modeling, particularly for complex conditions like neurological diseases. This shows how this niche field is likely to move towards the development of fully integrated human-on-a-chip systems for comprehensive drug testing and personalized medicine.

The recent advancements in automation and real-time monitoring will enable more precise and scalable OOC models, bridging gaps between preclinical and clinical studies (Kawakita 2022). Recent legislative accomplishments will enable the use of OOC in drug development. Specifically, the FDA Modernization Act 2.0 opens the door to the use of OOC as a replacement for *in vivo* animal testing in drug approval applications (Zushin 2023). When planning the future goals of this technology, it is important to focus on standardizing and scaling up OOC production to make the technology accessible for widespread use in research and industry. By prioritizing the development of models that can better mimic human physiological conditions, particularly for drug delivery across the blood-brain barrier and personalized disease modeling.

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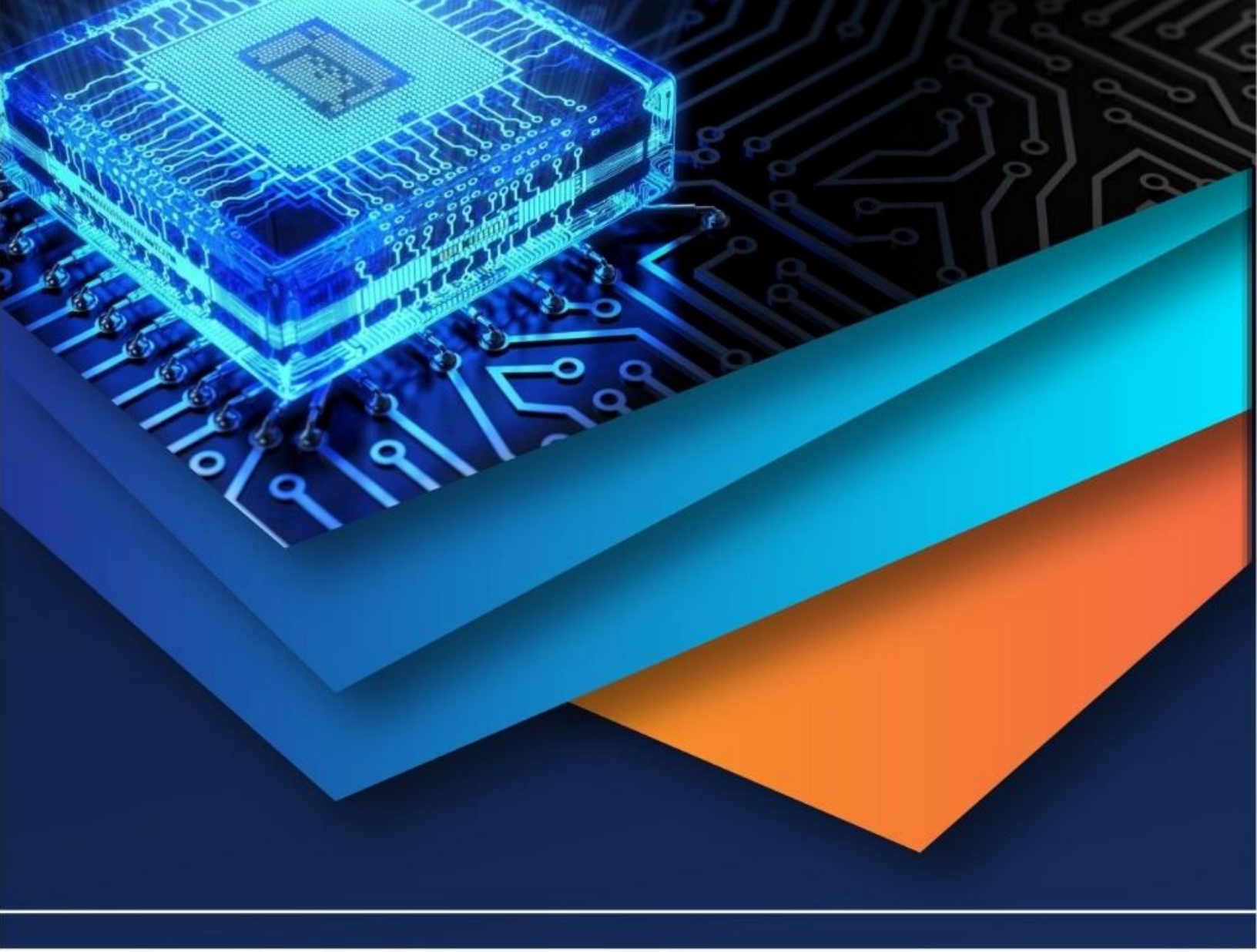

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