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RESEARCH ARTICLE

The Upcoming Drift of Organ-Chip in Pharmacological Trial Investigate

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ABSTRACT
The urgent need for a novel way to replicate human drug reactions in preclinical research has motivated the development of organ-on-a-chip (OoC) systems. These difficulties are not recognized during preclinical trials, owing to ineffective screening technologies that mimic the complexities of human tissues and provide quick, accurate screening readouts. Microfluidics and microfabrication are powerful methods for creating numerous systems with high spatiotemporal precision to simulate in vivo microenvironments for drug delivery, discovery, development, and screening. This method might be used to investigate cell responses to pharmacological and mechanical stimuli in a more physiologically effective way. In this paper, we examine current achievements in OoC with an emphasis on biomimicry, functionality, and characteristics, as well as multi-organ platforms that attempt to replicate the essential aspects of integrated human physiology. Finally, we explore future prospects and limits that must be addressed in order to get OoC systems closer to clinical translation.

Keywords: organ chip, future prospective, multi-organ chip, limitation

Introduction

The term "organ-on-a-chip" (OOC) refers to a multi-channel 3-D microfluidic cell culture integrated circuit (chip) that mimics the functions, mechanics, and physiological responses of a whole organ or organ system.[1][2] It serves as the focus of important biomedical engineering research, specifically in bio-MEMS. Cell biology and labs-on-chips (LOCs) have combined to make it possible to research human physiology in the setting of individual organs. They provide the possibility of serving as an alternative to animal models for drug development and toxicity testing by functioning as a more complicated in vitro approximation of complex tissues than normal cell culture.

The development of these microfluidic applications is still in its infancy, despite the assertions made in numerous articles that organ functions have been translated onto this interface. Different researchers use different designs and methodologies for their organs-on-chips. Microfluidic devices have been used to replicate a variety of organs, including the brain, lung, heart, kidney, liver, prostate, vasculature (artery), skin, bone, and cartilage.[3]

The simulation of an isolated organ may overlook important biological phenomena that occur in the body's intricate web of physiological processes, and this simplifying restricts the conclusions that can be reached. This is a drawback of the early organ-on-a-chip technique. Numerous parts of later microphysiometry strive to overcome these limitations by simulating more complex physiological responses via microfabrication, microelectronics, and microfluidics.[4]

The emergence of organ chips has made it possible to investigate the intricate pathophysiology of human viral infections [4]. The liver chip platform, which has made it possible to study viral hepatitis, is one example.

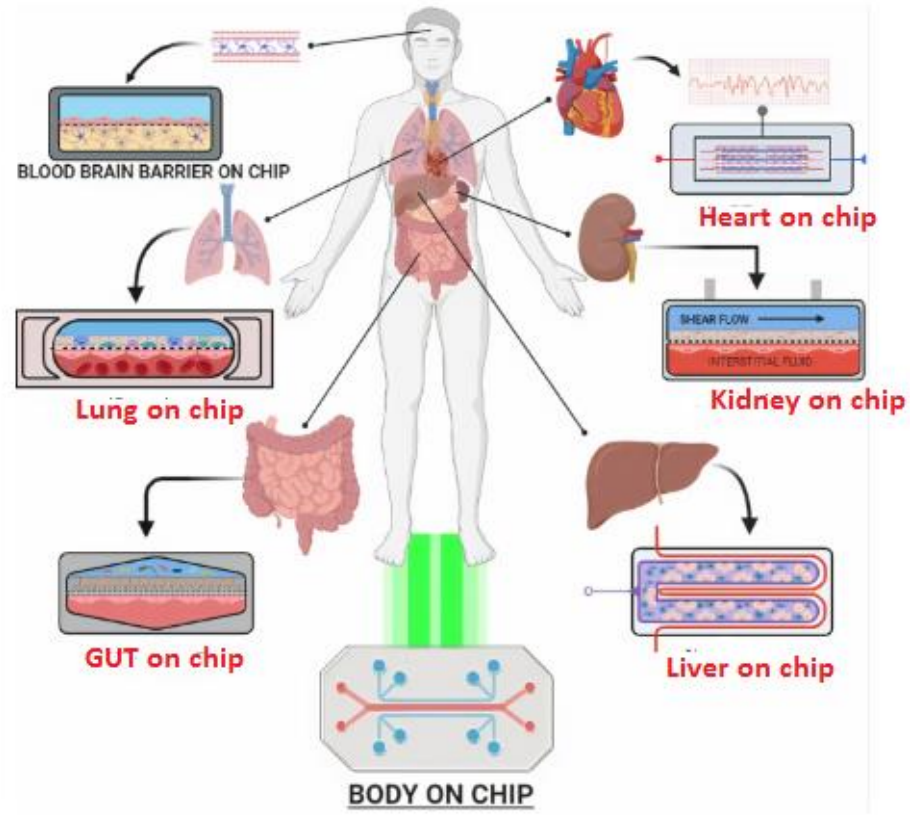

Fig 1: Organ chip

Single- and multiple-Organ-on-a-Chip systems

To enable regulated and organotypic cell culture for in vitro biochemical and pharmacological investigations, researchers have attempted to use a variety of microfluidic devices and lab-on-a-chip systems since the early 2000s [5,6]. This work helped to develop the idea of an Organ-on-a-Chip system. This model garnered a great deal of interest from the biology and engineering communities and was widely regarded as helping to launch the Organ-on-a-Chip revolution. Researchers may examine the breathing

mechanisms that take place at the alveoli-capillary interface of the human lungs by co-culturing the lung's alveolar and capillary cells on opposite sides of a porous membrane in the microfluidic channels of the Lung-on-a-Chip [7]. A biomimetic model is provided to understand the pathogenic mechanisms causing various pulmonary or other respiratory disorders, such as COVID-19, as well as the effects of the environment on lung cells in vitro. Since then, many single-organ chips, including liver chips, kidney chips, pancreas chips, heart chips, intestine and gut chips, blood-brain barrier (BBB) chips, and bone and bone marrow chips, have been successfully developed for tracing the development of disease and examining negative drug reactions. At the preclinical research stage, these single-organ chip assays can aid in identifying important biological mechanisms and assess medication efficacy and toxicity in target organs, serving as a trustworthy benchmark for clinical trials.

Multi-organ chips, which integrate multiple organ units, such as the gut compartment for drug absorbance, the liver compartment for drug metabolism, and the kidney compartment for drug elimination in a single chip, have recently become common to enable more thorough studies. Single-organ chips concentrate on simulating the functions of a single organ. For instance, a heart-liver-skin three-organ model was created to study the effects of acute and long-term drug exposure on the activities of the heart and liver [8]. A four-organ chip having sequentially connected compartments for the intestine, liver, skin, and kidney as well as stable homeostasis throughout the various organ compartments was also designed to investigate the systemic toxicity of medication candidates. A more advanced version, known as "Body-on-a-Chip" or "Human-on-a-Chip," is now being developed to replicate the full human body's physiology using a single platform for medication pharmacokinetic and pharmacodynamic analysis. As an illustration, Miller and Shuler created a proof-of-concept 13-organ system using different cell lines to represent the major parenchymal organs and physiological barrier tissues of humans. This system served as a physical model to study the inter-organ commutation in response to drug challenges at the human level. Undoubtedly, the Human-on-a-Chip platform has the potential to revolution is the pharmaceutical industry by serving as an alternative model system to replace animal models in drug development. However, given the complexity of the human system, there are many technical challenges that must be overcome.

Materials Required and External Equipment

The material used to create the organ-on-a-chip must not affect the elements of the cellular microenvironment and maintain a steady fluid connection. Polydimethylsiloxane (PDMS) is the most often utilised substance. This substance is a synthetic, polymetric elastomer made of silicon and carbon. The actual manufacturing process involves mixing liquid PDMS with a substance that aids in the solidification of PDMS. After that, the slurry is poured into a mould to create the shape of the chip [9]. The body can be bonded to a lass or to another chip after the mixture has dried and hardened the chips. The PDMS gained popularity as a result of many of its features, including its transparency, which benefits the user by allowing them to observe how the OoC behaves. It is simple to employ in this application because the material is inexpensive and has a low cytotoxicity reputation. Since PDMS doesn't deteriorate, other materials are occasionally used in its stead. However, some researchers have attempted to 3D print the chip using a single step, preventing any problematic occurrences that may arise utilising multiple step procedures that would necessitate the initial scaffold's solubilization.

Different biomaterials are needed to produce optimal results because each organ has a unique structure. For instance, collagen is frequently used due to its benefits, but it needs some mechanical support in order to maintain its integrity for an extended period of time. In some circumstances, additional tools are needed to get the best outcomes. Controlling the external flow of the micro- and nanofluids must come first. For this purpose, various kinds of pumps and pressure generators are used. The application of hydrostatic pressure is the best method for controlling flow. Pressure generators are often straightforward systems that include a pressure source, like a compressor, a pressure regulator, and a manometer to gauge the pressure at any given time. The system has many drawbacks while being straight forward, most of them are caused by its slow response times [10]. However, there are ways to get around this issue. The pressure can be altered much more quickly with a pressure multiplexer. The addition of flux sensors, which convert the control signal from pressure to flow, is another improvement that may be made to pressure generators. After a specific number of days, the cell culture's viscosity and density change. Since studies demonstrate that the pressure and stress on the walls rose dramatically in the construction of the chip, it is important to keep this attribute in mind. Another technology typically used

for flow control is pressure syringes. They are typically employed in perfusions, but researchers are now using them in microfluidic experiments as well [11]. They offer the benefit of allowing flow management without being impacted by disturbances brought on by fluid resistance. Similar to the pressure generator, the flow pulses' usage of small values results in a high settling time.

There are often two different types of pumps used to manage flow, the first of which are straightforward liquid pumps with the drawback of having a nonlinear model. To make the system modelling process simpler, a linear equation might be utilised as an alternative. For the devices to be able to detect slight flow variations, a suitable sensor is typically required. The other type of pumps are electro-osmotic ones, which have the drawback of requiring low conductivity liquids in order to function correctly but do not have issues with flow fluctuation and are resistant to high counter pressure.

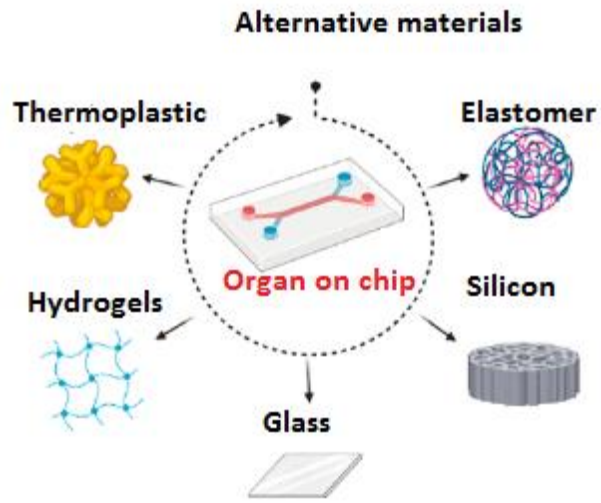

Fig 2: Alternative materials on chip

Organ-on-a-Chip marches toward the market

Once the Organ-on-a-Chip goods make their way into the drug discovery segment, the market is expected to rise dramatically and there will be a great need for drug development [12,13]. The Organ-on-a-Chip business is still in its infancy, therefore demands are fluid and influenced by a wide range of circumstances. For instance, biotech and pharmaceutical companies may prefer a high-throughput yet affordable platform for rapid screening of drug candidates, PK-PD studies, and toxicity and efficiency evaluations at the preclinical drug development stage; academic researchers may need complex microphysiological systems to reveal pathophysiological mechanisms at the early drug discovery stage; other end-users, such as clinics, may prefer a standardised system or tailored service. compiled publicly available data on key participants (Table 1) from a variety of sources [14,15]. Because liver and cancer chips are now in such high demand for medication PK-PD and toxicity research at the preclinical stage, the majority of Organ-on-a-Chip firms chose to offer standard versions of these chips instead. The reliability of the device and its nature are generally contributing elements to how well Organ-on-a-Chip firms are positioned in the market. Although the majority of current Organ-on-a-Chip devices use identical fabrication techniques, ongoing product improvement and differentiation with unique or tightly integrated solutions to meet end-user needs will allow these firms compete successfully in a crowded market. For passive liquid handling of cells and gel loading, Mimetas OrganoPlate®, for instance, provides a novel solution with PhaseguidesTM. For compatibility with industry-standard liquid handling and readout equipment, this platform is designed to handle up to 96 tissue models on a single 384-well plate. This allows for high-throughput drug screening. The "Human Emulation System," a more comprehensive solution sold by Emulate Inc. that consists of organ chips, hardware, and software applications, offers a highly standardised organ chip platform and has attracted a lot of interest from the scientific, pharmaceutical, and industrial communities as well as from the venture capital industry.

Table 1: A brief list of Organ-on-a-Chip startups worldwide.

Company	Found Year	University Spin-off	Scientific Founders	Major Products	Region
HμREL	2006	Cornell University	Greg Baxter Robert Freedman	Liver chip	United States
Kirkstall	2006	University of Pisa	John Wilkinson	Quasi Vivo® system	British
Hepregen, (merged into BioIVT)	2007	MIT	Sangeeta Bhatia	Liver, Islet, Cancer model, Accessory devices	United States
CN-Bio Innovations	2009	MIT	Linda G Griffith	Liver, Gut, Skin, Heart, Lung, Kidney, Brain chip,	British
InSphero	2009	N/A	Jan Lichtenberg Jens M. Kelm Wolfgang Moritz	Liver, Islet, Tumor cell culture	Switzerland
TissUse	2010	Berlin Institute of Technology	Uwe Marx	Multi-organ-chip, Accessory devices	Germany
Nortis	2012	Washington University	Thomas Neumann	Kidney, Liver, Multi-organ-chip, Accessory devices	United States
Emulate	2013	Harvard University	Donald Ingber	Liver, Kidney, Lung, Intestine chip, Accessory devices	United States
Mimetas	2013	Leiden University	Jos Joore Paul Vulto Thomas Hankermeier	Kidney, Gut, Tumors, Liver, Lung, Intestine, Blood vessel, Neuronal models, Accessory devices	The Netherland
Axosim	2014	Tulane University	Michael Moore	Nerve-on-chip	United States
SynVivo	2014	N/A	Kapil Pant B. Prabhakar Pandian	SynTumor, SynBBB, SynRAM, SynTox	United States
Tara Biosystems	2014	Toronto University	Milica Radisic Gordana Vunjak-Novakovic Robert Langer John M. Baldoni	Biowire™ II platform	United States
Alveolix	2015	University of Bern	Olivier Guenat	Lung-on-chip	Switzerland
ANANDA Devices	2015	N/A	Margaret Magdesian	Neuro Device	Canada
Hesperos	2015	Cornell University Central Florida University	Michael Shuler James Hickman	Heart, Liver, Lung, Brain, Skin, and Kidney chip, Multi-organ-chip	United States
Altis BioSystems	2016	University of North Carolina, Chapel Hill	Nancy Allbritton	RepliGut Kits	United States
MesoBioTech	2016	N/A	Yong Chen	Microfluidics Lung chip	France
BiomimX	2017	The Polytechnic University of Milan	Alberto Redaelli	Heart-on-chip	Italy
BI/OND	2017	Delft University of Technology	Cinzia Silvestri	Organoids cultivation, Tissue-tissue interface	The Netherland

Company	Found Year	University Spin-off	Scientific Founders	Major Products	Region
Jiksak Bioengineering	2017	N/A	Jiro Kawada Keita Shibuya Norihiro Yumoto Shinji Tokunaga	Nerve Organoids	Japan
DAXIANG	2018	N/A	Yu Zhou	Liver chip, cancer chip	China
Aracari Bio	2019	University of California, Irvine	G. Wesley Hatfield Christopher C.W. Hughes Steven C. George Abraham P. Lee	Vascularized micro-organ chip	United States
REVIVO Biosystems	2019	Agency for Science, Technology and Research	Massimo Alberti	Microfluidic Skin-on-a-Chip	Singapore

Limitation of organ on chip

The expedited research that the organ-on-a-chip concept can produce is its first key strength. Since the fabrication of the chips is relatively inexpensive, it is feasible to fabricate them using common office supplies without the need for specialised equipment [16,17]. This allows for the simultaneous testing of numerous medications and drug doses. When a novel medicine is developed, this could be advantageous because it eliminates the need for test volunteers while also addressing ethnic issues [18]. The OoC concept's ability to accurately reproduce the tissue microenvironment is one of its other strong points. The OoC is contrasted with straightforward Petri recipient microsystems. Due to the 3D structure, a crucial component of the test's reliability, the OoC triumphs [19]. The microfluidic chips can evaluate a wide range of physiological problems and are also user-friendly and, in certain situations, portable. Numerous microfluidic systems can be implemented on a single chip due to their small size, saving both time and money.

The existence of the surface effect is the first drawback taken into account. Due to the fluids' extremely tiny size, surface effects outweigh volume effects [20]. This might show in the analysis's low quality, and some interesting products might even be adsorbed. The necessary fluids may not mix effectively because laminar flow exists where several fluids converge. Another drawback of these platforms is the requirement for specialized equipment in some research in order to provide accurate findings.

The future advances in Organ-on-a-Chip: Challenges and opportunities

Over the past two decades, the early development of Organ-on-a-Chip systems has shown how powerful this new tool for drug discovery and development can be. As we move into the next decade, new Organ-on-a-Chip platforms are only beginning to emerge to fulfil the expanding demand for improved preclinical models for drug discovery [21]. These platforms have considerable advancements in functionality, integration, automation, production, and personalized precision medicine.

In order to address interesting biological and pharmaceutical problems, future Organ-on-a-Chip platforms will first show off a physiologically relevant and spatiotemporally responsive microenvironment [22,23]. Future Organ-on-a-Chip platforms' technological capabilities will enable the real-time, in-situ, and dynamic maintenance and monitoring of a wide range of biological parameters, including shear stress, pH, oxygen, cytokines, and chemokines, as well as downstream and off-chip analyses of molecular signature, cellular physiology, and tissue pathology using conventional analytical tools like enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), and others. In situ optical, electrical, chemical, and biological biosensors can be more advanced integrated as integrative microfluidic components to detect the key signals in a spatiotemporal manner [24], which is difficult in animal experimentation. Its potential as a high-throughput and integrated preclinical readout system for drug testing, for instance, has been highlighted by the integration of label-free and multiplexed nanoplasmonic sensors for in situ analysis of cytokine secretion during drug and pro-inflammatory stimulation in a biomimetic microfluidic adipose-tissue-on-a-chip platform. Deterministic barcoding in tissue for spatial omics sequencing (DBiT-seq), for example, will enable the spatial barcoding and sequencing of enormous amounts of

molecular data from tissues at a genome-scale resolution in the future when new multi-omics detecting approaches are developed and integrated into microfluidic Organ-on-a-Chip platforms [25,26]. We think that incorporating new ideas and technology will help Organ-on-a-Chip operate better over time, supporting its wider use in medication development.

In addition to improving and standardising the product production process, Organ-on-a-Chip platforms in the future will also need to classify system designs, configurable modules, and interfaces. The majority of Organ-on-a-Chip devices are currently made by hand in research labs utilising the soft lithography technique and PDMS. For the mass manufacture of devices for the market, the throughput and repeatability of fabrication are in doubt, demanding a standardised, high-throughput, yet affordable manufacturing procedure [27,28]. The use of more standardised, modular formats with biologically inert materials (such as plastics to replace PDMS) as well as advanced additive manufacturing methods (such as 3D printing) or current standard manufacturing materials and methods (such as injection modelling and laser cutting) should be taken into consideration. For instance, 3D bioprinting is a potential technique for creating Organ-on-a-Chip devices, allowing for the automatic printing of complex scaffolds, intricate tissue structures, or device templates with great precision and control. In the not-too-distant future, 3D bioprinting and other additive manufacturing techniques are anticipated to significantly alter the fabrication methodology for Organ-on-a-Chip by providing a one-step method of tissue reconstruction and culture platform engineering. In order to be compatible with the common biological laboratory experiments and work style of the pharmaceutical industry, Organ-on-a-Chip platforms should also operate in a more automated, high-throughput, and parallelized manner through a standardised user-friendly interface [29,30]. Initial attempts at using a robotic interrogator were successful in enabling tasks like automated cell culture, intercompartmental fluidic coupling, repeated sample collection, and in situ microscopic imaging over weeks in an integrated eight-organ chip. A microfluidic device called IFlowPlate, which is based on a 384-well plate, most recently made it possible to cultivate and vascularize patient-derived colon organoids in vitro, offering a higher throughput capacity than existing organ chips. The commercialization and promotion of Organ-on-a-Chip platforms will depend on this improvement in order for end users to accept them.

Last but not least, the future Organ-on-a-Chip platform will be created using patient-derived materials, including patient tissue, decellularized ECM, and other biological materials for personalised precision medicine, in which patient selection and stratification biomarkers will be crucial for successful drug development. Patient tissue cell sources are frequently unreliable and scarce, with low proliferative potential or a need for intrusive sample collection. These issues provide a major hurdle. As indicated by the development of glomeruli with selective filtration properties on human brain and cardiac chips, a lack of functional human podocytes, for instance, can obstruct this process. Patient-derived pluripotent stem cells (iPSCs), which have recently come to light in research [31,32,33], For the production of autologous target organs or tissues, such as those obtained from skin fibroblasts, serve as an alternative and limitless cell source. This enables the development of patient-specific organ chips for personalised disease modelling and drug screening [34,35]. For instance, a human BBB chip created using neurons, astrocytes, and endothelial-like cells from brain microvessels generated from patient iPSCs showed patient-specific breakdown of barrier integrity and blood-to-brain permeability of pharmaceuticals. Researchers have also succeeded in in vitro modelling of cardiovascular diseases, screening of potential drugs, and evaluation of cardiac toxicity resulting from drug interactions and nanomaterials using healthy or patient iPSC-derived cardiomyocytes, all of which could not be achieved due to a lack of human cardiac cells. Additionally, the addition of iPSC-based organoids—another idea in which an ex vivo organotypic microtissue is created through the self-organization and differentiation of stem cells in a 3D matrix—to the Organ-on-a-Chip platform led to the creation of a potent hybrid tool known as "Organoids-on-a-Chip". For example, it has been shown that microfluidic kidney and retinal organoid chips are more physiologically appropriate in terms of tissue maturity and functionality. The inadequacy of conventional "one-size-fits-all" therapeutics would surprisingly be overcome by efforts aimed at developing patient iPSC-derived organ chips, providing an ideal treatment for individual patients across large populations for the same disorder. However, not all studies could be listed due to space limitations. Future benefits are also anticipated, particularly in the modelling and analysis of rare human disorders, which are currently constrained by the lack of biological investigations and the high R&D costs that follow

Declaration

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Concluding remarks

The industrial drug development process is highly standardised, despite the fact that a strong argument for a paradigm shift in drug development has evolved in an effort to increase the overall pass rate of recently discovered medications. The design and integration of the Organ-on-a-Chip platforms into the drug development pipeline would undoubtedly be advantageous at all preclinical stages and even realise trial-on-chips for clinical validation because the entire drug development process may involve switching back and forth between disease modelling and drug testing. Organ-on-a-Chip systems can be a potential alternative to avoid ethical issues linked to animal use and adhere to the guiding 3R principles (i.e., replacement, reduction, and refinement) given the fast-growing concerns about animal welfare and rights in biological investigations. Because it is still difficult to meet the practical demands of quick drug development and precise preclinical evaluation, Organ-on-a-Chip systems are still at the periphery of the pharmaceutical industry (see "Outstanding Questions"). The Organ-on-a-Chip platform is anticipated to eventually close the biological and technical gaps between translational, preclinical, and clinical studies by continuous integration of fresh concepts and methods. In conclusion, we are excited about Organ-on-a-Chip's potential in the pharmaceutical sector and about its increasingly bright future in personalised precision medicine.

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