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Review Article

Micro Engineering To Create Bio Mimic Living Systems With Organ-On-A-Chip

Sabafarin H. Shaikh*, Sagar Patki, Rohit Karad, Niket Pradhan, Mohammad Sufiyan, Sushmita Chavan

Valmik Naik College Of Pharmacy, Telwadi Kannad Chh.Dambhajinagar

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ABSTRACT

Key components of real organs, such as essential microarchitecture, spatiotemporal cell-cell interactions, and extracellular microenvironments, are faithfully created by "organ-on-a-chip" systems, which combine microengineering, microfluidic technology, and biomimetic concept. a wide range of applications, including the creation of human in vitro models for healthy or diseased organs, can benefit greatly from this innovative platform's multiorgan integration, which recapitulates organ-level structures and functions potentially replacing animal testing, helping drug development with toxicity screening and target identification, and facilitating the study of basic mechanisms in disease etiology and organogenesis.. A review is conducted on the latest developments in innovative designs and instances of developing organ-on-a-chip platforms there is a discussion of how this new technology may be used to comprehend human physiology, including precise spatiotemporal controls over mechanical, chemical, and electrical signals for these proof-of-concept investigations, the present obstacles and necessary future paths are also emphasized

INTRODUCTION

The current drug-development process necessitates the expensive and time-consuming implementation of comprehensive preclinical testing and validation protocols.[1]Preclinical assessments of drug candidates conducted in laboratories involve both in vivo animal testing and in vitro cell culture techniques. Because cell culture assays use simple cell types, they cannot mimic the complexity of living systems, nor can they anticipate complicated drug metabolism or the impact of metabolite action on non-target tissues. Moreover, they cannot represent scenarios in which there is no connection between organs or tissues.[2] Animal models include many ethical considerations and are inherently complicated, making them difficult to analysed It has been

***Corresponding Author:** Sabafarin H. Shaikh
Address: *Valmik Naik College Of Pharmacy,Telwadi Kannad Chh.Dambhajinagar*
Email ✉: sabafarinhasinshaikh@gmail.com

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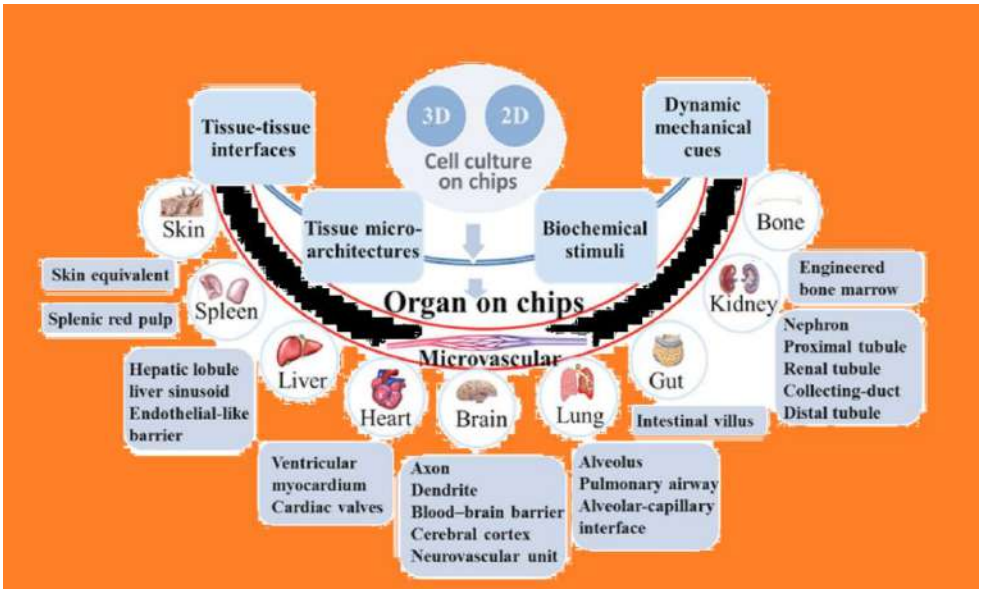
demonstrated that they do not accurately reflect how humans respond to medication treatments for illnesses or organ functioning, and they may even be detrimental to the health and recuperation of patients.[3]More representative model systems are therefore desperately needed by pharmaceutical companies, particularly for common human organs and disorders. Innovative systems referred to as "organs-on-a-chip,"[4]"human-on-a-chip,"[5]"chip-based body,"[6] Systems are being developed to create functional, single- or multiorgan, in vitro disease models that are physiologically realistic by using a variety of cell sources. Systems with an organ on a chip are intricately micro engineered Physiological systems that reconstruct the essential elements of certain human tissues and organs, as well as the relationships between them (Scheme 1) [7] Compared to 3D cell culture or simply cells grown on chips, this in vitro model is more physiologically relevant since it replicates activities, mechanics, and physiological response in a setting of tissues and organs.[8] In order to accomplish this, precise cellular Patterned barriers and channels that resemble artificial endothelial-like barriers between the internal and external interspaces are typical crucial features .manipulation and chip design are needed in addition to a thorough grasp of the basic complex microarchitectures and functions of the human organ. While the majority of the recently created organ-on-a-chip systems cannot be classified as organs, they could at least mimic some features of the tissue–tissue interfaces and functional units of special organs, and combine to produce the dynamic mechanical and biochemical stimuli needed to construct legitimate artificial engineering organs. Biological micro electromechanical systems (BIOMEMS) are typically integrated with organ-on-a-chip systems.[9] tiny fluids [10]in addition to biomimetics [11] BIOMEMS are systems that are micro engineered and allow for exact control over the microenvironments of individual cells in biological situations. With the use of microfluidics, system structures can be perfused by regulating fluid behaviour and establishing connections with discrete chip segments. Artificial organ-level stimuli, such as mechanical stretching obtained from breathing for lung cells and fluid shear stress applied to vascular cells, are at the centre of biomimetics. Combining microfluidic controls with the latest developments in technology,[12]The development of multi organ functionalities on a single chip is being facilitated by these innovative platforms. Finding important details of the geometrical, mechanical, and biochemical milieu of the tissue or organ of interest is necessary to develop an organ on a chip.[13] Patterned barriers and channels that resemble artificial endothelial-like barriers between the internal and external interspaces are typical crucial features.[14]within the channels, two-compartment membrane culture systems to generate air–liquid interfaces[15] and a moving air-liquid interface made of many membrane layers that may flex in a vacuum to provide mechanical stretching.[16]A number of distinct and crucial elements of the physiological milieu of the particular tissue or organ are initially identified and incorporated into the tissue model during development. After that, separated homologous tissue cells are precisely included into predetermined locations within the model, which allows for the possible application of stimuli via bio molecular gradients, flow-induced shear stress, and mechanical strain in addition to the microfluidics-mediated transfer of nutrients.[17]In the end, self organized tissues in micro engineered physiological models perform more realistically and more accurately than tissues grown in traditional systems to reflect the physiology of human organs.[18]In terms of cost and result dependability, functional human organ-on-a-chip

systems will have a major positive impact on basic science and medication discovery. The interactions between tissues or across organs that arise from the transfer of metabolites and information from one tissue to another in vitro can be replicated via multi organ integration.[19]These multi organ systems are important for mimicking human metabolism as well. Before the pharmaceutical agency moves into the costly phase of clinical trials, they involve the biotransformation of a pro drug to an effective metabolite, as well as its following therapeutic effects, potential harmful side effects, and dose response.[20]In order to build connected organs tailored to each patient, these systems can also use human induced pluripotent stem cell (hiPSC) technology. This could eventually result in the development of personalized medicine.[21]

Sources of Cells :

In particular, the choice of cell sources is crucial for organ-on-a-chip models. The reason for the research will determine whether the organ of interest is an animal or a human organ. And what variations in genetic backgrounds are necessary. The majority of cell types used in current experimental models are primarily derived from animals. However, because there might be significant variations in physiology, animal tissues cannot fully capture the complexity of the human experience.[22] Furthermore, they frequently become a significant reason for failure in the drug-development process, especially in the later phases, and they do not accurately represent human disorders.[23] Several human immunological and neurological illnesses lack animal model systems, to use the immune system and the brain as examples. [23] Spanning from brain tumors to autoimmune illnesses. Furthermore, a lot of pathophysiological illnesses are intimately linked to regulated interactions between particular cells and the patient's target organs, making them inappropriate for studies based on animal model systems.[24] Using the immune system and the brain as examples, many human immunological and neurological diseases, from autoimmune disorders to cerebral tumours lack animal model systems. Furthermore, a lot of pathophysiological illnesses are strongly linked to regulated interactions between particular cells and the patient's target organs, making them inappropriate for study using animal model systems.[25] Therefore, human cell sources with their inherent genetic mutations and variances are necessary for the construction of optimal in vitro model systems Different cell types can be obtained from a variety of sources, including ex vivo tissue, immortallised cell lines, primary cells, embryonic stem cells, 51,52, and HIPSCs [26]



Scheme 1. Concept modeling

Cell types should also be highly reliable and reproducible to meet the need for high-throughput screening, with thousands of compounds being processed simultaneously for pharmaceutical purposes. However, these cell types have their pros and cons when applied for developing organon-a-chip models. Different types of cells can be sustained viably over long periods of time to allow the development of normal tissue architecture or diseases and enable us to measure and monitor any pathological or physiological interactions when the cells are exposed to a drug.[27] With the exception of tumours, human ex vivo tissue is not widely available. Additionally, the function of organ-on-a-chip systems that are currently integrated with ex vivo animal tissues is rapidly compromised, making them suitable only for short-term assays conducted just a few hours after the tissues are extracted.[28] The drawbacks of immortalized cell lines include their genetic homogeneity and lack of patient specificity, as well as their small phenotypic mismatches with real tissues despite their widespread availability and reputation as reliable sources for in vitro research. Human primary cell types vary depending on the patient, including neurons The trauma of extraction makes their acquisition problematic, and it's possible they won't live long enough to allow for the best possible approach to be chosen for the drug evaluation.[29] Significant advancements in stem cell technologies over the last ten years have made it easier to produce functioning human cell types through genetic modification. [102] By conjugating a fluorescent reporter gene to a particular promoter or carrying it alone, these cell types' metabolic activity can be optically tracked in response to treatments.[30] It is simple to create human PSCs from particular patient tissues, and these cells can successfully develop into distinct lineages and genomes.[31] These cells are useful for researching heart and neurological conditions as well as genetically inherited illnesses that impact organs like the brain.[32] By homologous recombination, a single gain-of-function gene mutation, for instance, can be injected into a stem cell line and induce the disease. For such disorders caused by a loss-of-function mutation linked to any region of the gene, or even those with a complex genetic background, a HIPSC cell line produced from a single patient can be developed.[33] However, there are obstacles standing in the way of the dependability of HIPSCs, including stopped differentiation and equivocal illness phenotypes brought on by variations in the donor genotype and tissue of origin.[34] Therefore, it is currently difficult to create trustworthy protocols for managing stem cell differentiation, preventing mutations, chromosomal abnormalities, or epigenetic modifications to DNA methylation patterns.[35]The foundation is being established and should be accessible for any illness in the future, opening the door for "patient-on-a chip" models.

3. Physiological Systems Micro engineered on an Organ-on-a-Chip

Cell adhesion substrates were the basis for early attempts to create 2D and 3D cell culture models, which concentrated on managing microenvironments to govern and regulate cell growth, shape, orientation, aggregation, and differentiation.[36] Their physiological correctness and reliability to reconstitute aspects of tissue- or organ-specific functions and microenvironments are dramatically reduced when they lack 3D tissue-like microarchitecture.[37] On the other hand, the creation of organ-on-a-chip systems has presented completely new avenues for the development of in vitro models that include vital dynamic mechanical cues, biochemical signals, tissue–tissue interactions and interfaces, reconstituting tissue microarchitecture, and spatiotemporal chemical gradients[38] Sections 3–6 will showcase representative studies of particular tissue and organ models. 1. A microchannel network, an artery loading well, and an artery inspection area comprise the schematic representation of an arterial section on a chip, known as an artery-on-a-chip. Reversible techniques for loading, fixing, and inspecting arterial segments as well as the fluorescent micrograph of the artery segment are depicted in the illustrations. Endothelial cells (ECs) and smooth muscle cells (SMCs) are the two types of cells, respectively.[39] Royal Society of Chemistry, Copyright 2010. B) Spleen -on-a-chip: (left) schematic representation of the flow division zone, the pillar matrix, and microchannels within the slow-flow channel to mimic IES; (right) diagram of the human spleen illustrating the closed-fast and open-slow microcirculations as well as the inter endothelial slits (IES).[40] The Royal Society of Chemistry. All rights reserved.

Anatomically Inspired Organ Function Mimicking

Technological developments in microengineering, including photolithographic, soft lithographic, and microcontact printing procedures, have made it possible to create a variety of organ models for use in the biological sciences.[41] Numerous creative ideas for replicating organ architecture and functions have been made possible by extending tissue-engineered platforms to more accurately represent the organ microenvironment. Many research teams have shown how to design intricate microstructures in a variety of ways, allowing for the precise control of fluid flows and the incorporation of biological components that accurately mimic the activities of particular organs.[42] For instance, using a pillar matrix and microchannels, researchers were able to perform the red blood cell (RBC)-filtering capabilities of the spleen on a chip and reversibly load and fix an artery segment on a chip [43] This section showcases in vitro microfluidic platforms with anatomical fidelity, created by creating microstructures that replicate the unique functions of organs.

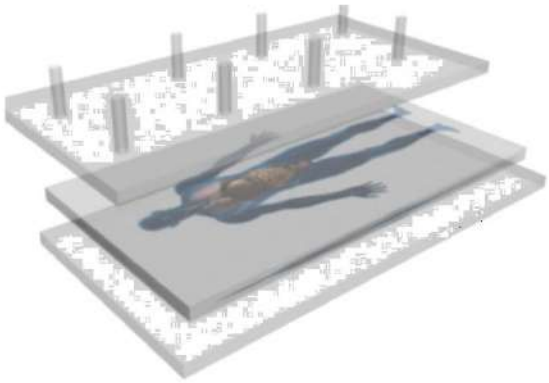
Chip-mounted arteries

One of the main risk factors for heart disease, stroke, and other cardiovascular disorders in people is high blood pressure. [120] Pathological alterations in the composition and functionality of tiny blood arteries give rise to variables that support and perpetuate a range of cardiovascular illnesses.[44] Enhancing my writing skills can be achieved by using microfluidic techniques that involve examining tissue slices, single and cocultured cell populations, and bioengineered tissues in order to uncover the underlying mechanisms.[45] Better treatment plans will require scalable methods to evaluate the composition and operation of intact cardiovascular tissues in both health and illness. Nevertheless, the majority of the systems in use today either place tiny arteries on two wires or employ glass micropipettes for perfusion, which necessitates the manual labor of specialized individuals and is not scalable.[46] In order to address this issue, Günther et al. introduced a scalable organ-based microfluidic technology (Figure 1 A) that enables regulated perfusion and super fusion of a frail resistance artery segment in addition to loading, placement, and fixation with precision.[47]With widths ranging from 30 to 300 μm, resistance arteries are highly specialized structures that control blood flow and organ redistribution. Their walls are made up of multiple layers of smooth muscle cells organized circumferentially and a single layer of lining endothelial cells (ECs). They are situated in the terminal parts of the arterial vascular tree (SMCs). Vasoconstricting and vasodilating substances can be released by ECs to alter vascular tone, which is defined as the degree of constriction in relation to the maximal diameter of the artery. The artery loading area, a microchannel network, and an additional artery

inspection space make up the three sections of the platform. To keep the temperature at 37 °C, a thermoelectric heater and a thermo resistor are linked to the artery examination region. In contrast For arterial fixation (yellow), perfusion (green), and super fusion (red), colored micro channel networks are utilized. The closed fixation and super fusion inlet/outlet lines, which function as a resistance artery segment, are submerged in a buffer at a fixed flow rate and moved by a syringe pump to their designated locations in order to initiate arterial loading. By providing a sub atmospheric pressure, a second set of yellow microchannels fixes the two ends of the artery segment reversibly. The loading well is then employed as a conduit for perfusion. Mimicking the body's natural method of delivering nutrients to a capillary through arterial blood. In order to preserve the organ model's physiological and metabolic activity, the final pair of red microchannels supplies a continuous sustaining medium over the abluminal wall and offers super fusion flow rates. This platform's unique strength is its capacity to examine the shape and function of tiny arteries by subjecting them to a well defined, diverse spatiotemporal milieu. The vasoconstrictor reaction did not spread to the contralateral side, and the authors observed that not all responses were distributed uniformly along the artery wall based on the platform. Furthermore, the unstimulated side was limited Spatially by using just one or two super fusion channels to supply phenylephrine to the outer walls. Potential uses for this scalable experimental platform include target identification and validation, medication design, and early stages of cardiovascular drug development.

The Chip-on-a-Spleen

The spleen is a secondary lymphoid organ that is well suited to filter and remove blood-borne pathogens, such as Plasmodium parasites, as well as senescent, damaged, or diseased red blood cells.[48] Blood monitoring is a unique physiological role that is intrinsically linked to the intricate organizational structure that includes the splenic white pulp, red pulp, and marginal zone. Its distinct ability to filter blood is mostly due to the slow blood microcirculation that increases hematocrit through the reticular meshwork of the splenic red pulp. It also makes it easier for specialist macrophages to identify and eliminate harmful red blood cells.[49] Furthermore, blood passes through inter endothelial slits (IES) in the open and sluggish microcirculation sections of sinusal kinds of spleens in a unidirectional manner prior to entering the venous system.[50] This physical restriction guarantees the strict removal of cells that are not deformable. Rigat Brugarolas et al. reported a novel micro engineered device to mimic the physical properties and hydrodynamic forces of the spleen , the minimal functional unit of the red pulp able to maintain filtering functions, in order to mimic the minimal functional unit of the red splenic pulp while maintaining its filtering functions (Figure 1B).[51] They created two primary microfluidic channels that replicate the open slow and closed-fast microcirculations by offering a physiological flow split. When blood enters the open-slow channel, a pillar matrix that resembles the reticular mesh augments the hematocrit. To prevent cells lacking deformability from reaching the fast-flow microcirculation, parallel 2 μm micro constrictions mimicking the IES are constructed at the junction of the end slow flow and fast-flow channel. They used a variety of blood cell types in multiple studies to confirm the precision and dependability of this spleen on a-chip technology. They revealed that compared to freshly obtained RBCs, aged



this spleen on a-chip technology. They revealed that compared to freshly obtained RBCs, aged RBCs were less deformable and had more difficulty passing through the micro constrictions. Furthermore, reticulocytes with a Plasmodium vivax infection were noticeably more malleable than those without an infection. This was consistent with the greater deformability of the human malarial parasite-infected reticulocytes, which is known. The system demonstrated statistically significant variations in the length of RBCs and plasmodium,-parasited RBCs in the pillar matrix zone, which makes the findings even more intriguing. According to all of these findings, the spleen-on-a-chip system may be able to differentiate between various RBC types according to their mechanical or deformable characteristics, in addition to simulating typical physiological circumstances in the spleen.

Mechanical stimuli and Membrane-Based Penetration

More opportunities to create more complex cell culture conditions have been made possible by microengineering techniques. These in vitro models reconstruct intricate three-dimensional organ-level microarchitecture, complete with crucial integrated dynamic mechanical cues, chemical, and electrical signals. It has been stated that the idea of 3D compartmentalization using membrane-based multilayer compartments can better approximate the in vivo microarchitecture. Particularly helpful in simulating human biological barriers like the blood-brain barrier are these structures

CONCLUSION:

This review focuses on organ-on-a-chip systems that create physiologically normal microenvironments by combining defined 3D microarchitectures, many living cells, and micro fluidiclinks and imitate noteworthy organs as functional models that have been thoroughly examined and talked about. The innovative microarchitectures of these novel single and multiorgan microengineering systems have been highlighted, along with their ability to meet functional requirements. Through the use of artificially created, physiologically realistic microenvironments, organ-on-a-chip technology seeks to replace animal experiment models in drug discovery and environmental toxicology testing while also offering new insights into the mechanisms of action at the tissue and organ levels. In order to facilitate the scale-up, future strategies will need to create new microsystem designs and find new cell sources and materials.

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