Review

ANNALS OF MEDICINE & SURGERY

OPEN

Tailoring epilepsy treatment: personalized micro-physiological systems illuminate individual drug responses

Sanobar Shariff, MD[a,b], Burhan Kantawala, MD[a,b], William Xochitun Gopar Franco, MD[a,c], Nitsuh Dejene Ayele, MD[a,d], Isabelle Munyangaju, MD[a,e], Fatima Esam Alzain, MD[a,f], Abubakar Nazir, MD[a,g,*], Madga Wojtara, MD[a], Olivier Uwishema, MD[a,h,i]

Introduction: Approximately 50 million people worldwide have epilepsy, with many not achieving seizure freedom. Organ-on-chip technology, which mimics organ-level physiology, could revolutionize drug development for epilepsy by replacing animal models in preclinical studies. The authors' goal is to determine if customized micro-physiological systems can lead to tailored drug treatments for epileptic patients.

Materials and methods: A comprehensive literature search was conducted utilizing various databases, including PubMed, Ebscohost, Medline, and the National Library of Medicine, using a predetermined search strategy. The authors focused on articles that addressed the role of personalized micro-physiological systems in individual drug responses and articles that discussed different types of epilepsy, diagnosis, and current treatment options. Additionally, articles that explored the components and design considerations of micro-physiological systems were reviewed to identify challenges and opportunities in drug development for challenging epilepsy cases.

Results: The micro-physiological system offers a more accurate and cost-effective alternative to traditional models for assessing drug effects, toxicities, and disease mechanisms. Nevertheless, designing patient-specific models presents critical considerations, including the integration of analytical biosensors and patient-derived cells, while addressing regulatory, material, and biological complexities. Material selection, standardization, integration of vascular systems, cost efficiency, real-time monitoring, and ethical considerations are also crucial to the successful use of this technology in drug development.

Conclusion: The future of organ-on-chip technology holds great promise, with the potential to integrate artificial intelligence and machine learning for personalized treatment of epileptic patients.

Keywords: anti-epileptic drugs (AEDs), drug development, epilepsy, microfluidics, micro-physiological systems (MPSs), organ-on-a-chip (OoC)

Introduction

Epilepsy is a neurological disorder that affects ~50 million people globally. It is a disease characterized by repeated seizures without any trigger[1]. Epilepsy encompasses a broad spectrum of conditions, with over 30 distinct epileptic syndromes and more than 15 types of seizures that have been recognized[2]. There are several causes of epilepsy, including traumatic brain injury,

HIGHLIGHTS

- Approximately 50 million people worldwide have epilepsy, with many not achieving seizure freedom
- There are several causes of epilepsy, including traumatic brain injury, perinatal asphyxia, congenital abnormalities, genetic syndromes, brain infections, brain tumours, and stroke.
- Some organs-on-a-chip develop a technique for organ/disease modelling on epileptic seizure models of the brain using pluripotent stem cells, which can replicate both local and circuit brain functions. Also, induced/human pluripotent stem cells have a promising outcome of mimicking and remodelling epilepsy.
- Advances in imaging methods, computer modelling, and the use of genomics phenotyping and remodelling to validate models that replicate *in vivo* are a few areas where research is required. Additionally, this ability to identify and characterize individuals more likely to respond, shows that within the domain of neurological disorders and specifically epilepsy.

[a]Oli Health Magazine Organization, Research and Education, Kigali, Rwanda, [b]Yerevan State Medical University, Yerevan, Armenia, [c]University of Guadalajara, Guadalajara, Mexico, [d]Department of Internal Medicine, Faculty of Medicine, Wolkite University, Wolkite, Ethiopia, [e]Barcelona Institute for Global Health—Hospital Clínic, Universitat de Barcelona, Barcelona, Spain, [f]College of Medicine and General Surgery, Sudan University Of Science and Technology, Khartoum, Sudan, [g]Department of Medicine, King Edward Medical University, Lahore, Pakistan, [h]Clinton Global Initiative University, New York, NY and [i]Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Oli Health Magazine Organization, Research and Education, Kigali, Rwanda. E-mail: abu07909@gmail.com (A. Nazir).

Annals of Medicine & Surgery (2024) 86:3557–3567

Received 9 November 2023; Accepted 9 April 2024

Published online 16 April 2024

http://dx.doi.org/10.1097/MS9.0000000000002078

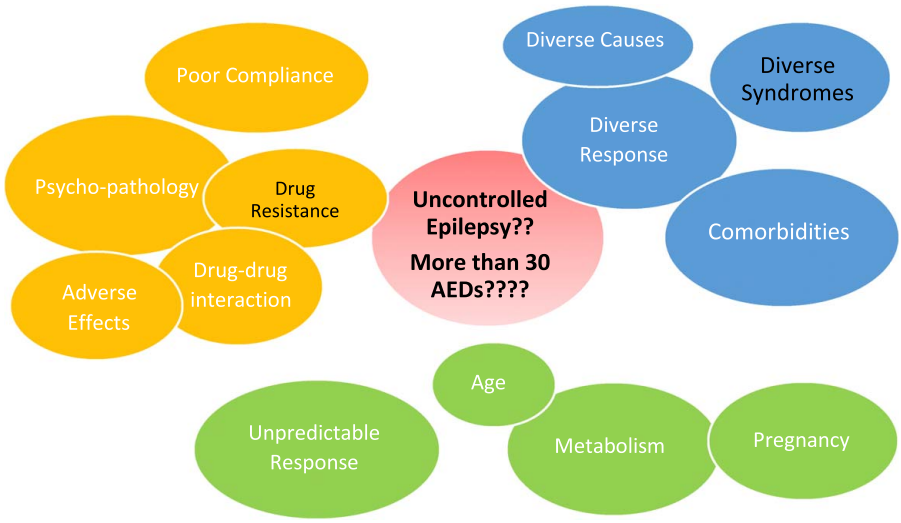

Figure 1. This shows factors associated with challenges of epilepsy treatment[3]. AED, anti-epileptic drug.

perinatal asphyxia, congenital abnormalities, genetic syndromes, brain infections, brain tumours, and stroke. These various causes alter the function of different parts of the brain, resulting in different manifestations. The heterogeneity of the causes and disease manifestations of epilepsy, in addition to other variable individual factors, poses an additional challenge in the treatment of epilepsy (Fig. 1).

Over the past three decades, the range of medications used to treat epilepsy has significantly expanded, now comprising over 30 different anti-seizure drugs. However, even with these extensive medication options, approximately one-third of individuals with epilepsy are unable to achieve sustained seizure freedom through currently available treatments[4]. Therefore, there is a need for a shift in the current syndrome-focused treatment to more personalized approaches for epilepsy treatment and drug response prediction. Recently, the concept of "personalized medicine" in epilepsy has expanded to include predictors of drug and surgical treatment responses[5]. One limitation of the personalized treatment approach for epilepsy is the limited understanding of the underlying disease mechanism.

The lack of appropriate models to predict the therapeutic efficacy of drugs in humans is a significant issue in the development and evaluation of drug efficacy. A micro-physiological system (MPS) is an in-vitro construct of two-dimensional (2D) or three-dimensional (3D) cellular components referred to as organs-on-chips. The use of organ-on-a-chip microfluidic devices, lined with living cells cultured under fluid flow, allows for the recapitulation of organ-level physiology and pathophysiology with high accuracy[6]. This innovative technology, which can recreate the physiological conditions and functionality of human organs on a microchip to model disease entities and test drugs, has the potential to significantly impact and streamline the process of drug development[2]. This technology holds great promise for substituting animals during the preclinical stages of pharmaceutical research and development.

The article aims to analyze the most recent literature regarding the application of personalized micro-physiological systems in guiding more individualized management of epilepsy. It identifies the current challenges in treating epilepsy and the values and challenges associated with personalized micro-physiological systems, particularly organ-on-a-chip technology. It offers possible evidence-based prediction and expert opinion of the authors on the future direction of using this emerging technology to identify individual drug responses. This review article also highlights numerous avenues for new research and collaboration to optimize and individualize epilepsy management.

Materials and methods

A comprehensive literature search was conducted utilizing various databases, including PubMed, Ebscohost, Medline, and the National Library of Medicine, using a predetermined search strategy. We focused on articles that addressed the role of personalized micro-physiological systems in individual drug responses and articles that discussed different types of epilepsy, diagnosis, and current treatment options. Additionally, articles that explored the components and design considerations of micro-physiological systems were reviewed to identify challenges and opportunities in drug development for challenging epilepsy cases.

Epilepsy: a complex neurological disorder

Epilepsy is a syndrome that occurs when a person experiences an epileptic seizure, and their brains show a persistent and abnormal tendency to have repeated seizures. To diagnose epilepsy, we must have one of the following criteria: an individual experiences at least two seizures caused by a non-medical condition and occur more than 24 h apart, when an individual has one seizure with a high probability ($>60\%$) that they will have another seizure in the next ten years, or when an individual has a specific pattern of seizures that is characteristic of a particular type of epilepsy[7]. The latest classification model developed by the ILAE in 2017 aimed to simplify the medical terminology for patients and their caregivers, identify seizures with both focal and generalized onset, and incorporate previously undefined seizures. The current classification by ILAE categorizes the clinical features of epilepsy

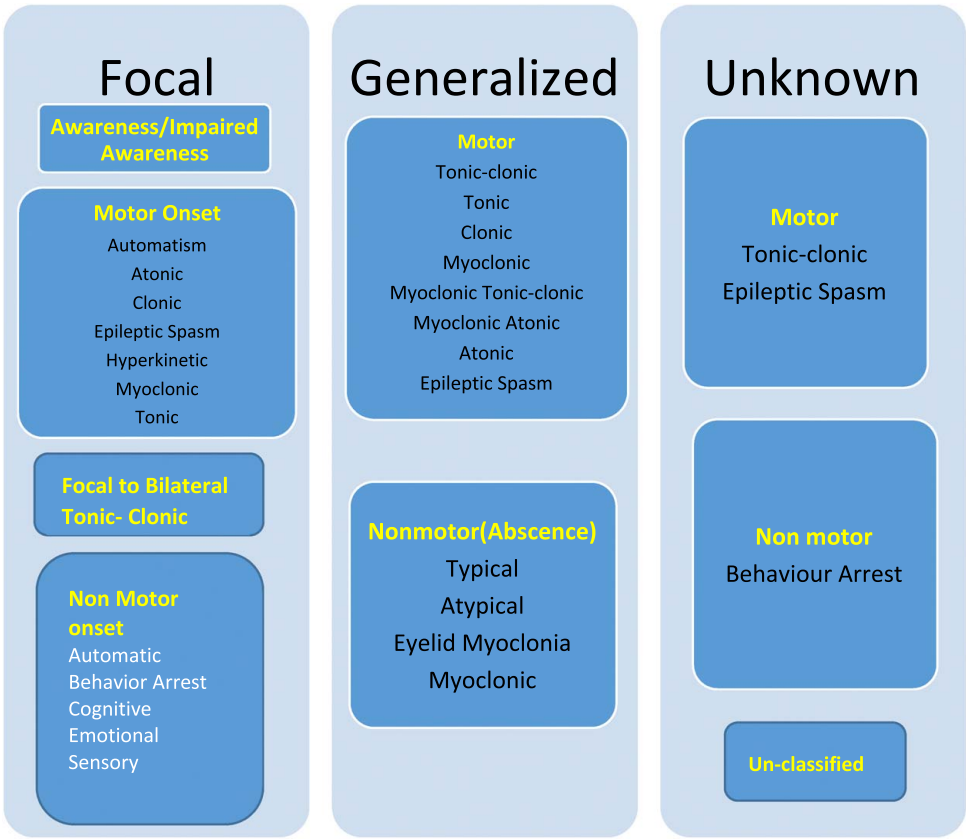

Figure 2. ILAE (International League Against Epilepsy) 2017 Classification of Seizure Types: Expanded Version.

into three levels: seizures, epilepsies, and epilepsy syndromes, taking into account aetiology and comorbidities at each level[8] (Fig. 2).

Although new anti-epileptic drugs (AEDs) are being discovered, current treatment strategies for epilepsy have many limitations in their inability to treat the cause of epileptic diseases, safety profile, and efficacy of seizure control. About 30% of people with epilepsy struggle with medication resistance, which can lead to social isolation, dependence, low marriage rates, unemployment, mental health issues, and a decreased quality of life[9]. Current treatment modalities have limitations such as drug-resistant epilepsy, complex drug-drug interaction with polytherapy, unpredictable safety profile, paradoxical aggravation of epilepsy with drugs, serious adverse effects after being introduced onto the market, pill burden for patients and patient noncompliance, teratogenicity of most of the AED, high cost of the newer anti-epileptic drugs.

There is a discrepancy in treatment response to AEDs among epileptic patients. Although genetic factors play a role in this variability, despite extensive research, no genetic marker accurately predicts AED resistance[10]. The treatment of epilepsy with drugs is unpredictable in their effectiveness, adverse reactions, and optimal dosage for individual patients, which is at least partly due to genetic differences[11]. Many AEDs get metabolized by the cytochrome P450 (CYP) family, and some of the CYPs have genetic variations that can affect the concentration of AEDs in the blood[12]. Additionally, patients with epilepsy who had a negative attitude toward medication, comorbidities, low medication adherence, and those who consumed alcohol were more likely to experience uncontrolled seizures[13]. This shows a need to determine individualized epilepsy drug responses for patients considering different patient factors.

The recent developments in the genetics and neurobiology of epilepsies are paving the way for a new era in epilepsy treatment tailored to each individual's specific condition. Despite the complex and multifaceted nature of clinical drug response, realizing the vision of accurate and individualized prediction of drug response to therapies is central to medicine[14]. The complexity of drug response arises from myriads of factors, such as environmental, anthropometric, genetic, and biological systems affected by the disease[15]. In light of this, it is highly improbable that a solitary biomarker or any other solitary stratifying factor will be capable of fully encompassing the intricacy of the situation. As a result, the realm of precision medicine is still in its infancy[16]. And the concept of precision medicine goes far beyond genomics. As a result, we need to develop an integrated system that can answer questions at different levels of AED use to apply the concept of precision medicine for epileptic patients.

Organ-on-a-chip technology

Overview of MPS (organ-on-a-chip)

MPS, also known as organ-on-a-chip (OOC), are micro-engineered biomimetic devices that replicate the human tissue architecture and function. The OOC is a combination of biology and microtechnology. With microfluidic channels as fine as hair, the

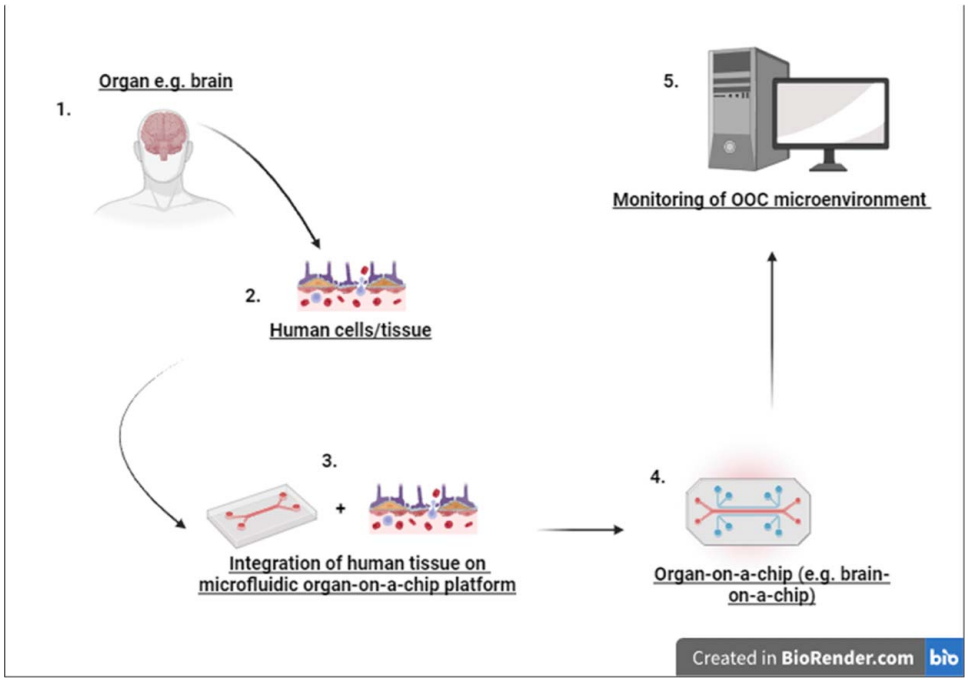

Figure 3. Graphical representation of micro-physiological systems (organ-on-a-chip). (1) The particular human organ identified for evaluation is chosen, (2) cells/tissue from the identified organ are harvested, (3) organ cells/tissue is integrated on the microfluidic organ-on-a-chip (OOC) platform, (4) the specific single-organ system (OOC) model is created and (5) biometrics of the OOC microenvironment are monitored and controlled.

chip manages solution volumes from picoliters to millilitres. Microscopic tissues of an organ are created on a microfluidic chip inside tubes to mimic the in-vivo physiology of different organs and diseases outside the human body. This microscale environment allows researchers to have a more controlled and realistic study of biological processes[17–19].

With the traditional use of 2D cell culture and animal models during drug discovery, it was difficult to predict the effects of drugs before human clinical trials. Preclinical testing with OOCs is more efficient and cost-effective than with traditional models[20,21] (Fig. 3).

Key components and design considerations

In designing an organ-on-chip model, it is important to keep several factors in mind[17,21–23]:

- A model's desired functionalities determine whether it should be a one-organ or multi-organ system. Single-organ systems determine how an organ responds to a given compound. Multi-organ systems investigate the exchange between various organs.
- The method of developing functional tissues: either a top-down method to integrate existing tissues into the system; or a bottom-up approach using cells cultured and assembled into functional tissues in a microfluidic environment.
- OOC architecture: this is determined by the functionality required. For 3D tissue cultures, solid organ chips are used. For the evaluation of distinct transport processes, barrier tissue chips are used.
- Material selection and fabrication process: PDMS (polydimethylsiloxane) is a commonly used silicone rubber because of its biocompatibility and fabrication simplicity.
- Reliability and repeatability are greatly impacted by the difficulties involved in creating organ-on-chip structures, including choosing the material and biological element choices. The accuracy of results can be impacted by inconsistencies introduced by variations in biological components and materials. These difficulties can be lessened by standardizing fabrication procedures, implementing quality control procedures, and guaranteeing uniformity in cell sources. By addressing these issues, organ-on-chip results become more dependable and repeatable, which increases their usefulness as instruments for illness modelling and drug testing.
- Sterilization and surface treatment: to preserve the biocompatibility and integrity of the system. Methods used depend on the components of the OOC. For example an extracellular matrix (ECM) coating or pluronic acid surface treatment can increase cell adhesion and function.
- The choice of biological elements, such as cells or tissues to use depends on patient factors, biocompatibility, cellular function, inclusion of support cells, and ability to expand.
- Microenvironment control and OOC system monitoring: this is important to ensure optimal cellular functionality. A variety of options exists such as visual or sensory read-outs.

Advantages and potential applications in drug development

By providing more accurate and predictive preclinical testing models, OOC technology could revolutionize and personalize drug development. OOC models can be used for screening drug candidates, evaluating drug toxicity, and investigating disease mechanisms in early drug development. By replicating interactions between organs and monitoring drug distribution and

Table 1

Previous research using organ-on-a-chip for neurological disorders[21]

Neurological OOCs models	Use
Brain-on-a-chip	A model of epilepsy and an analysis of brain function.
Brain-cancer-on-a-chip	This model aims to explore methods of delivering chemotherapy directly to cancer cells in the brain by opening the blood-brain barrier.
Alzheimer's-disease-on-a-chip	The 3D model allows for precise analysis of the disease *in vitro*. The signalling pathways and contacts in traditional 2D models were inadequate.
Parkinson's-disease-on-a-chip	The disease-causing protein α-synuclein accumulates within cells, resulting in uncontrollable tremors, slow movements, and stiffness. The spread of disease is accelerated when healthy cells replicate. Thus, to accurately study the disease, the OOC model needs to simulate the two cellular dynamics *in vitro*.

2D, two dimensional; 3D, three dimensional; OOC, organ-on-a-chip.

transport in preclinical trials, organ-on-a-chip models can determine whether drugs are safe and effective[21]. The OOC technology also allows for the prediction of drug effects on specific groups of patients, even in those unable to participate in clinical trials, without putting them at risk. Lastly, it can be used to identify therapeutic targets and to repurpose drugs for particular patient groups[21,24] (Table 1).

Designing patient-specific organ-on-a-chip models

Collection and analysis of patient-specific data (genetic, physiological, clinical)

By integrating analytical biosensors into OOCs, we can monitor cells and their microenvironment in real-time, as well as analyze physiological processes and regulate the microenvironment of tissue on the chip. The physiological and pathological activities of tissues can be tracked using different types of physical and chemical sensors[22].

There are three basic parts to a sensor: the sensing element, the signal transducer, and the detector. Three basic types of sensors can be incorporated into OOCs: electrical, electrochemical, and optical sensors. Chemical signals are typically picked up by optical and electrochemical sensors, while mechanical and growth factors are usually tracked by electrical signals. Several metrics can be monitored at the same time. There is also the potential for integration of artificial intelligence for the rapid and efficient monitoring and analysis of the high volume of data produced by OOCs[25,26].

Integration of patient-derived cells into the organ-on-a-chip device

Human tissues and cells are cultured in controlled dynamic microfluidic channels on OOC platforms, which precisely replicate the human organ physiology and pathology. Multiple organ chips can be fluidly connected to form multi-organ chip systems. A human body-on-chips can be created by extending this system and simulating all aspects of the body's physiological functions, metabolic activity, drug absorption, and distribution. It is possible to develop better human organ pathophysiological conditions and more realistic disease models by pairing OOC platforms and patient-specific induced pluripotent stem cells (iPSC). As a result of iPSC differentiation, OOCs can be personalized as well as translated into clinical benefit[27] (Table 2). For example in OOCs, researchers could expose the cells of a patient to certain drug agents and gain a greater understanding of how the individual will react to the treatment, preventing the administration of a harmful medication (Fig. 4).

Predicting individual drug responses

Currently, clinicians do not have any treatment available to prevent epilepsy onset (epileptogenesis). OOC research is not yet suitable for chronic illnesses, adaptive immunity, and hormonal, skeletal, or neurological responses as it is difficult to replicate complex system-level actions *in vitro*[28]. However, a research group in the USA recently developed an experimental high-throughput epilepsy-on-a-chip platform suitable for discovering new anti-epileptic drugs by the rapid identification of epileptogenic signal pathways[29]. These algorithms take into account biomarkers linked to medication response, optimize tailored dosing according to real-time data, and take into account dynamic network interactions. By improving the accuracy of anticipating unique reactions to anti-epileptic medications, these methods aid in the development of tailored treatment plans for patients with a variety of complex and varied disorders[29].

Through microfluidics, researchers have bridged the gap between in-vitro and in-vivo research[30–32], providing the ability

Table 2

Challenges and considerations in recreating patient-specific conditions[22,27]

Challenges	Considerations
Access to OOC	Most OOCs are handcrafted devices in academic labs and at a very slow production rate. Lack of Regulatory consistency and quality control hinder the reproducibility of these devices.
Biocompatible OOC materials	PDMS commonly used for OOCs binds to hydrophobic compounds such as oxygen and drugs interfere with cellular concentration control.
Complexity of biological systems	The ability to model vascular pathways, neuronal connections, immune responses, and cellular connections in OOCs would be valuable. iPSCs can be used to model immune responses, but this is a difficult process.
Achieve mature tissue morphology	There is a difference between the speed and magnitude at which molecular, structural, and functional characteristics develop. Maintaining phenotypic integrity over long periods without compromising communication is challenging.
Diversity in patient populations	OOCs will need to address racial diversity, age factors, and sex differences to reduce current health inequalities.
Volume of generated OOC data	Data analysis and experiment design are shifting to artificial intelligence and machine-learning methods due to the high volume of generated data.

OOC, iPSC, induced pluripotent stem cell; organ-on-a-chip; PDMS, polydimethylsiloxane.

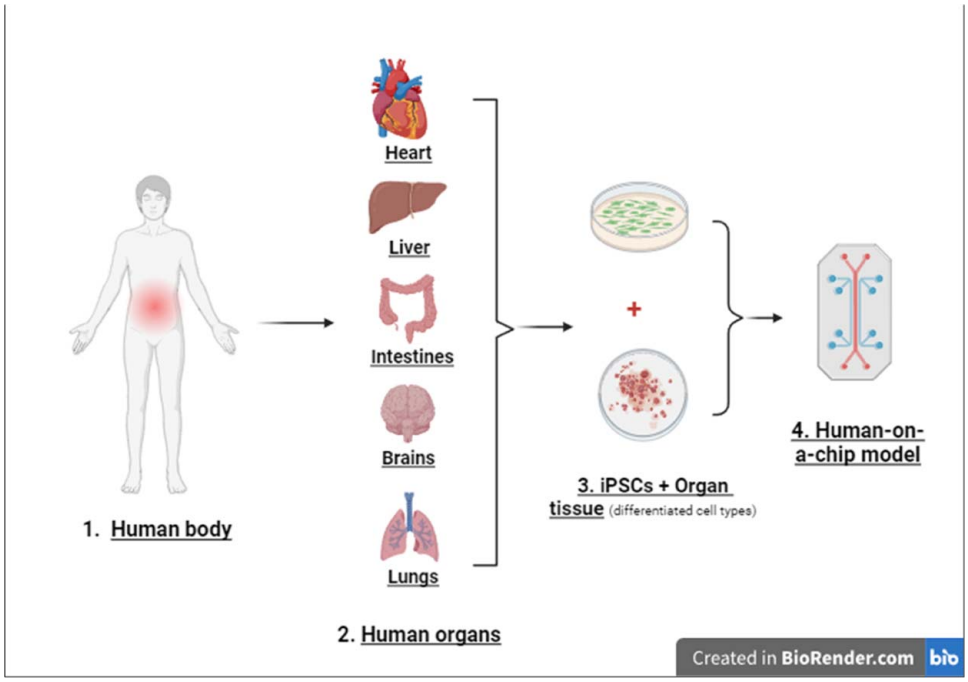

Figure 4. Schematic representation of a patient-specific organ-on-a-chip model. (1) the target patient type is/are identified, (2) tissues/cells of the different organs are harvested, (3) the different organ tissues are integrated with induced pluripotent stem cells (iPSCs) which are reprogrammed to develop into the cells of the different organs and (4) a patient-on-a-chip model is created as a realistic patient model.

to regulate fluid conditions, cell adhesion, and mechanical stimulation[33], which is how organ-on-chip technology was developed to replicate organ function[14,34].

Personalized drug response prediction

Usually, drug predictive models are developed under several stages including: (a) discovery of dataset, (b) Retrospective validation dataset. A drug response is defined as a reduction in seizure frequency of more than 50% after 12 weeks of baseline. An AED Brivaracetam was shown to be effective in treating partial-onset (focal) seizures in patients 4 years of age and older by blocking vesicle membrane protein (SV2A). In their study, they found that clinical and genetic factors were largely responsible for predicting drug response. Their study figures some areas of drug resistance that contributed to prior administration of levetiracetam (an AED), where levetiracetam naive shows a double response rate to Brivaracetam. They also observe a strong predictive genetic feature including the presence of structural variants overlapping brivaracetam's receptor gene SV2A, and the mutational load in the GO:0051011 gene set, a GO term representing microtubule minus end binding[35].

In another study a Modular platform for epilepsy modelling *in vitro* (MEMO), which is a lab-on-chip device, in which three hPSC-derived (human pluripotent stem cells) networks are separated by a novel microfluidic cell culture device that uses PDMS (transparent organosilicon) and allows controlled network-to-network axonal connections through microtunnels. The MEMO concept is to monitor the seizure-like activity of hPSC-derived neuronal networks with MEA technology in three separate but axonally connected compartments. They apply an experiment by adding phenytoin (AED) to the network and show a localized threat effect to the networks, mimicking the focal epilepsy nature[36].

Since data produced by an integration of complex tissues and organs are large; Artificial intelligence, especially machine learning, is the most appropriate method for the analysis of data and better prediction and application of relevant human health[37]. For patients with epilepsy, the combination of artificial intelligence (AI) and machine learning (ML) holds great promise for improving individualized care. The following are some particular ways that these technologies can help to improve patient outcomes, along with some potential implementation challenges:

AI/ML Contribution to Seizure Prediction: In order to forecast the chance of seizures, sophisticated algorithms can evaluate continuous data from a variety of sources, including electroencephalogram (EEG) recordings. Patients and healthcare professionals can take preventative action with the aid of this predictive skill.

Treatment Response Prediction: AI/ML Contribution: AI/ML models are able to predict individual reactions to certain anti-epileptic medicines (AEDs) by assessing patient data, comprising genetic information, therapy history, and clinical characteristics[38]. However, Table 3 shows the main analytical techniques reported for the online analysis of OoC[39].

Challenges and future directions

Complexities of building OoaCs

Organ-on-a-chip (OoaC), comprising Brain-on-a-Chip (BoC) , has achieved staggering popularity for drug development enhancing understanding of health and disease while preventing deviations associated with interspecies divergences[21,44–52]. They

Table 3

Organ-on-a-chip analytical techniques and their shortcomings[39]

Organ on a chip analytical technique	Considerations and shortcomings	Reference
Optical imaging	Measuring multiple properties of soft tissue. Measure metabolic changes that are early markers of abnormal functioning of organs and tissues. Appropriate technique for static analysis Fabrication challenge. Low field view at high magnification.	[38,39]
Fluorescent microscopy	Cell resolution and expression level detection. Require florence labelling.	[38,40]
Confocal microscopy	Generates high-resolution images of material stained with fluorescent probes. Phototoxicity	[38,41]
Thermoelectric ELISA	The concentration of the analyte is determined by measuring the heat of an enzymatic reaction between glucose and glucose oxidase using a thin-film antimony/bismuth thermopile. Heat loss. Low sensitivity.	[38,42]
TEER (Trans-Epithelial Electrical Resistance)	Non-invasive and label-free used with epithelial and endothelial cells in a monolayer as a strong indicator of cell barrier integrity and permeability. These indicators are often used *in vitro* to evaluate the transport of drug chemicals or drug screening assays. Difficulties in the integration of electrodes in OOC. Displacement of electrodes influences the result.	[38,43]
MS (mass spectrometry)	Sensitive, selective, and tentatively identify a large variety of unknown compounds. Hampered by the nature of the media used, and the presence of nonvolatile buffers.	[38,44]

OOC, organ-on-a-chip.

offer the advantages of in-vitro methods with increased accuracy by replicating the dynamism of native environments[50,53–63]. Microfluidic systems, rooted in the Lab-on-chip or micro total analysis systems (μTAS), have contributed by allowing precise control over chemical and physical stimuli, resembling in-vivo settings[64–66]. They have proven useful for drug screening and safety testing by controlling drug release and countering burst distribution seen in simple in-vitro approaches[46]. Control over spatiotemporal variables is deterministic to cell integrity and outcomes, thereby, hence the need to select appropriate material to cope with the mechanical stress conditions and resemble an extracellular matrix (ECM). Such can be monitored through sensors incorporated into the platform[44,46,67]. Concerns revolve around chip configuration and its influence on observed outcomes[68–74]. Material is selected from an extended array of options, each carrying its advantages and drawbacks. Polydimethylsiloxane (PDMS) has emerged as the preferred choice, considering its superiority in handling, transparency, biocompatibility, and gas permeability[75].

Integration of vascular systems is valuable but comes with challenges in assembling, often aided by analytical methods[45,47]. OoCs have been validated for the study of neural networks[66]. These introduce additional complexities, such as electricity to better resemble functioning and stimulate cell maturation within specialized environments such as the nervous system (CNS)[45,50].

Researchers advocate for a "universal medium", to provide nutrients and promote factors to sustain the systems[44,75]. Another consideration is the choice of cell source. Current means comprise cells undergoing indefinite proliferation or lineage precursors from donors or commercial providers[49]. Patient sourcing is beneficial in terms of precision medicine and rare diseases but may introduce epigenetic profiling, potentially affecting the result's generality[18,76]. Commercial sources carry an unknown genetic heterogeneity, potentially obscuring the results[48,49]. Therefore, establishing the lineage to be cultured is a key aspect of design[44]. Additionally, there must be an elucidation on the need to "capacitate" added components (i.e. immune cells, capillaries) to sensitize them to the intended setting and enhance homogeneity[70].

As MPSs increase, authors have inquired about the organoid size to represent drug response (or physiological process)[77]. Functional scaling has been proposed as the most appropriate approach to the issue of determining a meaningful ratio of tissue mass[48,67].

Ethical considerations in using patient-derived cells and data

OoCs were intended to prevent ethical dilemmas after the constraints on animal testing for drugs and cosmetics development[50,77]. Representativity of specific populations by mimicking settings as advanced age or certain genetic profiles could yield better cues into the response of this population to the drug in question but raises concerns about privacy and justice[61].

For CNS studies, donor sourcing is only available after biopsies or cadaver sourcing. This carries ethical concerns on its own about data privacy, letting aside how the "epigenetic memory" might condition the experiment outcomes and derived management[78]. iPSCs are the choice for this setting, but questions arise about the extent of stimulation required for a healthy specialization, necessitating close monitoring[52]. Protocol establishing protocols is crucial to address these concerns and enhance reproducibility[79].

Regulatory and commercialization hurdles

Pharmaceuticals seek aid in technologies for the lengthy and expensive drug development process, particularly for the lower success rates and extended time frames seen for CNS-focused agents[56,80]. OoCS ought to provide incentives for continued investment in research and development (R&D) to stakeholders[81]. Organizations recognize the limitations of toxicology data from animal studies and encourage the development of methods to enhance candidate selection and decision-making[82]. Significant

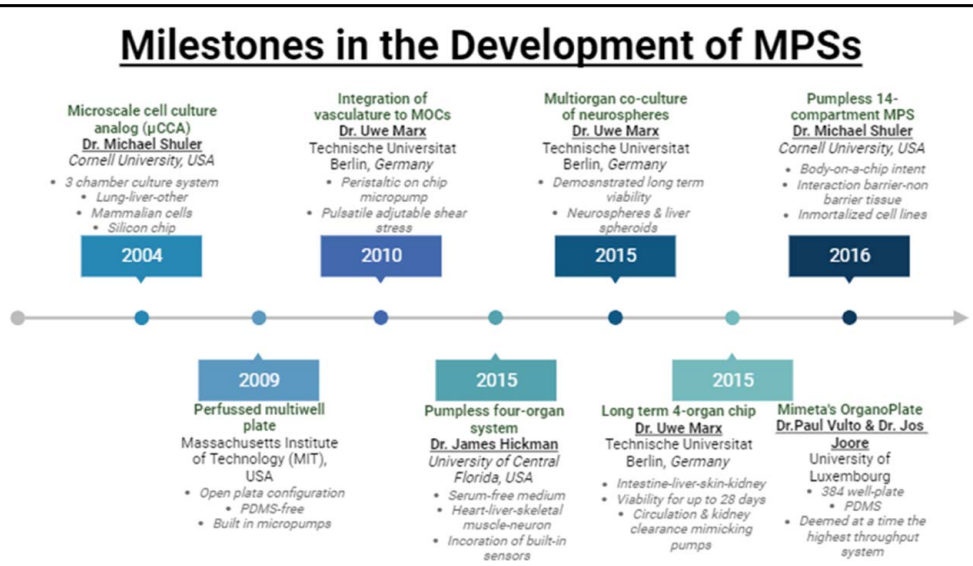

Figure 5. Milestones in the pursuit of micro-physiological systems (MPSs).

challenges are to be overcome such as high reagent consumption and costs. While PDMS is widely used for platform fabrication, it has limitations in replicating complex architectures, necessitating stepwise integration, and increasing labour, time, and costs[45]. Permeability to small molecules can hinder drug concentrations[21,49]. Sterilization and purification processes for natural materials, whereas chemical modification for synthetics add up in terms of time and costs.

Widespread use of these technologies prompts the establishment of standards to promote uniformity, and real-time monitoring and enhance their cost efficiency[45]. Regulatory agencies foster the usage of these technologies and even launched funding programs in this matter, namely Tissue Chips for Drug Screening. Their integration might be facilitated by the surge of organizations, along with workshops and committees[49].

OoCs handling needs to be aligned with standard procedures and their throughput increased for its marketability[49,83]. Automatization and parallelization of processes like media exchange will enable a larger testing capacity, transforming current systems into high-throughput systems (HTS)[18,68].

Emerging technologies and future prospects

Multi-organ-on-Chips (MoCs) represent the next step in enabling simultaneous study of available organoids, providing us with more accurate data on ADME and a step closer to the Body-on-a-chip stage (Fig. 5)[45,46,50]. Studies have already elucidated unknown toxicities, highlighting the need for comprehensive toxicological assessment[45]. OoCs seem useful for drug repurposing aimed at identifying additional uses for already marketed drugs[79].

Microfluidics has proven effective for disease modelling posing its potential to enhance our understanding of neurological disorders[72,83]. Different neurological conditions are already under study in these platforms such as those resembling Dementia and other Neurodegenerative Disorders (NDDs)[83].

Amidst the AI and ML era, these could help solve current issues in the design of MPSs and data processing. However, legal frameworks addressing data privacy and confidentiality are precise before broader implementation[49]. OoCs could follow up with analytic and modelling tools to validate targets identified by genomic and proteomic sequencing[63] (Fig. 5).

Conclusion

OoC is a relevant form of cell and tissue stimulation that attempts to mimic the real thing. Some organs-on-a-chip develop a technique for organ/disease modelling on epileptic seizure models of the brain using pluripotent stem cells, which can replicate both local and circuit brain functions. Also, induced/human pluripotent stem cells have a promising outcome of mimicking and remodelling epilepsy. In addition, Modular Platform for Epilepsy Modelling In Vitro (MEMO). Commercial 2D microelectrode arrays (MEA) have been used in the absence of electrophysiological measurement systems tools, which reduces the maximum use of the organoid 3D structure. However, modelling of epilepsy needs more feasible techniques and methods to make it fully beneficial.

Limitations of traditional models in assessing drug effects, toxicities, and disease mechanisms for epilepsy.

Mimicry on a microscale

Traditional Models: The microenvironment of human organs cannot always be faithfully replicated using conventional cell cultures and animal models.

OOC technology: OOC devices more accurately mimic the microarchitecture and milieu of particular organs, such the brain. As a result, the tissue's physiological circumstances may be represented more accurately, improving the model's suitability for researching illnesses like epilepsy.

Multiple cellular intricacy

Traditional models: Cell cultures have a tendency to oversimplify intricate relationships between many cell types that exist inside an organ.

OOC technology: OOC platforms enable the integration of several cell types, closely emulating the target organ's biological variety. OOC models are able to more accurately represent the intricacy of neural networks in the context of epilepsy, where aberrant interactions between neurons are a major factor.

An ever-changing microenvironment

Traditional models: The dynamic character of organ structure and responsiveness to stimuli may not be sufficiently reflected by static cell cultures and models of animals.

OOC technology: By combining mechanical forces, fluid flow, and other pertinent physical cues, OOC systems allow the generation of dynamic microenvironments. Its dynamic character aids in a more accurate simulation of in-vivo settings, facilitating a better understanding of the long-term effects of medications and illnesses on the organ.

Superior throughput of screening

Traditional models: In conventional models, drug screening and toxicity assessment can be costly and time-consuming processes.

OOC technologies: OOC devices can be made for high-throughput screening, which makes it possible to test several medications and medical problems at once. This offers more thorough data on drug reactions and toxicities and speeds up the drug discovery process.

The need for the development of organs-on-a-chip is fundamental for preclinical safety screening of drug synthesis. This is expected to reduce cost and time in experimental trials that lead to new drug formulation and patients' individualizing benefits. Toxicologists, biologists, and pharmaceutical scientists must collaborate with bioengineers to create a complicated, safe, and bio-like organ on a chip platform. Biomaterials, SC biology, microfabrication (alternative material to PDMS), and biosensors can now be used to make organs on a chip platform that works well and develop a sensor-integrated organ-on-a-chip platform. Advances in imaging methods, computer modelling, and the use of genomics phenotyping and remodelling to validate models that replicate *in vivo* are a few areas where research is required. Additionally, this ability to identify and characterize individuals more likely to respond, shows that within the domain of neurological disorders and specifically epilepsy, we can begin to think more systematically about rational and personalized clinical decision-making and reducing the disease burden for patients on an individual level.

Ethical approval

Ethics approval was not required for this article.

Consent

Informed consent was not required for this article.

Sources of funding

Not applicable.

Author contribution

Conceptualization of ideas: all authors. Critical reviews with comments: all authors. Final Draft: all authors approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Abubakar Nazir.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Beghi E, Giussani G, Abd-Allah F, *et al*. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:357–75.
[2] Jia D, Roy R, Moses MA. MMPs in biology and medicine. Matrix Met Biol 2015;239:183–213.
[3] Santulli L, Coppola A, Balestrini S, *et al*. The challenges of treating epilepsy with 25 antiepileptic drugs. Pharmacol Res 2016;107:211–9.
[4] Perucca E. The pharmacological treatment of epilepsy: recent advances and future perspectives. Acta Epileptol 2021;3:22.
[5] Steriade C. Entering the era of personalized medicine in epilepsy through neuroimaging machine learning. Epilepsy Curr 2022;22:168–9.
[6] Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. Nat Rev Genet 2022;23:467–91.
[7] Fisher RS, Acevedo C, Arzimanoglou A, *et al*. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.
[8] Falco-Walter JJ, Scheffer IE, Fisher RS. The new definition and classification of seizures and epilepsy. Epilepsy Res 2018;139:73–9.
[9] Wahab A. Difficulties in treatment and management of epilepsy and challenges in new drug development. Pharmaceuticals 2010;3:2090–110.
[10] Franco V, Perucca E. The pharmacogenomics of epilepsy. [Internet] 2015; 15:1161–70
[11] Löscher W, Klotz U, Zimprich F, *et al*. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia 2009;50:1–23.
[12] Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. Neurosci Lett 2018;667:27–39.
[13] Niriayo YL, Mamo A, Kassa TD, *et al*. Treatment outcome and associated factors among patients with epilepsy. Sci Rep 2018;8:1–9.
[14] de Jong J, Cutcutache I, Page M, *et al*. Towards realizing the vision of precision medicine: AI based prediction of clinical drug response. Brain 2021;144:1738–50.
[15] Armstrong M. The genetics of adverse drug reactions: promises and problems. Methods Pharmacol Toxicol 2008:121–47.
[16] Peck RW. Precision medicine is not just genomics: the right dose for every patient. Annu Rev Pharmacol Toxicol 2018;58:105–22.
[17] Leung CM, de Haan P, Ronaldson-Bouchard K, *et al*. A guide to the organ-on-a-chip. Nat Rev Methods Primers 2022;2:1–29.

[18] Baptista LS, Porrini C, Kronemberger GS, *et al*. 3D organ-on-a-chip: The convergence of microphysiological systems and organoids. Front Cell Dev Biol 2022;10:1043117.

[19] Tajeddin A, Mustafaoglu N. Design and fabrication of organ-on-chips: promises and challenges. Micromachines 2021;12:1443.

[20] Ahmed T. Organ-on-a-chip microengineering for bio-mimicking disease models and revolutionizing drug discovery. Biosens Bioelectr X 2022;11: 100194.

[21] Wang Y, Gao Y, Pan Y, *et al*. Emerging trends in organ-on-a-chip systems for drug screening. Acta Pharm Sin B 2023;13:2483–509.

[22] Koyilot MC, Natarajan P, Hunt CR, *et al*. Breakthroughs and applications of organ-on-a-chip technology. Cells 2022;11:1828.

[23] Fuchs S, Johansson S, Tjell AØ, *et al*. In-line analysis of organ-on-chip systems with sensors: integration, fabrication, challenges, and potential. ACS Biomater Sci Eng 2021;7:2926–48.

[24] Cho S, Lee S, Ahn SI. Design and engineering of organ-on-a-chip. Biomed Eng Lett 2023;13:97–109.

[25] Deng S, Li C, Cao J, *et al*. Organ-on-a-chip meets artificial intelligence in drug evaluation. Theranostics 2023;13:4526–58.

[26] Sunildutt N, Parihar P, Chethikkattuveli Salih AR, *et al*. Revolutionizing drug development: harnessing the potential of organ-on-chip technology for disease modeling and drug discovery. Front Pharmacol 2023;14: 1139229.

[27] Vunjak-Novakovic G, Ronaldson-Bouchard K, Radisic M. Organs-on-a-chip models for biological research. Cell 2021;184:4597–611.

[28] Ahmed Tanvir. Organ-on-a-chip microengineering for bio-mimicking disease models and revolutionizing drug discovery. Biosens Bioelectr X, 112022:100194.

[29] Liu J, Sternberg AR, Ghiasvand S, *et al*. Epilepsy-on-a-chip system for antiepileptic drug discovery. IEEE Trans Biomed Eng 2019;66:1231–41.

[30] Cruz-Moreira D, Visone R, Vasques-Nóvoa F, *et al*. Assessing the influence of perfusion on cardiac microtissue maturation: a heart-on-chip platform embedding peristaltic pump capabilities. Biotechnol Bioeng 2021;118:3128–37.

[31] Kulsharova G, Kurmangaliyeva A. Liver microphysiological platforms for drug metabolism applications. Cell Prolif 2021;54:1–13.

[32] Lin A, Sved Skottvoll F, Rayner S, *et al*. 3D cell culture models and organ-on-a-chip: meet separation science and mass spectrometry. Electrophoresis 2020;41:56–64.

[33] Mousavi Shaegh SA. Analysis of oxygen transport in microfluidic bioreactors for cell culture and organ-on-chip applications. Eng Rep 2020;2: 1–13.

[34] Pemathilaka RL, Caplin JD, Aykar SS, *et al*. Placenta-on-a-Chip: in vitro study of caffeine transport across placental barrier using liquid chromatography mass spectrometry. Glob Challenges 2019;3:1800112.

[35] Pelkonen A, Mzezewa R, Sukki L, *et al*. A modular brain-on-a-chip for modelling epileptic seizures with functionally connected human neuronal networks. Biosens Bioelectron 2020;168:112553.

[36] Koyilot MC, Natarajan P, Hunt CR, *et al*. Breakthroughs and applications of organ-on-a-chip technology. Cells 2022;11:1828.

[37] Hadavi D, Tosheva I, Siegel TP, *et al*. Technological advances for analyzing the content of organ-on-a-chip by mass spectrometry. Front Bioeng Biotechnol 2023;11:1197760.

[38] Optical Imaging. National Institute of Biomedical Imaging and Bioengineering | (.gov). optical- Optical Imaging. https://www.nibib.nih.gov

[39] Fluorescence Microscopy. Fuolro Finder.Sponsored fluorofinder.com. Fluorescence Microscopy - Confocal Microscopy. https://www.fluorofinder.com

[40] Encyclopedia of the Eye, 2010. ScienceDirect. co…Confocal Microscopy - an overview. https://www.sciencedirect.com›.

[41] Single-cell analysis based on lab on a chip fluidic system.Check for updatesAlireza Valizadeh†abc and Ahmad Yari Khosroushahi†*de Sponsoredthermonamic.com. Modules - Peltier Cooling - Peltier Modules. http://www.thermonamic.comThermoelectric.

[42] Trans-Epithelial Electrical Resistance (TEER). Axon biosystems. https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.axionbiosystems.com/resources/video/what-teer&ved=2ahUKEwiRmsbLpZ6BAxUYZsAKHQndDN0QFnoECCAQAQ&usg=AOvVaw0xPDLzm24crVb8sTBsLH9p

[43] Front. Bioeng. Biotechnol., 22 May 2023 Sec. Biosensors and Biomolecular Electronics Volume 11 – 2023. https://doi.org/10.3389/fbioe.2023.1197760

[44] Marthur A, Loskill P, Hong S, *et al*. Systems for high-content drug screening. 2013.

[45] Cecen B, Karavasili C, Nazir M, *et al*. Multi-organs-on-chips for testing small-molecule drugs: Challenges and perspectives. Pharmaceutics 2021; 10:1657.

[46] Cao UMN, Zhang Y, Chen J, *et al*. Microfluidic organ-on-a-chip: a guide to biomaterial choice and fabrication. Int J Mol Sci 2023;24:3232.

[47] Hwang SH, Lee S, Park JY, *et al*. Potential of drug efficacy evaluation in lung and kidney cancer models using organ-on-a-chip technology. Micromachines 2021;12:2015.

[48] Low LA, Mummery C, Berridge BR, *et al*. Organs-on-chips: into the next decade. Nat Rev Drug Discov Nat Res 2021;20:345–61.

[49] Zhang B, Radisic M. Organ-on-a-chip devices advance to market. Lab Chip R Soc Chem 2017;17:2395–420.

[50] Ronaldson-Bouchard K, Vunjak-Novakovic G. Organs-on-a-chip: a fast track for engineered human tissues in drug development. Cell Stem Cell: Cell Press 2018;22:310–24.

[51] Theobald J, Ghanem A, Wallisch P, *et al*. Liver-kidney-on-chip to study toxicity of drug metabolites. ACS Biomater Sci Eng 2018;4:78–89.

[52] Haring AP, Johnson BN. Brain-on-a-chip systems for modeling disease pathogenesis. Organ-on-a-chip: Engineered Microenvironments for Safety and Efficacy Testing. Elsevier; 2019:215–232.

[53] Jiang K, Dong C, Xu Y, *et al*. Microfluidic-based biomimetic models for life science research. RSC Adv 2016;6:26863–73.

[54] Kang TH, Kim HJ. Farewell to animal testing: Innovations on human intestinal microphysiological systems. Micromachines 2016;7:107.

[55] Vargas R, Egurbide-Sifre A, Medina L. Organ-on-a-Chip systems for new drugs development. ADMET DMPK 2021;9:111–41.

[56] Wang Z, Wang SN, Xu TY, *et al*. Organoid technology for brain and therapeutics research. CNS Neuroscience and Therapeutics. Blackwell Publishing Ltd; 2017:771–778.

[57] Cameron T, Bennet T, Rowe EM, *et al*. Review of design considerations for brain-on-a-chip models. Micromachines 2021;12:441.

[58] Lee H, Kim DS, Ha SK, *et al*. A pumpless multi-organ-on-a-chip (MOC) combined with a pharmacokinetic–pharmacodynamic (PK–PD) model. Biotechnol Bioeng 2017;114:432–43.

[59] Kilic O, Pamies D, Lavell E, *et al*. Brain-on-a-chip model enables analysis of human neuronal differentiation and chemotaxis. Lab Chip. 2016;16: 4152–62.

[60] Bang S, Lee S, Choi N, *et al*. Emerging brain-pathophysiology-mimetic platforms for studying neurodegenerative diseases: brain organoids and brains-on-a-chip. Advanced Healthcare Materials. John Wiley and Sons Inc; 2021.

[61] Kwon JS, Oh JH. Microfluidic technology for cell manipulation. Appl Sci 2018;8:992.

[62] Esch EW, Bahinski A, Huh D. Organs-on-chips at the frontiers of drug discovery. Nature Reviews Drug Discovery. at Rev Drug Discov. 2015: 248–260.

[63] Wu Q, Liu J, Wang X, *et al*. Organ-on-a-chip: Recent breakthroughs and future prospects. Biomed Eng Online. 2020;19:9.

[64] Maoz BM. Brain-on-a-Chip: characterizing the next generation of advanced in vitro platforms for modeling the central nervous system. APL Bioengineering. American Institute of Physics Inc.; 2021.

[65] Urzì O, Gasparro R, Costanzo E, *et al*. Three-dimensional cell cultures: the bridge between in vitro and in vivo models. Int J Mol Sci 2023;24: 12046.

[66] Antonelli F. 3D cell models in radiobiology: improving the predictive value of in vitro research. Int J Mol Sci 2023;24:10620.

[67] Probst C, Schneider S, Loskill P. High-throughput organ-on-a-chip systems: current status and remaining challenges. Curr Opin Biomed Eng 2018;6:33–41.

[68] Sosa-Hernández JE, Villalba-Rodríguez AM, Romero-Castillo KD, *et al*. Organs-on-a-chip module: a review from the development and applications perspective. Micromachines 2018;9:536.

[69] Jeong S, Kim J, Jeon HM, *et al*. Development of an aged full-thickness skin model using flexible skin-on-a-chip subjected to mechanical stimulus reflecting the circadian rhythm. Int J Mol Sci 2021;22:12788.

[70] Zamprogno P, Wüthrich S, Achenbach S, *et al*. Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane. Commun Biol 2021;4:168.

[71] Gong J, Meng T, Yang J, *et al*. Three-dimensional in vitro tissue culture models of brain organoids. Experimental Neurology. Academic Press Inc.; 2021.

[72] Akcay G, Luttge R. Microenvironments matter: advances in brain-on-chip. Biosensors 2023;16:551.

[73] Huh D, Matthews BD, Mammoto A, *et al*. Reconstituting organ-level lung functions on a chip. Science 2010;328:1662–8.

[74] Nikolakopoulou P, Rauti R, Voulgaris D, *et al*. Recent progress in translational engineered in vitro models of the central nervous system. Oxford University Press; 2021:3181–3213; Brain.
[75] Lee CT, Bendriem RM, Wu WW, *et al*. 3D brain Organoids derived from pluripotent stem cells: Promising experimental models for brain development and neurodegenerative disorders Julie Y.H. Chan. Journal of Biomedical Science. BioMed Central Ltd.; 2017.
[76] Danku AE, Dulf EH, Braicu C, *et al*. Organ-On-A-Chip: A Survey of Technical Results and Problems. Frontiers in Bioengineering and Biotechnology. Frontiers Media S.A.; 2022.
[77] Alépée N, Bahinski A, Daneshian M, , *et al*. t 4 Workshop Report * : State-of-the-Art of 3D Cultures (Organs-on-a-Chip) in Safety Testing and Pathophysiology HHS Public Access. 2014.
[78] Pushpakom S, Iorio F, Eyers PA, *et al*. Drug repurposing: Progress, challenges and recommendations. Nature Reviews Drug Discovery. Nature Publishing Group; 2018:41–58.
[79] Holloway PM, Willaime-Morawek S, Siow R, *et al*. Advances in microfluidic in vitro systems for neurological disease modeling. J Neurosci Res. 2021:1276–307.
[80] Fritsche E, Crofton KM, Hernandez AF, *et al*. Meeting Report: OECD/EFSA Workshop on Developmental Neurotoxicity (DNT): The Use of Non-Animal Test Methods for Regulatory Purposes. ALTEX Alternat Animal Exp 2017;34:311–5.
[81] Lantada AD, Pfleging W, Besser H, *et al*. Research on the methods for the mass production of multi-scale organs-on-chips. Polymers 2018; 10:1238.
[82] Mofazzal Jahromi MA, Abdoli A, Rahmanian M, *et al*. Microfluidic brain-on-a-chip: perspectives for mimicking neural system disorders. Molecular Neurobiology. Humana Press Inc.; 2019: 8489–8512.
[83] Frimat J-P, Luttge R. The need for physiological micro-nanofluidic systems of the brain. Front Bioeng Biotechnol 2019;7:100.