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Review Article

Mimicking the Human Body: The Rise of Organ-on-a-Chip Technologies

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A B S T R A C T

Organ-on-a-Chip (OoC) technology is transforming the way scientists study human biology by recreating organ functions on microfluidic chips. These small-scale devices replicate the conditions of human tissues, providing more accurate models for drug testing, disease research, and biological studies. Unlike traditional methods such as animal testing or 2D cell cultures, OoCs offer a more precise understanding of how organs work and respond to treatments. Advances in tissue engineering and microfabrication have led to the development of increasingly complex OoC systems. These platforms now allow for the study of multiple organ interactions, as well as the use of patient-specific cells to explore personalized treatments. Applications range from understanding diseases to testing drug safety and efficacy, with significant potential to reduce the high failure rates seen in clinical trials. As OoC technology continues to advance, its role in medical research and personalized medicine is expected to expand, offering a promising alternative to conventional testing methods and helping to pave the way for more effective therapies. The review highlights how OoCs have progressed from basic models to more complex systems, incorporating multiple cell types and even linking different organs together on a single chip. These advancements offer new insights into how the body works and how diseases develop, helping to speed up drug discovery and improve the testing of new treatments. OoC technology is also opening doors to personalized medicine by enabling experiments with cells derived from individual patients. Looking ahead, OoCs are set to become even more sophisticated, with the potential to model entire systems of the body. This could lead to more effective therapies and a better understanding of human biology, while reducing reliance on less accurate testing methods.

Keywords: Micro-engineering**,** Microfluidics, Organ-on-a-chip, Physiological microenvironments , Stem cell technologies, Tissue-on-a-chip

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INTRODUCTION

An interesting advancement in science and technology is the organ-on-a-chip (OoC), which combines microtechnology and biology to imitate important elements of the physiology of humans. The chip is shaped like a microfluidic apparatus with networks of minuscule microchannels for controlling and directing tiny volumes of solution (milliliters to picoliters). An easier way to understand OoC is it describes the mini tiny tissues that are developed and live in the microfluidic chips that have the ability to replicate one or more tissue-specific works. Despite being far more straightforward than native organs and tissues, researchers have found that these Systems can frequently function as accurate human replicas. OoCs include sophisticated in vitro techniques that make it possible to test biological cells and tissues externally. The OoC and micro-physiological systems fields have experienced significant growth following the development of early concepts such as animal-on-a-chip, body-on-a-chip, and lung-on-a-chip. In 2016, the World Economic Forum identified OoC as one of the top ten emerging technologies [1].

The capabilities of actuation and sensing in Organ-on-Chip (OoC) systems have caused shift in the design, operation, and monitoring of in vitro bioreactors and cellular biological systems. Traditional flat polystyrene surfaces in well plates and Petri dishes have been replaced. Customized chips are now used to observe organ function, tailored to replicate cellular and extracellular features and respond to biochemical and physical cues. These OoC systems allow for multi-parametric read-outs of organ function, offering insights into

the integrated biology of humans and animals. OoC technologies have significantly advanced and matured, and it is anticipated that the interest in them will continue to grow.The manipulation of fluids with precision using microscale devices is the essence of microfluidics. Initially, this field was developed by the semiconductor industry and later by the micro-electromechanical systems (MEMS) field. These devices, referred to as miniaturised total analysis systems (mTASs) or lab-on-a-chip (LoC) technologies, bring benefits such as simplifying assay protocols, reducing sample volume and costs, improving scalability for screening applications, and offering greater control over cell microenvironments.[2]

The pharmaceutical industry has a strong need for testing systems that mimic human functions, and the OoC technologies needed to develop them have reached a mature stage. Additionally, the cosmetic, food, and chemical industries can greatly benefit from OoC technologies for both production processes and testing, as there is a societal push for in vitro alternatives to animal testing that closely resemble human biology. OoC technology has advanced due to the convergence of progress in tissue engineering and microfabrication. The field of cell and tissue engineering has evolved from basic 2D monocultures to complex 3D coculture systems.

There has been a significant focus on the cellular microenvironment and geometric arrangement, allowing for manipulation of cells to achieve cell polarization, direct cell-cell interaction, and the propagation of chemical and electrical signaling. In addition to more advanced cell lines, the process of obtaining primary cell sources and incorporating them into artificial structures to enhance organ-like functions has become more reliable and robust. The emergence of induced pluripotent stem cell (iPSC) technology offers the potential for customizing Organ-on-Chip (OoC) systems, as cells specific to individual patients can be derived from iPSCs obtained from donors and integrated into the OoCs.

This allows for the examination of disease characteristics and drug reactions in a patient-specific manner.Another significant factor contributing to the success of OoCs is microsystems technology, which encompasses fabrication processes adapted from the integrated circuit industry. This method uses lithographic pattern transfer to produce structures at the nanometer and micrometer scale.

Key technological advancements in microsystems have coincided with milestones in the development of OoCs. Tissue chips (TCs), OoCs, or microphysiological systems (MPSs) are small-scale in vitro setups designed to recreate essential structural and functional aspects of organs or tissue components in a convenient layout for comprehensive analysis and control. Their aim is to offer consistent, costeffective, and highly relevant ex vivo models to facilitate the study of fundamental biological processes and enhance the effectiveness of the drug discovery process. Utilizing induced pluripotent stem cells (iPSCs) derived from patients and their offspring as cell sources enables them to potentially replicate an individual's disease on the chip for diagnostic and therapeutic testing. Consequently, these systems could become indispensable tools for personalized and/or precision applications.There have been many different single-organ systems put forth, and there are initiatives underway to create linked multiorgan platforms. Adequate models of the human immune system are needed to investigate its role in both pathogenesis and therapy. [3]

NEED FOR ORGAN ON A CHIP

Drug discovery and development is a long, expensive, and high-risk process that takes more than 10 to 15 years and costs an average of more than $1.2 billion for each new drug approved for clinical use.For any pharmaceutical company or academic institution, it is a great achievement to advance a drug candidate to Phase I clinical testing after drug candidates have been rigorously optimized in the preclinical stage. However, 9 out of 10 drug candidates that enter clinical trials will fail during Phase I, II, III clinical trials and drug approval.

It is also worth noting that the 90% failure rate refers to drug candidates that have already moved into clinical trials and does not include drug candidates that are in the preclinical stage. If we also consider drug candidates at the preclinical stage, the failure rate in drug discovery/development even exceeds 90 % [4].In recent years microfluidic chips have gained more importance in the process of drug discovery. The biggest reason for increased interest in ooc is that most drugs which enter clinical trials failed to become approved medicines as current preclinical tools such as conventional methods, 2D cell culture and animal models are not always effective tools to predict drug safety and efficacy.

This dearth between human and animal data has been a major challenge for the pharmaceutical industry. Laboratory conditions, such as housing and diet, can affect the biology of animal models, leading to results that may not be applicable to human diseases. Many preclinical studies use young, healthy animals, which do not accurately represent the age and health profiles of human patients suffering from chronic diseases.

The complexity of human diseases, including comorbidities and the effects of aging, is often inadequately modeled in animal studies, resulting in overestimated treatment effects. Ooc models can be used for disease modeling during the early discovery process, identifying novel drug targets and understanding the mechanisms underlying disease processes. Ooc has the potential to create patient-on-a-chip enabling position medicine with the response of an individual being predicted and treatments recommended. [5]

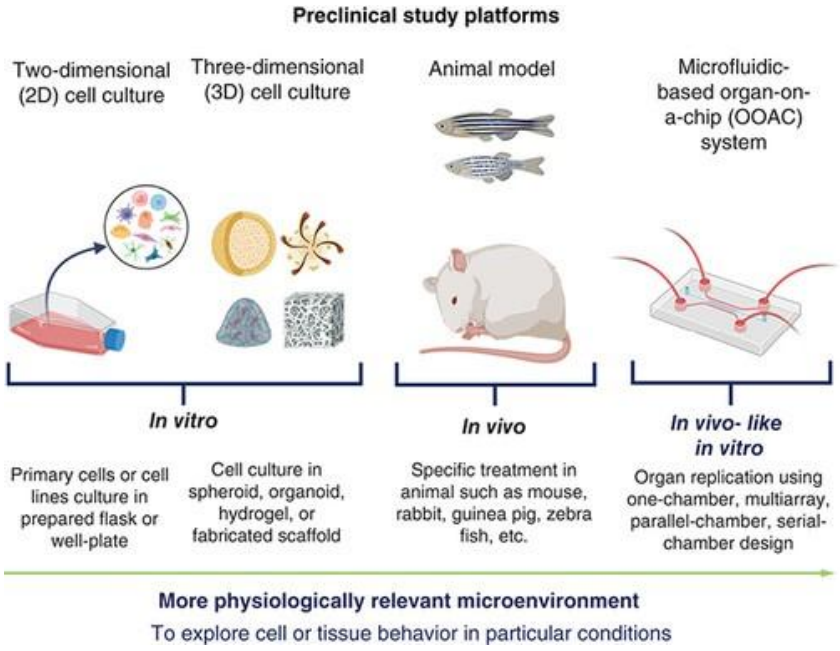

Figure1: Schematic diagram showing the preclinical models used in biomedical research.

MICROFLUIDICS - MATERIALS AND METHODOLOGY

Microfluidics cell culture techniques are able to mimic microenvironments as well as their influence on organ function. Cultivating cells in microfluidic devices necessitates comprehension of essential principles that encompass various fields such as biology, biochemistry, physics, and engineering. Understanding the crucial aspects of the cellular microenvironment is essential for the development of in vitro models that closely replicate in vivo conditions. Secondly, having a command on the techniques in cell culture to aid translation from macro to micro scale. When designing microfluidic cell culture systems, it is crucial to consider the following: (1) the material used for device fabrication, (2) the shape and size of the culture area, and (3) the method for pumping and controlling fluid flow. The last aspect determines how the microfluidic device is linked to the external components of the entire system. Although microfluidics provides engineers and biologists with extensive flexibility in system and experimental design due to numerous options, it also means that experiment participants need to be familiar with all available choices to optimize designs based on the specific application. [6]

MATERIALS

PDMS -The materials utilized for creating microfluidic systems have advanced to enhance their functionality. Initially, microfluidic systems were produced using glass and silicon. However, the fabrication of glass/silicon involves intricate etching processes and is essentially restricted to very flat, passive devices. The advent of soft lithography—a set of methods centered on molding the elastomer poly dimethylsiloxane (PDMS)—enabled the production of affordable polymeric devices and, for nearly the same cost, the incorporation of valves and pumps. Currently, the majority of microfluidic systems are still crafted from PDMS. PDMS is a cost-effective material that is simple to shape; its physical and chemical properties are ideal for applications in biomedical and physical sciences, and its design cycle durations are typically sufficient for prototype development. For the production of valves and pumps, PDMS is more advantageous than plastics due to the Young's modulus of PDMS being about 1000 times smaller than that of rigid plastics (allowing PDMS valves and pumps to be constructed smaller and faster than their plastic equivalents).[7]

Thermoplastics- The performance of synthetic and natural polymers in OOC applications depends on factors such as polymer structure, porosity, transparency, flexibility, and stiffness. For the preparation of porous-compartmentseparation membranes, synthetic polymers like polycarbonate (PC), polyethylene terephthalate (PET), polystyrene, polymethyl methacrylate (PMMA), aliphatic polyesters, and polyurethanes have been utilized due to their ability to easily adjust porosity, surface roughness, and mechanical properties. Natural polymers such as collagen, gelatin, or polysaccharides have gained attention recently for their improved biocompatibility and ability to faithfully replicate native tissues with channel interconnections that facilitate the perfusion of oxygen and nutrients, simulating natural cell behaviors like differentiation, spreading, and adhesion along the separating membrane. [8]

PC is commonly utilized in OOCs and is frequently used for creating porous filter membranes and membranes in Transwell inserts. OOCs have implemented PC membranes sourced from Transwell inserts. PC is hydrophobic, seethrough, chemically inert, and non-biodegradable. To allow cells to adhere and grow on PC, the surface is often modified through protein coating or gas plasma treatment, similar to PDMS. PC, however, is a rigid polymer with a Tg of 1458C and a Young's modulus of 2–2.4 GPa. Consequently, PC is not suitable for OOCs that require membrane stretching or for culturing tissues that require a

soft substrate. PC has many applications in OOCs like studies on blood brain barrier, skin liver, gut.

PET membranes are frequently used in OOCs and microfluidic cell culture systems, either as direct membranes or porous filter membranes. PET is transparent, inert, and non-biodegradable, but it does require treatment to enhance cell adhesion, such as plasma treatment. It has a Tg of 70°C and a Young's modulus of around 2 – 3 GPa. Similar to PC, PET is not suitable for OOCs that necessitate mechanical strain on the cells. Nevertheless, it has been employed in OOCs simulating the gut, as well as in studies involving endothelial cells , fat , liver, and kidney.

PLA and PCL, which are aliphatic polyesters, have been utilized in laboratory models imitating the blood-brain barrier. Both of these polymers are biodegradable and hydrophobic. This characteristic could make them suitable for serving as a temporary membrane that is later replaced by the extracellular matrix of cells to form a completely natural cell layer. However, it's important to consider that due to the degradation, the pores of the membrane might change over time. Additionally, the acidic degradation products of these esters could potentially impact cells. The Tg (glass transition temperature) of PLA and PCL varies significantly, at approximately 55 – 65°C and 26°C, respectively. Consequently, PCL is in a more flexible state at room or body temperature compared to PLA.The PCL has a Young's modulus of 400 MPa, , while PLA has a modulus of 3 – 4 GPa. The high modulus of PLA makes it inappropriate for membranes that will experience mechanical strain.(pasmen)[9]

Cyclic olefin polymers (COP) and cyclic olefin copolymers (COC) are types of polyolefins used in the production of microfluidic devices due to their lower gas permeability compared to PDMS. These materials are resistant to lipophilic substances and do not attract small molecules, making them suitable for drug development and diffusion studies. Additionally, they offer optical clarity, strong resistance to polar solvents, thermal stability, and consistent mass production.

Hydrogels are polymeric materials with high water content that can mimic the essential elements of the natural extracellular matrix (ECM), and therefore have high biocompatibility and tunable properties such as elasticity, porosity, permeability, hardness, and degradability. The properties of these hydrogels vary widely depending on the type, gelation method and manufacturing technique. Hydrogels can be broadly divided into natural, synthetic and hybrid, depending on the source. Typical natural hydrogels include collagen, alginate, gelatin, agarose, and fibrin. They are generally highly biocompatible and contain cell binding sites for cell attachment, spreading, growth, and differentiation. Collagen is the most abundant ECM component in the body and one of the most widely used hydrogels for bioengineered tissue microenvironments. Gelatin has a similar composition to collagen. Methacryloylgelatin (GelMA) hydrogels are close to some fundamental properties of native ECMs and can be microfabricated using various methods. In recent studies, ECM hydrogels have been used to provide support for decellularized tissue, a microenvironment for long-term culture of islets and direction of cell proliferation. Synthetic hydrogels include polyethylene glycol (PEG) and its derivatives. [10]

Gelatin is an animal protein produced by the hydrolysis of collagen and is widely used in drug delivery and tissue engineering due to its ability to transport drugs and stimulate cell growth. Gelatin is biocompatible and flexible, and can also form complexes with proteins, growth factors nucleotides and biopolymers into colorless gels. Additionally, photocrosslinkedgelatin methacrylate (GelMa) is widely used in tissue engineering and has been shown to be beneficial for OOC formation. [11]

Collagen-based ECM gel (known as Matrigel) is a commercially available product that contains an ECM hydrogel made from tumor-derived basement membrane proteins used for cell culture. Matigel gives structures and signals. Tumor cells are often used to show aggressive actions in the matrix environment, evaluate malignant tumors in cancer cells, and monitor the mechanism of tumor growth. Bacterial cellulose paper is also of interest for its application in tumor-on-a-chips, as it is a naturally derived polymer with excellent biocompatibility and dense vascularity due to nanofibers. Recent advances in bioprinting have multiplied the methods for creating complex perfusion systems, and the discovery of new materials that fully meet the requirements of native cells is still under extensive development. [12]

METHODOLOGY

The art of miniaturizing devices, or microfabrication, is entirely distinct from traditional machining and manufacturing. Adding or removing materials, patterning the substrate to produce the required geometry, and carrying out other tasks all require different techniques. The most common methods of manufacture of microfluidic devices are photo lithography, soft lithography [6], 3D printing,[13],hot embossing. [6]

Soft lithography

A popular method for creating microfluidic devices,[14]PDMS casting or soft lithography has the advantages of being simple to use and biocompatible. However, because casting, peeling, and bonding require physical effort, bulk manufacture is difficult. It's becoming common practice to 3D print molds for PDMS devices, surface roughness needs to be taken into account. It could be required to coat the surface of the 3D printed template before PDMS casting in order to promote peeling and avoid polymerization inhibition. An alternative, albeit less popular, is to dissolve the template after molding. By creating parts that can be maneuvered out of vacant areas or by selectively tearing the PDMS during template removal, PDMS soft lithography may take full advantage of 3D printing technology. [15]The advantages of soft lithography are combined with the capacity to fuse several patterned elastomer layers together in multilayer soft lithography. With the use of this technique, monolithic three-dimensional buildings are made completely of elastomer. [16]

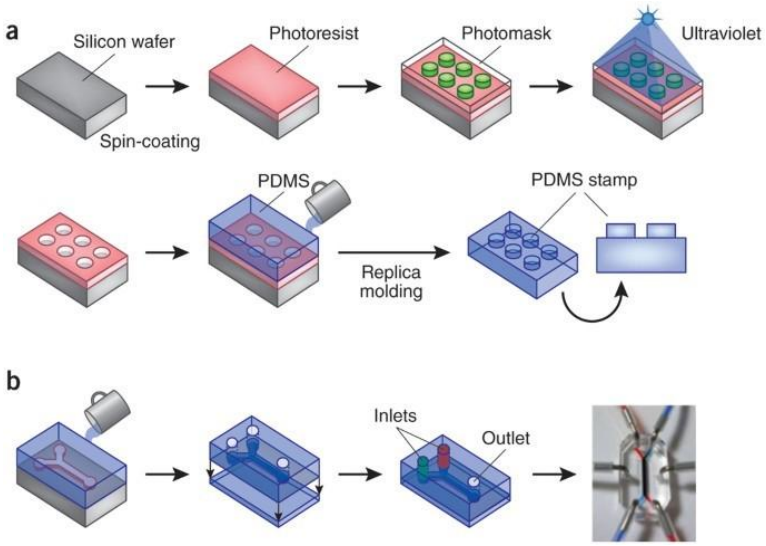

Figure 2: Fabrication methods of microfluidic chips, a) Photolithography, b)Soft lithography

3D printing

A series of manufacturing procedures known as the ―layer-by-layer approach‖—which involves adding layers of material to a product by laying them from the bottom to the top—are collectively referred to as three-dimensional printing.[13] 3D bioprinting has been utilized to create bone, cardiovascular, cartilage, corneal and neural constructs in animal species.[17] It has been first developed by Charles Hull in 1984[18] The known techniques of 3D printing are discussed below.

Stereolithography

Stereolithography (SLA) essentially involves UV-triggered photopolymerization in a liquid bath which is dependent upon a computer controlled laser beam. [19] With the presentation of a patent by Swainson for the use of intersecting radiation beams and photochemical processes to create three-dimensional objects, the first noteworthy work in contemporary stereolithography AM systems appeared in the 1970s. Four generations of stereolithography have been developed which are Laser scanning stereolithography, projection stereolithography, continuous stereolithography and volumetric stereolithography. The most recent is volumetric stereolithography, which produces intricate 3D things quickly. In this summary, other technologies such as color and thermal stereolithography are not covered. [20] Digital light processing (DLP) stereolithography

A digital micro-mirror device (DMD) is used in DLP, an alternative method for crosslinking photo-curable bio-resins, to enable the instantaneous crosslinking of a layer of resin rather than a single dot as in SLA. To make photocrosslinking of images easier, these DMDs are big arrays of micro-mirrors that can be turned to be in either a ―on‖ or ―off‖ position. A coating of bio-resin. As a result, the build time is significantly reduced because it depends solely on the layer thickness and the necessary amount of exposure time. The energy of the light in the DLP system that the resin is exposed to determines the cure depth for each specific bio-resin. The power of the light source can be changed to control this energy.[21]The smallest feature size recorded using DLP method is 0. 6 µm, with resolution as low as 25 µm. Resins including ceramic particles are printed with 40 µm lateral resolution and layer heights of 15 µm. Using a digital micromirror device (DMD) as a dynamic mask, DLP simultaneously illuminates the full layer cross-section. The DMD, which is made up of mirrors for every pixel, enables quick switching for accurate light cross-section projection.

[22]

Inkjet Printing Process

For liquid-phase materials, inkjet printing is a material-saving method used. These substances, referred to as inks, are made up of a solute combined with a solvent. Using piezoelectric action to quickly lower the chamber capacity, a nozzle is used to discharge a predetermined amount of ink from the chamber. A shockwave is produced as the liquidfilled chamber shrinks as a result of an external voltage, ejecting a drop from the nozzle. Gravity and air resistance cause the dropped liquid to spread out across the substrate before the solvent evaporates and dries. According to recent research, the viscosity of the ink has a significant impact on the printed drop's ultimate shape. Conventional inkjet printing techniques consider ink to flow like a Newtonian fluid, however this may not be accurate. [23,24] Among the several additive manufacturing processes, inkjet technology is thought to be the fastest and most economical. Still, it's also regarded as the least precise one. [25]

Extrusion based lithography

Using computer-aided design (CAD) data, solid freeform fabrication, also known as rapid prototyping (RP), is a technique for layer-by-layer item creation. 3D models or

clinical imaging such as CT or MRI scans can be used to characterize the scaffold's internal and exterior structure. Extrusion-based bioprinting (EBB) is a prominent RP technology that uses bio-inks to create 3D tissue constructs. Its benefits include reduced cell damage, faster printing speeds, and higher cell seeding densities. EBB uses a variety of crosslinking processes to print diverse bio-inks into aggregates with high cell density. EBB allows for the simultaneous use of multiple bio-inks for the creation of complex tissues. [26]The two primary techniques for producing heterogeneous tissues in biofabrication are top-down and bottom-up approaches. The bottom-up method uses self-assembly to assemble microscale building elements, such as cells, to create tissues. Nevertheless, this approach has limits when it comes to regulating tissue architecture and establishing particular cell habitats. Conversely, the top-down approach, which frequently makes use of 3D printing technology, builds macroscale scaffolding first, then cultivates cells on them to generate tissues. A variety of 3D printing methods, including extrusion-based 3D printing (E3DP), provide affordable means of creating intricate tissue architectures out of a variety of biomaterials. [27]

Embossing and injection modeling

By imprinting or injecting softened polymer into molds, embossing and injection molding produce microstructures in thermoplastic polymers. These high-throughput, reasonably priced methods are perfect for production, such as making CDs out of polycarbonate. They are currently being investigated for the purpose of fabricating metal and semiconductor nanostructures for microelectronic circuits. Applications that are successful point to the necessity of reevaluating high-resolution printing techniques and current microfabrication techniques for high-resolution patterning. [27]

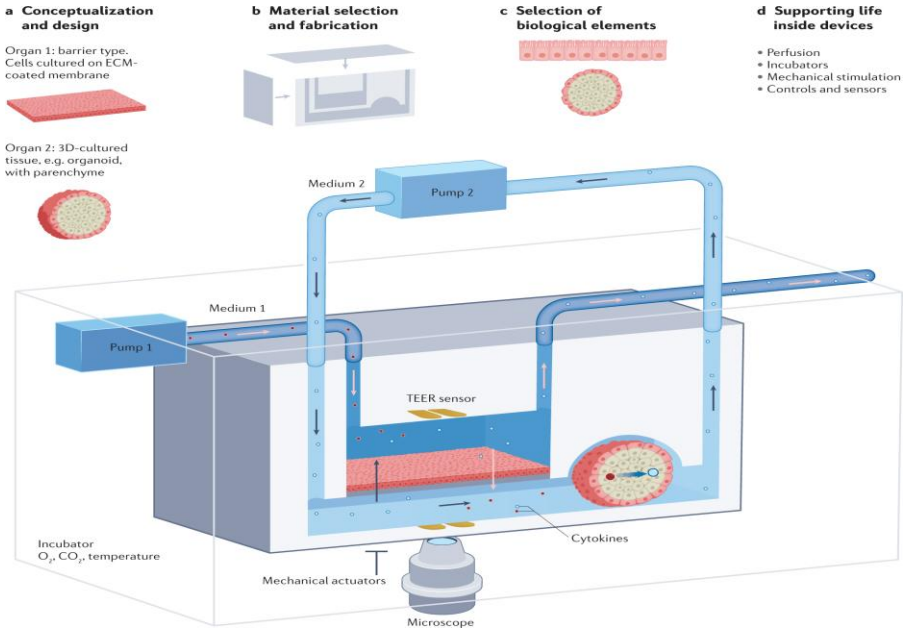

Figure 3: Process of fabrication on microfluidic chips

Types

Brain on a chip

The physiological and pathological activities of the CNS in NDDs have been studied using a variety of neural system models, including animal models, 2D and 3D cell cultures, and clinical investigations. Nonetheless, investigators must overcome many obstacles that restrict the different models. In order to better understand how the CNS and NDDs function, animal models are crucial, even if they frequently are not applicable to humans in general. For example, the brains of rodents have a simpler structure and several mental processes. Some transgenic animal models of human diseases may not provide the physiopathological features of the human neural system and NDDs. As such, significant differences at the molecular and cellular levels exist between rodents and humans. It has been reported that many clinical trials in humans have failed despite promising results that were achieved in preclinical studies on animal models. Traditional two-dimensional (2D) monolayer cell culture has been widely used for the discovery of therapeutic molecules and prediction of their side effects, including nano-drug delivery.However, these models have a poor ability to assess drug responses in complex diseases, and they cannot fully simulate the physiological condition of tissue microenvironment. [28]."Bbb-on-A-chip", OOC system can effectively imitate human functional units brain. Thanks to the integration of advanced micro -free technology, it is now possible. To develop an OOC device that can be performed in a joint culture with the multi -cholic improvement camera. Many types of cells when activating a flow system that stimulates blood circulation. Thus, compared with conventional 2D in vitro models, the BBB-on-a-chip can better mimic the highly dynamic brain microenvironment with physicochemical cues essential for NVU formation and maintenance. Furthermore, unlike animal models, the BBB-

on-a-chip can be easily adapted to humans with welldefined and highly controlled microenvironments, allowing it to isolate and establish the roles of specific factors.[29] Bbbooc often consists of two compartment separated by a thin membrane, with a couple compartment is aligned with endothelial brain cells, while the brain compartment is formed with pericytes and astrocytes. Trans-epithelial electrical resistance (TEER) values through the BBB OoC are usually obtained as a measure of barrier integrity. The BBB OoC should be engineered to have TEER values within an appropriate range (~1500-8000 ohm.cm2).It has physiological value in drug functional studies and disease modeling. Conducting long-term studies In this framework, it is necessary to culture the BBB OoC in hypoxic conditions to maintain the integrity of the BBB for a long period (up to 1 week). Spinal cord OoC recapitulates the blood-spinal cord barrier and resembles the BBB-Chip. Spinal cord OoC may have a similar compartmentalized design, but as with BBB OoC, important biological differences prevent their interchangeable use, as the role of the blood-spinal cord barrier and the BBB are similar. Instead of using pericytes and astrocytes in the brain region, spinal cord OoCs comprise cells capable of differentiating into spinal motor neurons such as iPSC-derived spinal cord neural progenitor cells. Applications involving neurotoxicity testing or modeling of human brain diseases will require OoC systems, which support not only the survival of neurons and glial cells, but also their electrophysiological functions. The electrophysiological function of neurons can usually be visualized using calcium currents, while the presence of glial cells can be confirmed by looking for the corresponding neuronal markers. The main types of glial cells in the CNS include astrocytes and microglia, which can be identified by screening for GFAP and CD45, respectively.[1]The use of iPSCs cells within 3D brain models can reveal the complex physiology and function of the brain, including migration, neuronal differentiation, network elaboration, cell-cell interactions, myelination, and synapse formation.. Neuronal differentiation is a complex process, and various techniques have been developed to measure it. MEAs are a promising tool for electrical activity measurements, and cell-specific markers or biochemical assays can be used to assess glial maturation and function. [30].

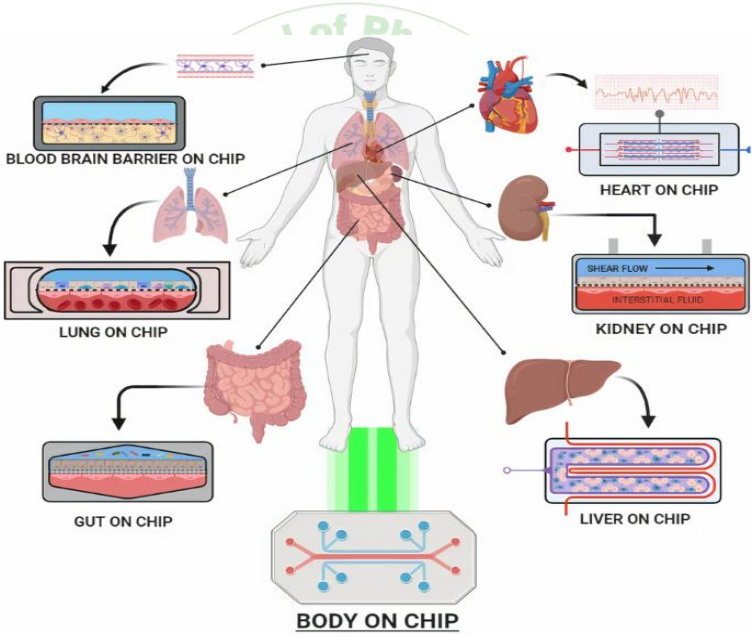

Figure 4: Types of organ on a chip.

Kidney on a chip

The kidney is responsible for the maintenance of osmotic pressure drug excretion. Kidney toxicity leads to an irreversible loss of renal filtration highlighting the need for drug screening systems. Filtration and reabsorption occur in the nephron, glomerulus, renal capsule, and tubule. Microfluidics can mimic the fluid medium that supports tubular cell growth and the porous membrane to maintain cell polarity. Conventional two –dimensional (2D) Cellular culture, absent physiological micro-infection, for exampleThe extracellular matrix (ECM) and the fluid shift voltage (FSS) do not save Irreplaceable characteristics of in vivo cells, which makes them Inadequate forecasting models . OOC technology solves this restriction by providing a flow of fluid, mechanical signals, and the calendar of the body level, ensuring the reconstruction of the three Dimensional structures (3D) of organs and the physiological environment with facilitation of dynamic observations of physiology or Physiopathological process.[31] Over the past few years, biometric microfluidic devices have been developed to mimic the action of various functional units of kidney like glomerulus on a chip, proximal tubule on a chip,distal tubule on a chip,collecting duct on a chip,nephron on a chip. [31,32].Unlike PT cells, few studies have investigated the physiology of distal tubule and cortical collecting duct cells cultured on a biomimetic platform.PT cells have high energy requirements and are therefore particularly sensitive to drug toxicity.The development of in vitro models of proximal tubule function is of great interest to drug developers. The

high absorption and transport of molecules allows the transport of drugs and chemicals that accumulate in PT cells and in the intercellular space.Various 2D models of PT cell culture are valuable for studying nephrotoxicity of drugs like cisplatin, specifically in the proximal tubule cells. These models can also help in exploring cimetidine-mediated recovery post cisplatin-induced dysfunction. To better mimic in vivo physiology, 3D culture models and organoids have been developed, yet they have limitations such as lack of natural flow dynamics. Recent focus has shifted towards integrating microfluidic technologies into 3D models for improved reliability in screening nephrotoxicity and studying drug-induced tubular dysfunction effectively. [33]

Lung-on-a-chip

Gas exchange in lungs is regulated by the alveoli, but this is difficult to replicate outside the body. Microfluidics can create in vitro lung models with accurate fluid flow and robust gas exchange. They created a model of pulmonary edema by delivering inflammatory stimuli such as interleukin-2 via neutrophils, demonstrating the potential of organon-a-chip models to improve in vivo studies. Several studies have used lung chips to mimic lung parenchyma, airway culture models, and respiratory expansion with microfluidic systems. These models allow for deeper physiological studies of the lung environment and can be used for modeling chronic lung diseases, tissue engineering, and precision treatment of lung tumors. An organ-chip based on lung tissue has also been designed as an implantable respiratory support device. They developed a device to support the lungs of premature infants using large diameter channels of the umbilical artery and umbilical vein to increase gas exchange in case of respiratory failure. Furthermore, a microfluidic artificial lung was created to improve oxygen intake, and a microfluidic chip platform has been used to simulate lung cancer and asthma for drug testing purposes. Generally, the pulmonary model on the chip provides a promising approach to study lung physiology and the pathology of the disease, functions as a potential tool for treatment development, and improves respiratory support technology. [34].Microfluidic lung-on-a-chip models are valuable tools that can mimic the in vivo lung environment. These devices, based on microfluidics technology, allow for precise control of physical and chemical properties using small volumes. They offer benefits such as fast mixing speeds and the ability to create concentration gradients and control shear force. While many lung-on-a-chip models focus on replicating the alveoli, there is a need for models that incorporate cell types found in the sub-mucosa layer to better study lung biology and diseases related to this region. The cell selection process is essential for creating in vitro models that include key cell phenotypes and enable natural interactions. The lung has about 40 cell types, making modeling challenging. Choose cell types, origin, and structure that reflect the region of interest for more accurate models, preferring primary cells over cell lines for in vivo-like characteristics.The epithelium is the physical barrier of the respiratory pipe and plays a role in the balance of the liquid, immunity, and the repair of cloth. Various areas have a variety of epithelium compositions, such as fibroids, club boxes, and cells. Lung-on-a-chip models recapitulate the cellular composition of pathological conditions such as COPD. The sub-mucosa beneath the epithelium contains fibroblasts, myofibroblasts, and neurons that support repair, inflammation, and remodeling. The pulmonary microvasculature delivers oxygen, nutrients, and removes waste, while endothelial barriers regulate passage for gas exchange and immunity. Microfluidic devices in lung-on-a-chip models mimic the forces acting on endothelial cells to support the immune response. Mimicking physiological interfaces such as tissue-tissue and air-liquid interfaces is essential for in vivo structures and phenotypes. Most chips use microfabricated features to create microstructures with physiological dimensions and porous membranes for nutrient exchange and intercellular communication. Hydrogels enhance the three-dimensionality of on-chip lung models. In conclusion, the selection of appropriate cells and the replication of physiological interfaces are key aspects in creating accurate in vitro lung models. These models have shown promise in replicating region-specific phenotypes using primary cells and advanced microfabrication techniques to mimic in vivo structures and functions for studying lung development, diseases, and personalized medicine. [34]

Heart on a chip

Cardiac tissue engineering presents challenges in translating research from the lab to the clinic. Cardiac organoids, such as hearts-on-chips, are essential for modeling pathology, cardiotoxicity, and therapy. Mature cardiomyocytes have limited self-renewal capacity, making induced pluripotent stem cells attractive for differentiation. Aligning cardiomyocytes into bundles is essential for tissue development. Microbial network is required for oxygen and nutrients. Various approaches, such as a soulroid without a frame or framework method, are being studied, and a functional organizational structure has been created. Sufelloids are easy to manufacture, but frames based on frames support cell memberships better. The architecture of the frame modulation can enhance fabric relevance. Anisotropic scaffolds are capable of generating highly oriented cardiac fibers. [35].Four components make up the highly integrated heart-on-a-chip: microfluidic chip, cells/microtissues, microactuators for chemical and physical stimuli, and microsensors. for tracking the condition of cells. In actuality studies, a heart-on-a-chip might not have every the microfluidic chip and these four components, but Microtissues and cells are required. During the past few years, with technological developments in manufacturing such as 3D microactuators, microsensors, and bioprinting have been incorporated into the chip for a heart. The objective behind microactuators is to encourage the maturation of heart cells and functionality, whereas the purpose of microsensors is to identify cells standing.[36] To enhance the analysis of cardiac functionality, heart-on-a-chip systems now include advanced microsensors that enable real-time monitoring. These systems primarily focus on two key aspects:

Electrophysiological signals and **cardiac contractility**.

1. **Electrophysiological Signals**: These signals are crucial for understanding heart function. Microelectrode arrays

(MEAs) are used to record extracellular action potentials and track their propagation across the cardiac tissue. For intracellular recordings, nanoscale electrodes are used to improve signal clarity, allowing for a more detailed analysis of cell membrane activity.

2. **Cardiac Contractility**: To assess contractile behavior, techniques such as micro-pillar arrays and micro-cantilevers are utilized to measure the forces generated by individual cardiomyocytes or larger cardiac tissues. These methods provide high precision and sensitivity, enabling accurate measurement of contraction force, frequency, and coordination.

By incorporating biocompatible microsensors, heart-on-a-chip systems allow for precise, real-time monitoring of both electrical and mechanical functions, improving our understanding of heart diseases and the effects of drugs.[37]

Liver on a chip

Various liver chip models have been developed to model drug metabolism, drug interactions, hepatotoxicity, inflammation, and infection. These chips accurately reproduced metabolic processes, inflammatory responses, and drug interactions observed in humans. They also demonstrated donor-to-donor variability in drug metabolism and liver function. One important application of Liver-Chips is modeling human-specific hepatotoxicity, which is often missed in animal models. The liver chip reproduces liver toxicity, such as hepatocellular injury, fat, bile, and fibrosis. [38] The hepatic system is a key site for drug and toxin metabolism, with complex hepatic lobules allowing functional communication. Maintaining hepatocyte physiology is challenging over time periods. Various innovative liver-based systems have been designed, such as microfluidic pores co-cultured with fibroblasts and rat liver cells mimicking an airway interface. Other techniques include chips that mirror endothelial cell structures and 3D hepatocyte culture techniques using microfluidic chips. These systems are used to study drug toxicity, liver tumors, viral replication like hepatitis B, alcohol injury, and to improve disease models for anti-cancer pharmacological studies. Characterization of cytoplasm through advanced analysis methods will enhance the functional outcomes of these studies, offering valuable insights for drug screening and disease modeling. [39].Most drugs are metabolized by enzymes that are highly expressed in the liver, making the liver vulnerable to drug-induced damage. Conventional 2D cell culture conditions do not accurately reflect drug metabolizing activity. The liver on the chip maintains these actions and can use BI processes to evaluate the injury in real time. The liver shaving is designed to cultivate human cells and evaluate damages induced by drugs such as bile, oxidative stress, and liver fat. These chips can accurately predict species-specific toxicity and provide insight into drug-induced liver injury. Liver microarrays play an important role in drug screening, and platforms like MPCC have shown improved drug metabolism capabilities. High-performance systems for toxicology studies have been developed. These chips accurately classify hepatotoxic drugs and reduce drug-related side effects. Alcoholic liver disease can lead to liver fibrosis and cirrhosis due to excessive alcohol consumption. A liver-on-a-chip was developed to mimic the effects of alcohol on hepatocytes and hepatic stellate cells. These chips can monitor TGF-β secretion and ROS production, which can help understand the progression of alcoholic liver disease. Abstaining from alcohol can prevent the progression of alcoholic liver disease, and liver-on-a-chip provides a platform to study the effects of alcohol exposure and recovery. These chips can be used to study varying degrees of severity of alcoholrelated liver disease, highlighting the impact of alcohol abstinence on liver health. Liver-on-a-chip accurately mimics the reversible and irreversible damage of alcoholic liver disease, providing insight into therapeutic targets and drug development for these conditions. These chips will be valuable tools for studying the mechanisms behind alcoholinduced liver injury. Non-alcoholic fatty liver disease (NAFLD) is a fatty liver disease not caused by alcohol or viral infection and is strongly associated with obesity. NAFLD can be classified as simple steatosis or nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and cancer, necessitating therapeutic intervention. The Liveron-a-chip model successfully reconstituted NAFLD in patients by inducing fatty acid steatosis and ROS production, and drug treatments such as metformin and pioglitazone reversed lipid accumulation in these models. Another liver-ona-chip model mimicked the progression of NASH, showing increased lipid accumulation and altered gene expression under lipotoxic conditions, with promising agents such as obeticholic acid and elafibranor showing beneficial effects. Liver-on-a-chip platforms are also being used to study the effects of genetic variants on NAFLD/NASH severity. Infectious liver diseases like hepatitis B and hepatitis C can also be studied using liver-on-a-chip models. For HBV, models using human hepatocytes and endothelial cells have demonstrated effective immune and infection responses, and other studies have demonstrated the importance of nonparenchymal cells such as Kupffer cells in the immune response to viral infection. These results highlight the potential of liver-on-a-chip models for understanding liver disease and testing therapeutic interventions. Overall, liver-on-a-chip technology provides a valuable tool for studying liver diseases such as NAFLD, NASH and viral hepatitis. These models allow researchers to recreate disease conditions, test the efficacy of drugs, and study the role of genetic and immune factors in liver pathology. Liver-on-achip models have shown promise in studying infectious liver diseases such as NAFLD, NASH, and Hepatitis B. [40]

Intestine on a chip

To reach the bloodstream, oral medications need to move through the small intestine, where absorption is aided by villi. Several studies have created chips that imitate the gastrointestinal system, with features like permeable membranes and channels for growing Caco-2 cells. Scientists have also developed 3D hydrogel formations and bionic tools to mimic human intestinal villi, replicating a complex setting similar to the human intestine. These developments offer a foundation for conducting drug screenings and studying the influence of the intestinal microbiome, inflammatory cells, and mechanical deformation in intestinal diseases. The chips enable research on the causes of intestinal diseases,

pinpointing therapeutic targets, and testing drugs, presenting opportunities for personalized medicine. When paired with endothelial cells such as HUVECs, these chips effectively replicate intestinal function, providing valuable information on the intestinal microbiome and structure. Recent research has improved our knowledge of intestinal tissue engineering and the biological models of the human duodenum. [39]. First intestine-on-a-chip microfluidic devices were created using soft lithography and PDMS chips, allowing for nutrient distribution and waste removal. Mechanical cues led to villi formation and differentiation of different epithelial cells. Microfluidics improved barrier integrity and tight junction functioning compared to traditional static cultures. Fluid shear stress was found to affect cell differentiation and function in intestine-on-a-chip models. Peristaltic-like motions induced by a PDMS chip increased protein expression related to metabolism and signaling pathways. Combining intestinal epithelium cells with endothelium in microfluidic devices showed promise in mimicking the in vivo intestine.

Different approaches, such as using extracellular matrix hydrogels or hollow fiber membranes, were explored to study barrier integrity and metabolic capacity. Microfluidic devices were developed to maintain tissue barriers between apical and basolateral compartments, with intact barrier integrity demonstrated by FITC-labeled molecules.

While some models allowed for interaction with microbes and immune cells, limitations existed based on the age and species of the intestinal tissue used, such as young mice. Mimicking the architectural structure and dynamic microenvironment of the in vivo intestine is crucial for studying normal intestinal function in vitro.(intestine)[41]

Microfluidic devices with hollow microchannels less than 1 mm in width allow for precise control of fluid flow in nanoliter to microliter volumes, making them ideal for culturing living cells. The Gut Chip is made of a flexible, transparent polymer that enables high-resolution imaging and contains two parallel microchannels separated by a thin membrane coated with cells to recreate the tissue-tissue interface. The Gut Chip model can induce villus morphogenesis, establish a crypt-villus axis, and exhibit drug metabolizing activity, mucus production, and glucose reuptake similar to the living intestine.

Importantly, continuous fluid flow in the Gut Chip allows for prolonged culture times and the ability to co-culture living commensal microbes or probiotics directly with the intestinal cells. This advanced model provides a more accurate representation of the human intestine's 3D structure and function, making it a valuable tool for studying host-microbial interactions and intestinal pathophysiology. The previous models had limitations such as short culture times and lack of real-time barrier integrity assessment. To address these limitations, a more advanced Gut Chip model has been developed that incorporates human intestinal epithelium, capillary endothelium, immune cells, and commensal microbial cells. This model allows these different cell types to grow and interact in physiologically relevant conditions, including fluid flow and mechanical deformations similar to peristalsis.[42]

Within the luminal channel of the parenchymal tissue for weeks, in vitro studies have shown that barrier function can increase with the presence of L rhamnosus GG, without compromising cell function. In dynamic conditions, such as those mimicked by the Gut Chip model, gene expression profiles in human intestinal cells change significantly compared to static cultures. [43]

Skin on a chip

Organ-on-chip technologies have led to the development of skin-on-a-chip models, which are microfluidic devices that culture skin tissue under controlled conditions. The devices vary in fabrication process and tissue maintenance, with two main approaches: transferred skin-on-a-chip and in situ skin-on-a-chip. In device-transfer skin-on-a-chip models, skin fragments from biopsies or in vitro equivalents of human skin are introduced into the device. These models provide a more realistic representation of the layers of the skin. For example, one study used a single tissue transferred to a skin chip to study neutrophil responses to bacteria on the skin. Some models use commercially available skin counterparts, while others use human biopsies. These models were used to test drugs and clinical edges.

The skin sent to the chips is also used for the multiple organic development of chips, and research shows the intersection between different organizations and the sensitivity to the toxicity of drugs. For example, a four-organ system including skin modeled from a human biopsy successfully maintained cell viability for 28 days. [44] Perfusion of culture media in microfluidic devices is essential for sustaining cell growth through waste removal and nutrient replenishment.

Fluid flow-induced shear stress also impacts cell function, influencing both blood vessels and skin tissue. Pump-based systems provide accurate flow regulation but are intricate and susceptible to contamination, whereas gravity-based systems are straightforward but lack precision. Research on cell stretching began in the 1970s, with a particular focus on dermal fibroblasts and keratinocytes.

There is a lack of skin models containing both types, as well as research on the impacts of shear stress and cyclic stretch. Stretch models have the ability to replicate aging impacts and evaluate antiwrinkle therapies. Microfluidic systems provide a more accurate representation of human tissue, featuring flexible skinon-a-chip devices. Vascularization plays a vital role in providing nutrients to skin tissue in regenerative medicine, utilizing autografts, allografts, and xenografts as choices for skin grafts.

The main goal is to improve protocols for creating functional blood vessels in skin tissue engineering. [45] The skin-on-a-chip model has the potential to be utilised in creating in vitro skin disease models or for evaluating the toxicity of cosmetics or medications. [46] The innovative microfluidic device provides a new method for conducting skin penetration studies, providing a dependable and affordable system for pharmaceutical research and development. [47] The skin is made up of four primary layers: the stratum corneum, epidermis, dermis, and hypodermis. Medications that are put on the skin can pass through hair follicles,

sebaceous glands, and the outermost layer of the skin through molecular diffusion.

Modifications in lipid composition, temperature, hydration levels, and pH levels impact the permeability of the skin. Drugs are taken in by capillaries and the circulatory system from the dermis. Microfluidic skin-on-a-chip platforms employ skin cells to investigate drug toxicity, possessing distinct porosity and permeability characteristics. Mathematical models and Computational Fluid Dynamics forecast fluid movement and transportation within porous skin layers, which is essential for drug dispersion in microfluidic devices. [48]

Multiple organs

The advancement of multi-organ chips (MOCs) for drug screening and toxicology testing, incorporating elements like the liver, is essential for revolutionizing healthcare and enhancing patient outcomes. These MOCs integrate various organs, such as the gut for drug absorption and the liver for drug metabolism, in order to investigate drug responses and metabolism. Different MOCs, such as heart-liver-skin and gut-liver-kidney models, have been developed to study the impact of drug exposure on tissue function. Furthermore, MOCs containing immune cells have been utilized to examine immune reactions to drugs. Research using MOCs has demonstrated potential in assessing viral infections and drug development with increased accuracy, thanks to their well-understood physiology in compact 3-D models.[49] Through the integration of body-on-a-chip technology and pharmacokinetic models, new connections between organs can be uncovered, thereby improving the testing of pharmacological toxicity. This new method shows potential for enhancing drug development and evaluation procedures in the years to come. [50]

Several multiorgan microphysiological(MOMs) systems have been developed like a microfluidic, human-on-a-chip system with a functional immune cell component utilizing a monocyte-derived cell line (THP-1) which demonstrates selective and nonselective monocyte/macrophage activation in the presence of three functional tissues[51].

The reproductive tract tissues and peripheral organs integrated into a microfluidic platform, termed EVATAR,represents a powerful new in vitro tool that allows organ–organ integration of hormonal signaling as a phenocopy of menstrual cycle and pregnancylike endocrine loops[52],The combination of Gut and Liver Microphysiological Systems is utilized for conducting quantitative In Vitro Pharmacokinetic Studies[53],Presentation of toxic effects on multiple organs inside a working human in a lab setting system consisting of four organs[54]an organ-chip that can house many 3D tissues grown from primary cells, cell lines, and organ biopsies.[55]

An advanced, perfusion-based, microfluidic multi-tissue organ-on-achip platform consisting of liver, heart, and lung organoids[56],at a minute but standardized microsystem size, a microphysiological system that sustains the functionality of four organs(intestine, liver,skin and kidney)over a 28-day period in co-culture has been constructed. [57]

Another example of multiple organ on a chip is liver MPS and cardiac MPS from the same hiPSC line were combined to investigate drug-drug interaction (DDI). A case of drug-drug interaction with cisapride and ketoconazole showed suppressed metabolism causing a cardiac MPS arrhythmia. [58]. The immune system of this species, including the liver, kidney, intestine, skeletal muscle, and associated BBB fragments, displayed drug metabolism and entry barriers consistent with clinical data. Organ chips coated with human primary cells have recently been used to model these processes, enabling predictions of drug PK/PD parameters and toxicities in various studies. [39, 59]

CONCLUSION:

Organ-on-a-Chip (OoC) technology is a groundbreaking innovation in biomedical research, offering a new way to study human physiology, drug reactions, and disease mechanisms. These microfluidic devices replicate the dynamic environments of human organs, making them essential tools for drug testing, toxicity assessments, and disease modeling. By facilitating more accurate and human-relevant experiments, OoC systems have the potential to greatly reduce dependence on animal models, improving the precision and ethical standards of preclinical studies.As the field advances, OoC technology is evolving from simple organ models to more complex platforms that can simulate entire organ systems. With the integration of cutting-edge microfabrication methods, stem cell-based models, and personalized patient-specific approaches, OoC technology is becoming increasingly capable of replicating the complex behaviors of tissues and organs. This progress is unlocking new opportunities for disease research, drug development, and personalized medicine.

Future Advancements:

The future of Organ-on-a-Chip technology is filled with exciting possibilities, with several key advancements on the horizon:

1. **Enhanced Multi-Organ Platforms:** The next major step in OoC technology is the development of fully integrated multi-organ systems that can replicate interactions between different organs. These platforms will allow for a more comprehensive study of how diseases affect the body as a whole, as well as how drugs and treatments impact multiple organs simultaneously. The development of human-on-a-chip models could revolutionize toxicology and pharmacology by enabling more accurate predictions of drug responses across organ systems.
2. **Personalized Disease Models:** As **induced pluripotent stem cell (iPSC)** technologies continue to mature, OoCs will become more personalized. Patient-specific models created from iPSCs can simulate individual disease characteristics and responses to treatment, offering unparalleled potential for personalized drug testing and targeted therapies. This approach could also extend to rare diseases that are difficult to model in traditional preclinical research.
3. **Real-Time Monitoring and Feedback:** Future OoC platforms will increasingly incorporate sensors and biosensors to allow for real-time monitoring of organ

function, disease progression, and drug interactions. Integration of wearable sensors and feedback systems will enable researchers to continuously track physiological changes, enhancing the precision of experimental outcomes and providing immediate data for decision-making in drug development.

4. **Improved Disease Modeling:** The focus will shift towards creating more complex disease models, particularly for chronic conditions such as cancer, neurodegenerative diseases, and autoimmune disorders. pharmaceutical companies to test hundreds or even thousands of drug candidates simultaneously on human-like models, dramatically accelerating the pace of drug discovery and clinical trial processes.
6. **Regulatory Acceptance and Standardization:** As OoC technology matures, it will likely gain more recognition and approval from regulatory bodies for use in drug testing and disease modeling. This acceptance will spur widespread adoption in both industry and academia. Alongside this, the establishment of universal standards for OoC designs and protocols will facilitate reproducibility and integration into the broader biomedical research community.
7. **Integration with Advanced Materials:** The future of OoCs will see the incorporation of **novel** biomaterials such as nanocomposites, biodegradable polymers, and self-healing hydrogels. These materials will enhance the performance of OoC systems, improving cell viability, mimicking mechanical properties of human tissues, and enabling the long-term culture of complex cell types for more accurate disease and drug models.
8. **Expansion of Organ-Specific Models:** In addition to the most common models—like liver, lung, and brain-on-achip—future research will expand to include other critical organs, such as the pancreas, kidney, and heart. These new models will allow for more detailed exploration of organ-specific diseases, like diabetes, kidney failure, and heart disease, and will play a key role in advancing cardiotoxicity and nephrotoxicity testing.
9. In conclusion, Organ-on-a-Chip technology is set to revolutionize biomedical research by providing more accurate, ethical, and personalized approaches to studying human biology. As the technology continues to evolve, it holds tremendous potential for advancing our understanding of disease, optimizing drug development, and creating patient-specific treatment strategies that could transform the future of healthcare.

Advances in tissue engineering and the ability to simulate **tumor**microenvironments, for example, will allow for more accurate testing of cancer therapies, while neurodegenerative models can deepen our understanding of diseases like Alzheimer's and Parkinson's.

5. **Automation and High-Throughput Capabilities:** The integration of automated systems and high-throughput screening will make OoC technology more scalable and efficient for large-scale drug screening. This would allow

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