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ORGAN ON CHIP

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ABSTRACT
Organ-on-a-chip (OoC) technology has emerged as a transformative platform in biomedical research by integrating microfluidics, tissue engineering, biomaterials, and cell biology to recreate the structural and functional characteristics of human organs under physiologically relevant conditions. Unlike conventional two-dimensional cell cultures and animal models, OoC systems provide dynamic microenvironments that closely mimic in vivo tissue architecture, mechanical forces, biochemical gradients, and cellular interactions. This review summarizes the principles, fabrication strategies, and recent advances in organ-on-a-chip technology, highlighting applications in skin-, lung-, liver-, gut-, heart-, placenta-, kidney-, and brain-on-a-chip models. These platforms have demonstrated significant potential in disease modeling, drug screening, toxicity assessment, personalized medicine, and regenerative medicine while reducing dependence on animal experimentation. The review also discusses multi-organ-on-chip systems, which simulate inter-organ communication and improve the prediction of systemic drug responses. Despite remarkable progress, challenges such as standardization, large-scale manufacturing, sensor integration, long-term culture stability, and regulatory acceptance remain barriers to widespread clinical and industrial adoption. Continued advancements in biomaterials, stem cell technologies, bioprinting, and artificial intelligence are expected to further enhance the physiological relevance and translational potential of organ-on-a-chip systems. Overall, organ-on-a-chip technology represents a promising next-generation platform for precision medicine and pharmaceutical research, offering more reliable, ethical, and cost-effective alternatives for studying human physiology and accelerating drug development.

1. INTRODUCTION:

In recent years, the field of biomedical research has witnessed remarkable advancements with the emergence of organ-on-a-chip technology. This innovative approach seeks to replicate the complex physiological and pathological features of human organs in microscale devices, commonly referred to as organ-on-a-chip platforms. These platforms offer a transformative paradigm in studying human biology, disease modeling, drug screening, and personalized medicine.In this review article, we delve into the diverse landscape of organ-on-a-chip technologies, exploring various types of organ-on-a-chip models and their applications across different fields of biomedical research. We discuss the fundamental principles underlying organ-on-a-chip platforms, highlighting their potential to revolutionize drug discovery, disease understanding, and therapeutic interventions. By examining the latest developments and future prospects of organ-on-a-chip technology, this review aims to provide a comprehensive overview of this cutting-edge approach and its implications for advancing human health.

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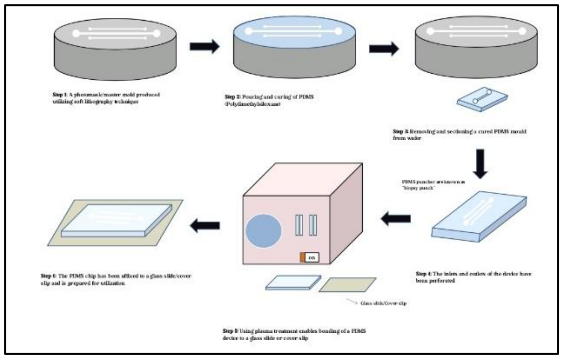

Fig.1 Schematic representation of the step-by-step process of PDMS formation

(1) Skin on chip:
General overview: Skin disease affect one third of population world widely like chronic skin disease, psoriasis eczema dermatitis causes morbidity and affect patient life(1). High frequencies of skin disease are main starting point of advance drug development and leads to the requirement for physiological tissue model create new technology for cell culture such as organ-on-a-chip or micro physiological systems. This technology have aim to overcome the limitation of 3D cell-based culture platform and increase prediction power of vitro models (2). These systems are have power of experimental controllability and reproducibility same as 2D culture (3).

Key Requirements for development of SOC device: SOC model includes various layer of human skin and vascular (blood nutrient) system.

1.1 Cell Sourcing: FTS cell are obtained from healthy human skin via surgical procedures. FTS cells consists of epidermis formed by primary keratinocytes and Primary fibroblasts of dermal compartment. By using FTS cells donors' in vivo phenotypes are also captured (4).

HaCat cells are have potential to undergo proliferation and differentiation but low possibility to generate stratum corneum compared to primary keratinocytes, epidermal tissues are also formed using HaCat cells, thatswhy Hacat cells are unsuitable to formed SOC (4). . Induced Pluripotent stem cells (IPSC) are source of tissue engineering derived from somatic cells, cells produced from IPSC have same character of original donor. Gledhill et al. Generated FTS from IPSC derived keratinocytes melanocytes and melanin unit (5).

1.2 Cell Scaffolds: ECM composed of proteins likes collagen glycosaminoglycans proteoglycans and adhesive protein (fibronectin & laminin) (5).

In conventional method natural hydrogels and collagen which are derived from animal are used to create dermal compartment (6). Lotz et al. Generates cross linked collagen hyrogels that are more stable and have less enzymatic degradation. By combining in vivo ECM with perfusion system there are possibility to recreate physiological interstistial flow. The flow are in between ECM or interstitium of tissues that composed of essential components (7)

1.3 Vascularization: Strategy to create vascularization is Seeding onto scaffolds or hydrogels and cell sheeting engineering are alternative methods to incude vascularization in skin tissues. Most of these approaches are slow and complex therby not fitted in SOC (8).

Perfusable vascular networks are developed in microfluidics, prevascular pattern method are used to create vascular like network on chip and divided according to soft lithography technique and 3D printing method (8).

Most commonly method are to produce 3D barrier tissue on chip is the introduction of porous membrane between two channels. Another method are to implant hydrogels in PDMS device.3D patterning method are also used to produce more physiological related vascularised network on chip these methods include layer by layer manufacturing.By combining 3D printing with microfliudics produces complex structure that mimics the native skin and haave high precision and versatility (9).

1.4 Mechanical stimulus: Mechanical stimulus are used to OOC for continous deliver culture media and removal of cell metabolites. The response are important and necessary part of cell microenvironment that shows various processes in healthy and disease conditions (10).

Biomechanical forces are includes shear stress, tensile and compressive forces, Agarwall et al. Says that keratinocytes are have sensitivity to microflow-induced shear stress. Shear stress affects fibroblasts behaviours like orientation migration and adhesion. The tensile strength on cellular microenviroment causes tissue stretching (10).

Cyclic stretch result in synthesis of basement membrane proteins and epidermal layer.

1.5 Design and fabrication: FTS generation there are two chambers one is apical and second one is basal chamber. Apical chamber form stratum corneum epithelial layer and have air circulation wheras lower chamber are perfused with the medium. In this system a leakage free sepration are created between apical and basal surfaces of skin for establishment of ALI.

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Most common approach to create sepration in OOC are introducing semipermeable membrane between two elastomeic fliud channels. Most of the OOC are fabricated from PDMS have property to absorb small hydrophobic molecules and organic compounds of drug but some limitation are is have higher cost due to this it is challange to commercialized PDMS based devices.(11)

1.6 Sensor integration: The monitoring cannot be done using microscopic studies due to limited light penetration and scattering effects. Sensors are introduced into skin to interact with different stimulus.(11)

(2) Lungs on chip

Drug development and toxicology research face significant challenges due to the absence of reliable predictive models for assessing human body responses to drug compounds and toxins. Although various surrogate models based on in vitro cell culture techniques have been developed, most of these systems do not accurately replicate the structural and functional complexity of living tissues and organs.(12)

Establishing 3D cultures as a mainstream approach necessitates the development of standard protocols, new cell lines, and quantitative analysis methods, along with appropriate three-dimensional imaging techniques. We anticipate that 3D cultures will significantly influence drug screening and reduce the reliance on laboratory animals, particularly in toxicity assays. (13)

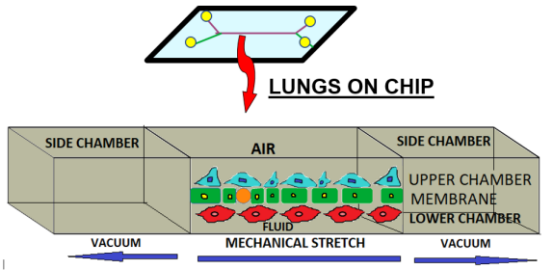
Lungs on chip helps to reconstitute 3D microarchitecture mechanical activity and functions of alveolar-capillary interface. We have created microfluidic device which replicates the microarchitecture and microenvironment of alveolar-capillary unit the human lung. (12)

2.1 Development of lungs on chip:-

Soft lithography-based micro fabrication techniques were employed to create a compartmentalized three-dimensional microchannel system, comprising upper and lower cell culture chambers separated by a 10-µm-thick microporous elastomeric membrane crafted from poly(dimethylsiloxane).

Human alveolar epithelial cells and pulmonary microvascular endothelial cells were seeded into the upper and lower chambers, respectively, and allowed to adhere to extracellular matrix-coated membrane surfaces to form an alveolar-capillary interface. Following cell attachment, the microchannels were perfused with culture media to facilitate cell growth until confluence was achieved.

Subsequently, the alveolar epithelial cells underwent air exposure to induce differentiation while being nourished from the basal side, resulting in the development of a microengineered barrier tissue composed of the alveolar epithelium and capillary endothelium closely positioned together. Furthermore, cyclic vacuum suction was utilized on the side hollow chambers next to the cell culture channels to create cyclic mechanical stretching of the adherent cell layers, mimicking physiological breathing motions. This process led to the deformation of the alveolar-capillary barrier, simulating the effects of breathing on the barrier. (12)



2.2 3D inkjet method to develop lung on chip

Various lung-on-a-chip models have been developed, but the traditional fabrication method has limitations in recreating a thin, multilayered architecture and spatial arrangement of multiple cell types in a microfluidic device. To address these challenges, a physiologically relevant human alveolar lung-on-a-chip model integrated with an inkjet-printed, micron-thick, three-layered tissue was designed.

This innovative approach involves bioprinting lung tissues layer by layer inside four culture inserts, which are then implanted into a biochip providing a continuous flow of culture medium. This modular implantation process allows for the creation of a lung-on-a-chip system that supports the culture of 3D-structured inkjet-bioprinted lung models under perfusion at the air-liquid interface.

Bioprinted models, cultured on the chip, maintained their structural integrity with three layers of tens of micrometers thickness and developed tight junctions in the epithelial layer, key properties of an alveolar barrier. Additionally, the upregulation of genes essential for alveoli functions in our model was confirmed. This culture insert-mountable organ-on-a-chip platform is versatile and can be adapted to various organ models by implanting and replacing culture inserts. It is suitable for mass production and allows for the development of customized models through integration with bioprinting technology. (14)

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2.3 Lung alveolus-on-a-chip model of acute radiation-induced lung injury

High-dose gamma radiation exposure, whether from radiological disasters or cancer radiotherapy, can lead to radiation-induced lung injury (RILI), characterized by acute pneumonitis followed by lung fibrosis. To model acute RILI in vitro, a microfluidic organ-on-a-chip lined with human lung alveolar epithelium and pulmonary endothelium (Lung Alveolus Chip) is employed. Within 6 hours of radiation exposure, both the lung epithelium and endothelium display DNA damage, cellular hypertrophy, increased levels of inflammatory cytokines, and compromised barrier function, with the endothelium experiencing greater damage.

The on-chip radiation dose sensitivity closely resembles that of the human lung compared to animal preclinical models. Furthermore, the Alveolus Chip assesses the potential of two drugs, lovastatin and prednisolone, to mitigate the effects of acute RILI. These findings highlight the Lung Alveolus Chip as a relevant human model for studying the molecular mechanisms underlying acute RILI and for evaluating new radiation countermeasure therapeutics. (15)

2.4 Lung on chip use in disease simulation

The lung-on-a-chip technology is presently employed for simulating diseases such as inflammation, pathogen infection, and lung tumors. In 2016, Benam et al. developed a small bronchial chip specifically designed to mimic inflammatory responses in the small airways at the sub-organ level (16)

Following this development, researchers acknowledged that pathogens could impact the lung epithelial structure and function in lung-on-a-chip models. As a result, they gradually started to explore models incorporating host-pathogenic microorganisms. These studies included lung-on-a-chip models containing Mycobacterium tuberculosis (17), *Staphylococcus aureus* and influenza A virus co-infected pneumonia (18), rhinovirus (19). Furthermore, the construction of NSCLC (non-small cell lung cancer) models using lung-on-a-chip technology has emerged as a significant area of interest. Researchers have utilized NSCLC models to investigate various aspects of lung cancer, including its development, metastasis, and drug resistance.

ORGAN	LATEST ADVANCES	REFERENCES
HEART	Capability to replicate Frank-Starling mechanisms in heart muscle cells and exhibit correct auxotonic contractions.	Sidorov et al. (2017) and Skardal et al. (2017
BONE	Advancements in 3D printing procedures involving vascularization, novel scaffolds, and seeding methods; developments in bone-on-a-chip technology and its diverse applications, such as investigating metastasis to the bone from different organs	Sithole et al. (2018), Hernandez, Kumar, and Joddar (2017), Nyberg, Rindone, Dorafshar, and Grayson (2017), Alluri et al. (2018), and Daly, Pitacco, Nulty, Cunniffe, and Kelly (2018)
LUNGS	The application of biomechanical ventilation has demonstrated an ability to enhance the resistance of specific lung cancers to conventional treatments, both in relevant models used by pharmaceutical companies for drug discovery.	Hassell et al. (2017), Jain et al. (2018), and Benam et al. (2017)
KIDNEY	Recreating mature and functional podocytes within the glomerulus enables enhanced selective filtration in kidney models. Simulating diabetic nephropathy type II at the glomerulus.	Musah et al. (2017) and L. Wang, Tao, Su, Yu, Yu, and Qin (2017)
LIVER	Developing liver tissue through bioprinting with prolonged functional viability, providing an extended window for studying drug metabolism.	Kizawa, Nagao, Shimamura, Zhang. and Torii (2017)
BRAIN	Capable of replicating initial stages of embryonic brain development, investigating teratogens, and identifying drugs that hinder the entry of the Zika virus into developing embryonic brains.	Zhou et al. (2017), Watanabe et al. (2017), and Qian et al. (2016)
RETINA	Capable of efficiently modeling in vivo scenarios using organoids, advancements in organoid fabrication techniques, and imaging capabilities.	Chen, Kaya, Dong, and Swaroop (2016), DiStefano et al. (2018), Browne et al. (2017), Vergara et al. (2017), and Lorber, Hsiao, Hutchings, and Martin (2014
GUT	Numerous interactions between hosts and microbes observed in intestinal organoids include Salmonella, H. pylori, and C. difficile.	Eicher et al. (2018
PLACENTA	Effective simulation of drug transportation achieved through a placenta-on-a-chip model.	Kuo et al. (2018) and Blundell and Torii (2017)
ADIPOSE	Generating adipospheres that replicate adipose cells in living organisms, employing constructs for investigating glucose uptake, and devising techniques for cell retention.	Daquinag, Souza, and Kolonin (2013), Zambon et al. (2015), Loskill et al. (2017), and Brooks, Judd, and Easley (2017)

(3) Liver on a chip

The ability of scientists develop new drugs is hampered by the fact of testing on animals has limitations when it comes to use in humans whilst testing in human has the potential for dangerous side effects but new technologies being developed

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around the world are now replicating human organs on chips allowing scientists to test drugs in a safe and controlled way

3.1 Culture Environment Of Liver-On-Chips

we will summarize the culture environment of the different liver-on-chips

- 2D liver-on-chips

Traditional dish-based culture techniques for hepatocytes are difficult to show cell–cell interactions and cell–matrix interactions and simulate the complex liver microenvironment due to its limitations, of which different kinds of hepatocytes are mixed and seeded randomly.To overcome this limitation, a novel approach co-cultures two or more cell types in a specific order and position through cell patterning techniques, thereby coordinating heterotypic cell interactions and mimicking the true distribution profile of liver cells. Some strategies were used to improve the precision of cell patterning, such as Hannachi and coworkers, who used the microcontact printing technique to fabricate micropatterned co-cultured cell sheets, and Nahmas et al., who used laser-guided direct writing technique to draw cell patterns with high accuracy., In addition to passive patterning, dielectrophoresis (DEP), (20)

- Matrixfree 3D liver-on-chips

Despite the unique advantages of 2D liver-on-chips, there is still an obvious gap in simulating the in vivo microenvironment in comparison with 3D culture.147 3D culture of hepatocytes facilitates the maintenance of cellular morphological stability and function, and is beneficial for quantitatively understanding cell–cell interaction effects under a simulated environment.148-151 In order to investigate the interaction between hepatocytes and HSCs and to distinguish between direct cell contact and paracrine effects on hepatocytes, Lee and his colleagues innovatively proposed a meniscal-based method to rapidly and simply construct 3D liver-on-chips with size-controllable hepatocyte spheroids.152 The chip

consisted of a flat chamber to culture HSCs and a concave chamber to culture hepatocyte spheroids. The two chambers were connected using a connecting tube with a Polyethylene glycol (PEG) solution flowing from the stellate cell medium to the hepatocyte spheroid, which mimicked the velocity of in vivo intercellular interstitial flow . Hepatocyte spheroids cultured in flow medium showed a significant increase in survival and exhibited the highest functional activity at day 8 compared to liver-on-chips lacking medium flow. It was also investigated that hepatocyte spheroids were optimally maintained at the PEG solution flow rate of 5.53 mm/h (21)

- Matrix-dependent 3D liver-on-chips

In liver-on-chips engineering, how to prolong the survival time of hepatocytes and maintain liver function in vitro is still a challenge to be addressed. Achieving optimal liver function relies on the interaction not only between hepatocytes and NPCs but also the cell and matrix. In recent years, many natural or synthetic ECM components have been applied in in vitro liver models. Natural source components include proteins (including but not limited to collagen and silk fibroin), sugars (chitosan and alginate), polylactic acid and other derivatives, and synthetic components including PEG and others. ECM has a proven effect in promoting cell adhesion, maintaining cell survival, and promoting cell–matrix interactions. (20)

3.2 Cell System Classification

- **Single-type cell culture**

In microfluidic chips, the most frequently adopted cell culture system is single-type cell microspheres because it is well established, inexpensive, and easily reproducible, and therefore it is widely used in drug toxicity testing and cell metabolism models. Kizawa et al. designed a scaffold-free spheroid of hepatocytes that did not contain any ECM or NPCs. They used the hepatocyte spheroids to investigate bile acid secretion and used insulin to inhibit the camp/protein kinase A pathway to reduce glucose production in hepatocyte spheroids. Bhise et al. encapsulated HepG2/C3A cells in photocrosslinkable gelatin methacryloyl (GelMA) hydrogels. They used bioprinting to rapidly fabricate large quantities of liver models and were able to control the thickness of the hydrogel outer layer of the encapsulated hepatocytes . (22)

- **Multiple type cell co-culture**

There are complex interactions and interactions between two or more types of cells in the liver, so single-type cell culture is not enough to mimic the real liver microenvironment. Co-culture of hepatocytes with NPCs has been shown to maintain hepatocyte morphology and a variety of liver functions, because NPC populations have important roles in metabolizing transforming drugs, detoxifying, and modulating hepatocyte metabolic competence. Therefore, the adding of one or more types of NPCs enables the chip more liver functions.188-190 For example, SCs remodel the phenotype of the liver ECM through myofibroblasts, KCs play an important role in the liver's response to injury through the production of cytokines and reactive oxygen species, and LSECs are involved in the liver's powerful regenerative capacity. (23)

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- **Multi-organ collection system**

The various organs within the human body are not isolated, and the complete process of drug metabolism and the normal life activities of humans require the joint participation of multiple organs. Therefore, it is difficult for a single-organ chip to represent the physiological functions of all the systems in the human body.[,] Many scholars load multiple organ chips on a single microfluidic device to explore the connection between individual organs.[-] For example, Bauer et al. co-cultured liver tissue and islet tissue in an insulin-free microfluidic device to explore the link between the liver and pancreas, two key organs for maintaining glucose homeostasis It is known that insulin released by pancreatic islet b cells promotes glucose uptake by hepatocytes and conversion into hepatic glycogen for storage, whereas insulin resistance in the liver of patients with type 2 diabetes mellitus (T2DM) leads (24)

3.3 Establishment of liver disease models

- **Liver cancer organoid chip**

An in vitro 3D liver tumor model is a reliable strategy for studying the mechanism of tumor spread and drug screening.established a liver cancer model in a rotating wall vascular bioreactor.The rotational wall vessel is an in vitro suspension culture system. HepG2 cells metastatic colon carcinoma cells were added to RWV at the ratio of 10:1, and the microgravity state generated from the rotation promoted the aggregation of the cells on the microcarrier beads, generating liver tissue containing colon carcinoma tumor foci(24)

- **Nonalcoholic fatty liver disease chip**

NAFLD refers to the excessive deposition of fat in the liver that caused excluding excessive alcohol and other clear pathogenic factors. To date, researchers have not defined the mechanism of NAFLD. NAFLD can be classified into NAFL, NASH, and NASH-related cirrhosis based on the degree of pathologic change and whether hepatic fibrosis occurs. Rodent models of NAFLD are widely used, but there are major differences between humans and animal models, such as the mechanisms of fat accumulation, the degree of liver fibrosis, and so on. In vitro 3D models based on human liver cells are therefore promising research directions. To better understand and explore NAFLD, it is important to develop accurate, low-cost, and long-term culturable in vitro models. (25)

- **Alcoholic liver disease chip**

Alcohol is one of the important causes of liver disease, and ALD has become an important problem faced by both developed and developing countries. The Organ-on-chip offers advantages over animal models in terms of lower cost, shorter experimental cycles, and no ethical concerns involved, and thus the organ-on-chip offers great advantages in modeling the progression of ALD in vitro. (26)

- **Other liver disease chip**

Hepatitis B caused by hepatitis B virus (HBV) is considered a major global health problem. However, the studies on host/pathogen interactions have been limited due to the difficulty in establishing suitable models for the entire viral life cycle and the narrow host range of HBV. With the help of microfluidic technologies, there are many attempts that have been explored to develop more precise in vitro liver models (27)

(4) Gut-on-chip

The human gut has important functions in digestion, absorption, disease management, and immunological function, making it a focus of contemporary study on the human microbiome. The digestive system is responsible for the absorption of most nutrients and oral medicines. The intestinal mucosa contains about 70% of immune cells, with a larger concentration of lymphocytes compared to other lymphoid organs.(28)

The intestine acts as a natural barrier against dangerous germs. In addition, microorganisms in the human intestine have been linked to a variety of disorders, including dyspepsia, obesity, and immunological harm.3-5 Thus, in vitro simulation of the intestinal milieu is critical for drug development and illness therapy (28)]. Currently, mammalian animal models and static Transwall models are extensively used to study human gut physiology and microbiota (28).

Mammals are commonly used in preclinical testing for drug metabolism, toxicity, and efficacy(28). Two-dimensional (2D) Transwall culture systems provide a simple in vitro method for observing and detecting microbiome-host interactions by growing a monolayer intestinal epithelium (28)

Design of Gut-On-Chip- Microfluidic technology now effectively mimics the human gastrointestinal tract due to significant advancements. This device, known as "gut-on-chip," offers low cost and consumption, flexible control over numerous system parameters (e.g., fluid flow and oxygen concentration), and compatibility with cell culture and real-time imaging. Gut-on-chip platforms have progressed from simple 2D structures to more advanced features including villi, intestinal peristalsis, oxygen gradients, and immune systems in the last decade.(28)

2D Gut-on-chip model- Initially, devices typically had two channels (upper and lower) separated by a

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semi permeable membrane made of polycarbonate or polyester materials. A monolayer epithelium is made up of intestinal epithelial cells that develop on the membrane, with apical and basolateral sides. This basic model is often used to evaluate medication and nutrient absorption in vitro(28). Kimura et al. created a comparable system that includes on-chip pumping and optical detection. The 2D gut-on-chip model simulates fluid shear stress on intestinal cells, reducing demand on both cells and the medium. Continuous flow maintains nourishment supply and removes metabolic waste over time (28). Intestinal epithelium often has higher vitality than Transwell, enabling for long-term co-culture of microbiota and host cells. How (28) ever, the villous microstructure, a highly functional unit in the intestine, has not been adequately mimicked or studied. 3D Gut-On-Chip Model - The digestive tract's villi microstructures provide both a physiological barrier for the epithelial layer and an increase in absorption area[64]. Various villi-like structures have been developed to mimic the in vivo gut microenvironment (28). Sung et al. created a hydrogel array using laser ablation and soft lithography technologies. They then cultivated epithelial cells on the 3D structures to mimic the shape and density of human intestinal villi(29). Similar research have shown that villi-shaped scaffolds can alter physiological intestinal activities like drug absorption, mucus formation, and bacterial resistance. (29)

- **Applications of GOC Models** Gut-on-a-Chip (GOC) models are extensively used to study cellular and tissue-level interactions in vitro. They serve as a powerful tool for studying the physiology of the gut, conducting drug testing and development, and investigating host-microbiome interactions.GOC models are also utilized to understand the correlation between host-microbe relationships, human nutrition, and the human microbiom. Organ-on-a-Chip (OoC) models are gaining interest for studying tissue-tissue interfaces.(30) Gut-brain-axis (GBA) chips, helps to understand how changes in gut physiology due to factors like diet or medication affect brain physiology or lead to neurodegenerative disorders. Gut-liver-chips are developed to study the intestinal barrier under variant conditions, including the correlation between hepatic dysfunction and barrier permeability(31)

(5) Heart on chip

Heart on a chip is a cell culturing to create a highly controlled microfluidic device which is able to create environment to mimic the natural habitat of the heart cells.

The heart-on-a-chip device made of many microchamber and microchannel.

Microchamber and microchannel made of polymer that is sealed by another material.

It is capable to handling hypoxic conditions during a heart attack. Hypoxia is a condition when the amount of oxygen in the blood becom very low. The chip contains many electronic sensors which are placed outside and inside the cells. They easily detect rises and falls of voltage across cellular membranes, as well as voltage waves traveling across the cell membrane, causing cells in the chip to beat in unison, similar to what happens in a heart. (32)

whe reducing the oxygen level in the fluid within the device, the sensors detect the onset of an abnormal increase in heart rate. Often, heart beat becomes irregular due to decrease in heart rate. It happen like a heart attack. If it is detected on time, life can be saved.

This is very important step to understanding the electrophysiological responses to ischemic heart attack at the cellular level, and may be us in future drug development. Ischemic heart attacks or ischemic heart diseases are diseases which occur due to decreased blood flow.(33)

Cardiovascular disease (CVD) is the leading cause of death worldwide, with most patients suffering from cardiac ischemia. It occur at that time when the artery that supplies blood to the heart becomes partially or completely blocked. These include changes in cardiac cells and tissues with hypoxia, including changes in the voltage potential across the cell membrane, changes in gene function, altered metabolic function, and activation or deactivation of ion channels.(34)

Biosensor technology use in microfluidic chips combine multiple electrode,which provide information about voltage patterns in cells. These enter the membrane to signal the voltage level within each cell. Researchers will continuously reduce the amount of oxygen through a small channel in the chip to understand the condition of hypoxia. In this the oxygen level will be reduceto about 1-4 percent or the oxygen wil be increased to 21 percent like normal conditions.(34)

For create a valuable model the microchip must mimic the heart's main properties such as mechanical contraction, molecular transport, electrical activity, and specific responses to certain drug stimuli. It may also be interesting to combine specific measurement systems for possible recording of contraction or action or even calculation of tissue elastic modulus.The heart-on-

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chip should reproduce the cellular organization level in the living heart by demonstrating sarcomere assembly with aligned tissue structure.(34)

The heart is one of the rare organs with active tissues who show intrinsic contraction.

Tissues are known to having best cardiac differentiation at that time when stimulated by a stretching pulse.Contraction speed is important for a robust model containing mature cardiomyocytes. (34) The heart is a pump as well as a muscle, which mean energy consumption and molecular transport. This aspect of the organ will be take into account to model the supply of nutrients and elimination of waste products. Another important point to create a future automated large-scale method for the pharmaceutical industry is to obtain measurement data directly from the microchip to evaluate the efficacy of the tested therapeutic treatment. Integrates registration systems into the chip can be avoid disassembling devices, and hence reduce costs while increasing accuracy.This technique also allows proper control of stimulation.(35)

- **Composition of heart on chip:**

Heart-on-a-chip include four important elements:

1. microfluidic chip,
2. cells/microtissues,
3. microactuators for physical/chemical stimuli,
4. microsensors for monitoring cells status

Microfluidic chip is important part of heart-on-a-chip, it provide habitat for cells**.** Glass, silicon, polydimethylsiloxane (PDMS), polymethyl methacrylate (PMMA), and papers are commonly useable materials.(36)

The second important elements of heart-on-a-chip is the microtissue. microtissue can divided into 2D microtissue and 3D microtissue. Based on the cells in microtissue it devided on single type of cells and co-culture of multiple types of cells. cardiomycytes (CMs), human cardiac fibroblasts (hCFs), endothelial cells, induced pluripotent stem cells,are mainly participated cells.(37)

The third important element of heart-on-a-chip i microactuators, which use to impose external stimuli to cells or microtissues.Electrical and mechanical situation microactuators are use.

Microsensors are the fourth important elements in heart-on-a-chip to monitor cells/microtissues. biochemical reagents are us to stain cells to characterize functionalities. (38)

Polydimethlysiloxane polymer is use to made chip because it have the tranparancy and biocompatibility characteristics. (38)

- **Significance and Applications of heart on chip:**

Heart-on-a-chip helps to physiology study, disease modeling, and drug screening. Compared with the traditional techniques, heart-on-a-chip can better mimic the cellular microenvironment and promotes the maturation of microtissues. In addition, heart-on-a-chip enables the real-time monitoring of the status of cells/microtissues. (39)
Heart-on-a-chip models are a powerful tool for treating diseases. The current equipment being used to study electrophysiology has some shortcomings, as it does not work on every part of the heart, which leads to excessive pressure on the cells, which can cause damage to them. The transmission of information between molecules and electrophysiology occurs very rapidly during hypoxia, and our device can capture a lot of information from cells in real time without harming them.(39)

During testing the device provided a two-dimensional map of voltage waves passing over a layer of heart cells, which revealed a predictable wave pattern under normal (21 percent) oxygen levels.(40) In contrast, the researchers observed irregular and slower wave patterns, especially when blood oxygen levels dropped to 1 percent. Nanoprobe sensors provide precise information about what goes on inside each cell.(41)

Extracellular and intracellular sensors together provide information about the electrophysiological effects of ischemic stroke, which results in temporary cell death. In this situation, microfluidic chip can play an important role in drug discovery, which helps cells and tissues to recover faster to normal function.(41)

3D microfluidic hearts-on-a-chips facilitate research into cardiovascular diseases.cardiac hypertrophy and fibrosis are studied through the respective biomarker levels of mechanically stimulated μECTs, such as atrial natriuretic peptide (ANP) for the former [52] and transforming growth factor-β (TGF-β).knowledge of ischemia is obtained from action potential observations.Microfluidic approaches use to dissect specific mechanisms at the single-cell level and tissue-level are becoming increasingly sophisticate as are the fabrication methods.(42)

(6) Placenta on chip

Placenta-on-a-chip models are designed using microfluidic chip devices, incorporating cultured human placenta cells to investigate drug transport mechanisms.(43) One significant advantage of this technology is its avoidance of invasive procedures

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and the need for cell samples from the developing fetus, making it an ethically preferable approach (44).These innovative platforms aim to accurately replicate both the structure and function of the human placental barrier, as well as the dynamics of blood circulation within placental tissue (45, 46). This emulation of physiological conditions is a key strength of placenta-on-a-chip models. Furthermore, the utilization of placenta-on-a-chip systems as an alternative to traditional in vitro, in vivo, and ex vivo models has demonstrated considerable potential in studying how drugs administered to the mother can impact fetal exposure(45).

Advances in current trophoblast fusion models
For an extended period, the placenta was often overlooked and referred to as a "forgotten organ." It wasn't until the mid-20th century that researchers began to shift their focus from descriptive studies of the placenta to more in-depth mechanistic research, recognizing its crucial role in successful pregnancies. During this transition, various traditional placental cell lines were gradually developed and utilized in placental research endeavors. However, it wasn't until 1986 that primary human trophoblast cells (PHTs) were first utilized to establish the initial trophoblast fusion model. (47)

With the advancement of technology and the accumulation of knowledge, researchers quickly progressed to develop various trophoblast models, which in turn led to the creation of trophoblast fusion models. Over the last seven years, there has been significant progress in trophoblast fusion models, including the development of placenta-on-a-chip models, various human pluripotent stem cells (PSCs), and organoids. These innovative models show great promise in advancing placental research and overcoming current challenges and limitations. (47)

The placenta-on-a-chip technology allows for the reconstruction of both the multilayer structure of the placental barrier and the hemodynamic environment. The multicellular co-culture and fluid shear stress environment within this system provide a closer simulation of the in vivo environment compared to static culture methods. Specifically, fluid shear stress plays a role in inducing the formation of microvilli in human placental trophoblast cells (48).

In contrast to static culture methods, the microarray placenta demonstrates a higher density and more comprehensive development of microvilli protrusions on the surface of trophoblast cells. Moreover, the multicellular co-culture setup facilitates the investigation of intercellular communication and its influence on placental function, significantly enhancing our comprehension of the relationships between structure and function within organs. The downsizing of the system will lead to a substantial reduction in the variety of required reagents and enable real-time monitoring of dynamic data changes across all types, ultimately leading to cost savings in research endeavors (49, 50).

The placenta-on-a-chip technology has been utilized for studying trophoblast invasion, toxicological screening, microvilli formation, placental pathology, and capturing placental exosomes. However, to achieve a mature technology suitable for large-scale low-cost applications, enhancements are necessary in areas such as liquid flow control, monitoring technology, and the development of co-culture systems that involve a broader range of cells and microorganisms (47)

(7) Kidney - on - chip:
Kidney-on-a-chip design has two compartments that has been disclosed, in which the bottom chamber resembles interstitial space and is filled with media, the top channel mimics the urinary lumen and has fluid flow. Shear stress on kidney cells is less than by lung or endothelial cells. The shear stress of this apparatus, which employed MDCK (Madin – Darby Canine Kidney) or rat distal tubular cells, was around 1 dyn/cm2 (51, 52). The identical design was employed in a second publication; however human proximal tubular cells were used instead. The authors tried to mimic the nephrotoxicity of cisplatin in this model. Shear stress is substantially less in proximal tubular cells (~0.2 dyn/cm2) (52). Some scientists have tried podocyte-on-a-chip, but it is still challenging. It may be because podocyte is exposed under a very low shear stress in vivo and requires a sophisticated culturing condition (53).

Human proximal tubular cells were used in the kidney-on-a-chip model to assess the nephrotoxicity of cisplatin (52). After adding cisplatin to the bottom area, the cells response to the drug was observed for a full day. Shear stress helped the wounded cells and related indicators heal over the course of the next 72 hours. A notable example of a physiological experiment using kidney-on-a-chip is the use of primary cultured inner medullary collecting duct cells of rat kidneys (54) in kidney-on-a-chip, where shear stress in the devices can enable translocation of aquaporin-2 and displacement of actin cytoskeleton. Renal tubular epithelial cells are also constantly exposed to variations in the extracellular microenvironment, such as transepithelial osmotic gradients and luminal or interstitial pH shifts. (55, 56)

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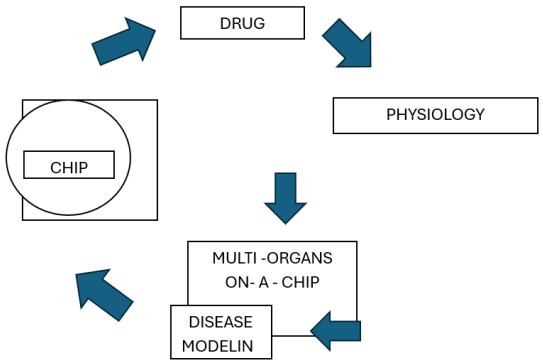
The influence of these physiological parameters on the functioning of renal tubular cells could also be studied using microfluidics. If the illness's problematic antigens or mechanisms are characterised, disease modelling in the kidney-on-a-chip can be easily implemented. Kidney injury models including nephrotoxic medicines may be suitable candidates for the application. Kidney-on-a-chip is just one component of a larger multiorgan-on-a-chip system.(51)

However, some multi organs-on-a-chip systems use kidney tubular cells to measure kidney damage rather than renal excretion. Animal renal clearance is typically higher than human renal clearance. Using pharmacokinetic data from animal models raises the possibility of underestimating human nephrotoxicity. Applications of human kidneys on a chip may fill such gaps through control of drug concentrations and flow rates that mimic human drug clearance or metabolism. (51)



Despite significant efforts and breakthroughs in animal models of human kidney illnesses, many findings from animal studies have not been successfully translated into clinical therapy in people. Inhibiting TGF-β signaling has been shown to slow the course of CKD in animal models, but human trials for patients have been disappointing. (57, 58) The disparity between animal models and humans raises questions regarding the relevance of animal studies' conclusions.

Currently, the great majority of animal models are tested on healthy young mice and rats, although kidney disorders in the clinical setting frequently occur in older patients with a variety of comorbidities. In this context, the translational effectiveness of animal models necessitates the evaluation of comorbidities such as old age, diabetes, hypertension, anemia, and preexisting CKD, to name a few, in order to develop models that more properly reflect the clinical situation. For example, a comorbidity model of DKD has been created to represent consequences such as hypertension and atherosclerosis(59). The comorbidity model of AKI in aged mice has been proven to better represent the older patient population (60, 61). The AKI model with preexisting CKD verifies the clinical concept that loss of renal mass caused by past illness negatively impacts (62).

In the future, establishing animal models using several harmful stimuli to mimic patients' illnesses with varied comorbidities should be carefully explored and widely deployed. Another potential difficulty is that all existing animal investigations are conducted in a pathogen-free setting. Given the growing importance of an altered gut microbiome in the etiology of renal disorders (63) it is unclear whether or not the differences in housing habitats between experimental animals and people contribute to clinical trial failures.(63)

(8) Brain on chip

The brain is the most complex organ in the human body, and it forms part of the central nervous system (CNS) alongside the spinal cord. The brain, as the CNS's upper backbone, processes, integrates, and coordinates acquired information before making decisions that organise the activity of different bodily organs. The brain is made up of neurons that connect unidirectionally through synapses, which occur when the axon terminal of one cell touches the dendrites of another in a certain direction (64). According to animal research, Huntington's disease (HD), a heritable neurodegenerative condition, causes brain cell death and has a significant impact on synaptic changes in the corticostriatal network(65, 66). The brain's functions are maintained by transmitting electrical or chemical signals between neurons via synapses, and if this does not work properly, it can develop into a neurodegenerative disease (Hunter's disease, Alzheimer's disease).

- **Development of BOC:-**

The brain is made up of many layers in which countless neuronal, glial, and immune cells interact. The skull protects the brain from mechanical stress, while the tight BBB protects it from toxins.
Neuronal cells have been cultivated in open environments such as glass substrates or Petri plates. Whitesides et al. introduced soft lithography, which permitted cell culture in a physically constrained microenvironment like microchannels (67). Myelination is the process by which oligodendrocytic feet sheath axons. Myelination, which electrically shields the axon from the environment, is crucial to the propagation of action potential. Neurodegenerative brain illnesses, such as multiple sclerosis, can arise as a result of demyelination caused by immunological responses or a traumatic brain injury. If the myelination

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process can be replicated in BoC, this platform can serve as an optical window for fundamental research into myelination. Recent research, for example, have used the segmented BoC system to visualize the myelination process. Furthermore, the compartmentalized BoC system was used to assess the efficacy of optical and electrical stimulations in myelination, with improved oligodendrocyte differentiatio and wrapping observed(68).

However, these microchannel-mediated BoCs have various drawbacks, including 2D cell adhesion and the significantly stiffer mechanical characteristics of glass substrates. Furthermore, this monolayer structure cannot be employed to create a transport barrier, like the BBB.

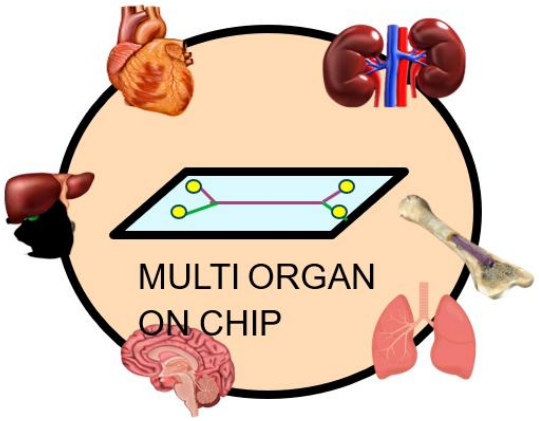
Future of BOC

First, human cell sources are necessary to mimic human brain physiology and produce tailored therapeutics. As previously stated, animal-derived cells differ from human cells in terms of genetics, and cell lines typically lose essential activities. Furthermore, human-derived primary cells are difficult to get. In this regard, induced pluripotent stem cell (iPSC) technology, which was established in 2006, is a promising candidate for supplying human cells (69). iPSCs can be generated by giving essential factors to stromal cells, which are subsequently stimulated to develop into any cell, particularly neurons, which are difficult to isolate from the human brain. Furthermore, because genetic information is conserved during pluripotent stem cell generation and differentiation, it enables the development of customized medicine, including patient-specific cocktail medication compositions (70). Recently, patient-specific BBB models have been developed .Vatine et al., Park et al., and Sances et al. created BBB models using iPSC-derived cells and proved its potential for personalized medicine applications.

Second, cell-cell interactions should be carefully studied in order to better understand brain illnesses. The on-chip technique is excellent for investigating cell-cell interactions because it can simplify complex interactions between cells and discover how the disease begins and evolves via cell-cell communication. In the case of Alzheimer's disease, microglia were activated by amyloid-beta, a representative marker that accelerated neuronal cell death by contact with neurons via secreted neurotoxic inflammatory substances and microglial activators[62]. Another example is the synapse, which is often used to transmit electrical or chemical information between neurons but can also serve as a pathway for the spread of neurodegenerative illnesses.

The characteristic marker, phosphorylated tau, was transferred to additional neurons via synapses, (71, 72, 73, 74) indicating that neurodegenerative disorders spread and progress through intercellular connections (75). Furthermore, on-chip research simplifies the cell population and allows one to monitor the response of each cell type to the created medications, enabling commercialization by selecting active drugs and reducing unwanted side effects.

Finally, it is vital to identify which ECM component should be used for in vitro culture, as the ECM not only performs simple physical adhesion but also serves as a signaling activator for cells (76).As demonstrated in the decellularized brain, the extracellular matrix (ECM) can be used to cultivate neurons formed through direct reprogramming (77).



Multi Organ Chip

CONCLUSION:

In this review, we have explored a range of organ-on-a-chip models, from single-organ systems to multi-organ interactions, each designed to emulate specific physiological functions and disease mechanisms. These models have been instrumental in advancing our understanding of organ-level responses, drug efficacy, toxicity profiles, and disease progression, thereby accelerating the pace of drug discovery and development.The versatility and scalability of organ-on-a-chip platforms offer unprecedented opportunities for personalized medicine, where patient-specific cells or tissues can be incorporated into microfluidic devices for tailored therapeutic interventions. Furthermore, the ability to mimic dynamic microenvironments, such as blood flow, tissue interfaces, and immune cell interactions, opens new avenues for studying complex diseases and designing targeted therapies.As we look towards the future, ongoing innovations in organ-on-a-chip technology, coupled with advances in biomaterials, bioengineering, and computational modeling, hold immense promise for revolutionizing healthcare. From enhancing preclinical drug screening to facilitating patient-specific treatment strategies, organ-on-a-chip platforms are poised to shape the future of

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biomedical research and improve human health outcomes.the journey from traditional cell culture to organ-on-a-chip systems represents a paradigm shift in biomedical engineering, offering a glimpse into a future where precision medicine and personalized therapeutics are the norm. By harnessing the power of microscale technologies and human-relevant models, organ-on-a-chip technology paves the way for a more efficient, ethical, and effective approach to healthcare innovation.

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