

## Engineering Human Physiology on Chips: Advances and Applications of Organ-on-a-Chip Technology

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### ABSTRACT

Organ-on-a-chip (OOC) is a revolutionary interdisciplinary approach that integrates microfluidics, tissue engineering, biomaterials and cell biology for recreating the structure and function of human organs on microscale microdevices. OOCs are the most relevant in vitro models to mimic the dynamic microenvironment such as mechanical stimuli, biochemical gradients and tissue-tissue interactions encountered by cells. In recent years, OOC technology has been recognized as an attractive alternative to traditional 2D cell culture and animal models with superior predictive power, lower ethical concern and enhanced human specificity for studying biological processes, and it has gained much interest from various research fields. Here, the fundamental concepts of organ-on-a-chip development as well as microfluidics principles, designs and Fabrication techniques including biomaterials, tissue engineering, microfluidics and microfabrication (soft lithography and 3D bioprinting, etc) are addressed. Main types of OOCs namely lung-on-a-chip, liver-on-a-chip, heart-on-a-chip, brain-on-a-chip and kidney-on-a-chip and their biomedical applications in drug discovery and toxicity evaluation, disease modeling and personalized medicine, are also presented. Technical challenges and progress, including limitations and future development of the system (e.g. Multi-organ systems and artificial intelligence) are discussed. Overall, organ-on-a-chip technology has huge potential to revolutionize biomedical research toward translational medicine, precision therapeutics, and decreased animal use.

Literature for this review was taken from databases like Pubmed, Scopus, Google scholar followed by using relevant keywords which are related to organ-on-chip technology and biomedical applications.

### KEYWORDS

Organ-on-a-chip; Microfluidics; Tissue engineering; Biomaterials; 3D bioprinting; Drug discovery; Disease modeling; Personalized medicine; Microfabrication; Toxicity testing; Multi-organ chips; Biomedical engineering

### INTRODUCTION

Organ-on-a-chip (OOC) technology is a revolutionizing biomedical engineering technology that synergistically combine microfluidics, tissue engineering, biomaterials science, and cellular biology in order to create the physiological and functional features of human organs in miniature devices. Microengineered organs, that replicate microenvironment of living tissue including dynamic fluid flow, mechanical forces, and multicellular structure in a defined in vitro system(1). This in-vitro system differ from conventional 2D cell culture which lacks in vivo features such as cell-cell interaction and biochemical gradients and animal models, that show interspecies differences and ethical concern(2). OOC technology provides biologically relevant and human-like microenvironment which can replace 2D cell culture and animal models(3). Since its introduction into the fields, OOC technology have had impact on drug development, toxicity screening, personalized medicine and disease

modeling, because it enables studying of organ-specific reaction under physiologically relevant environment (4). Over the past decade, significant progress in microfabrication techniques and biomaterials has enable fabricating organ-chips which can recapitulate tissue-tissue interaction and vascularization(5). These devices offer a promising and powerful platform which can contribute to biomedical research and has replaced conventional experimental models (6).

## II.OVERVIEW OF ORGAN-ON-A-CHIP

Organ-on-a-chip is defined as a microfluidic cell culture device, which can recapitulate functional and structural elements of human tissues by housing cells in a microenvironment engineered from microfluidics(7). Originated from development of microelectromechanical systems and microfluidics for controlling microscale flow, modern organ-on-a-chip system uses biological relevant micro-environmental features to recreate the cell function including material/oxygen transport

## III. IMPORTANCE IN BIOMEDICAL RESEARCH

The growing relevance of organ-on-a-chip technology in biomedical research is closely related to its advantages over conventional in vivo and in vitro models. The technology serves as a high fidelity system for mechanistic study of diseases, toxic evaluation and therapy development because its design recreates human physiology more precisely(13). As an essential tool in pharmaceutical research for pre-clinical drug discovery, OOC technology helps in better predicting drug-induced toxicity and avoid late-stage clinical failure(14). Additionally, OOC technology supports the principles of reduction, replacement and refinement for ethical and reduced animal use in the life sciences(15). Organ-chips for specific disease have been developed such as cancer chips, neurodegenerative disease chips, cardiovascular disease chips and infectious disease chips which mimic certain aspect of the specific disease under defined micro-environmental control(16). Personalized medicine and diagnostics is also one of the emerging applications for placing patient

## LITERATURE SEARCH

### METHODOLOGY

Subsequently, related literature for organ-on-a-chip technologies was collected from standard databases including PubMed, Scopus, Google Scholar, and ScienceDirect which has the keywords such as: organ-on-a-chip, microfluidics, drug screening, disease modeling. Recent studies and review articles were then retrieved from English research and were carefully reviewed and summarized.

and signaling events(8,9). Devices which are designed to mimic the liver, lung, heart, kidney, gut and brain etc. Enable organ-specific analysis in vitro(10). Furthermore, combination of multiple organs on a single chip can better recapitulate inter-organ interactions and study pharmacokinetics and drug metabolism in integrated systems(11). OOC technology is the best candidate for the future biomedical research and medical practice due to its physiological relevant and high throughput (12).

derived cells in OOC to study the patient's responses to therapy(17). Finally, integrated sensor and imaging system provide real-time monitoring and functional readout in OOC platforms(18).

## IV. DESIGN AND PRINCIPLE

The organ-on-a-chip systems aim to replicate the critical biological, chemical, and mechanical factors of human tissues using micro-engineering. They usually comprise microchannels, chambers, porous membranes and extracellular matrix in their architecture to facilitate the growth of cells and tissues(19). One of the important principles in designing these organs is recreating the in vivo conditions, including fluid shear stress, biochemical gradients, oxygen diffusion, and cell-cell communication(20). Microfluidic perfusion helps in constant supply of nutrients and removal of wastes, while maintaining the laminar flow as seen in capillary networks(21). In most cases, a pliable membrane along with a mechanical actuator are used in chip fabrication to create the organ-specific movements such as breathing, peristalsis, or cardiac contractions(22). Endothelial barriers

and vascular channels further contribute in creating realistic models by simulating vascularity and immune cell(23). More recent designs aim at fabricating modular or interlinked platforms to connect and simulate several organs simultaneously for the investigation of their crosstalk and systemic toxicity(24). This kind of device fabrication requires multi-disciplinary expertise, involving biologists, engineers, materials scientists and computational modelers(25).

### V. MICROFLUIDICS

Microfluidics provides the basis for developing the organ-on-a-chip models as it facilitates easy manipulation of micro-volumes of fluids in microchannels. In the micro regime, fluid exhibits a laminar flow, with the prediction of diffusion patterns and mass transport which are beneficial in reproducing physiological environment in vitro(26). Controlled microfluidic flow in organ chips can generate concentration gradients, provide nutrients, or subject the cells to various mechanical stimuli like shear stress(27). All these aspects are crucial in regulating specific cell behaviour. Chemical signaling at specified spatial and temporal location in these systems is also feasible, which enables its application for simulating complex dynamic physiological environments(28). Moreover, organ chips can host more than one tissue compartment and blood vessel, simulating organ functions more effectively(29). The applications of microfluidics have evolved through developing perfusable vascular networks, droplet systems, and gradient generating devices for high throughput applications(30). Challenges for using microfluidics in large scale and industrial applications include establishing their stability over long period, scalability and standardization(31).

### VI. CELL CULTURE ENVIRONMENT

The cell culture environment within the organ-chips are designed to recreate the native extracellular matrix and physiology of the human tissues. Unlike the static cultures of cells used earlier, organ-chips create a

dynamic environment, maintain cell growth via perfusions and mechanical stimulation and also promote the three-dimensional organization of cells and tissues(32). Cell behaviour including morphology, proliferation, differentiation and functionality is governed by this environment. Presence of extracellular matrix proteins or hydrogel scaffold helps cells attach well and adopt specific morphology(33). Mechanical forces like cyclic stretch or compression, or shear stress are generally employed to ensure that the cell environment is more similar to the in vivo environment (34). Multicellular co-cultures are very commonly used in the fabrication of organ-chips so that the interactions between tissues can be simulated effectively(35). Oxygen gradients, nutrient diffusion and biochemical signaling pathways are regulated accurately to provide optimal conditions for the longevity of cell(36). Patient specific models for disease studies or regenerative medicine can also be developed using induced pluripotent stem cells which contribute to the advanced possibilities of organ chips(37). Developing an appropriate environment for cells in the chip is critical for the predictability and translational significance of organ-chip devices(38).

### VII. BIOMATERIALS USED

Biomaterials are indispensable to organ-chips as they render them support, biocompatibility and the required mechanical strength. PDMS (polydimethylsiloxane) is one of the most commonly used biomaterials owing to its excellent optical properties, gaseous permeability and easiness in micro fabrication(39). Its shortcomings, such as absorption of hydrophilic molecules thereby affecting drug testing results and limitation of the types of drugs it can be used with, have lead to investigations in the use of various alternative materials such as plastics, hydrogels, collagen, gelatin methacrylate, polyethylene glycol based polymers etc.,(40,41). The application of hydrogel material is promising as they are capable of mimicking the extracellular matrix. Moreover,

these provide a highly bio compatible environment, favourable for the growth and organization of cells in 3- dimensions(42). Other natural materials such as alginate, fibrin and hyaluronic acid are highly effective as they impart favourable biological properties. Conversely, synthetic materials offer advantages of controlled mechanical properties and higher reproducibility(43). Use of new bio-active and stimulus-responsive materials helps to make a cell environment which can be dynamically responsive to chemical or mechanical stimuli(44). Appropriate biomaterial selection is essential in designing organs which are functionally viable and mimics biological nature(45).

#### VIII. FABRICATION TECHNIQUES

The organ-chips require precise microarchitecture for functional performance and fabrication methods are the critical aspect for creating the microarchitecture. The choice of fabrication method relies on several parameters such as compatible material, required complexity and precision, and the production speed required (46). Microfabrication methods originated from the semiconductor technology, like photolithography and soft lithography are routinely used in manufacturing high-resolution microdevices(47). The fabrication of 3D complex tissues and vascular network is possible with the advanced 3D bioprinting and additive manufacturing methods(48). Other processes like hot embossing, injection molding, laser ablation and micro-machining have been used to speed up the production or rapidly create prototyping(49). Furthermore, advanced fabrication processes are required for incorporating additional features into organ chips, such as biosensors, electrodes, and imaging components(50). Recently, high through-put and scalable manufacturing process are a growing concern for the translation of these chips for industrial applications(51). Fabrication methods are expected to enhance the 3D complexity, predictability and cost-effectiveness in the future organ chips(52).

#### IX. SOFT LITHOGRAPHY

One of the most widely used fabrication techniques in OOC design due to its ability to create microfluidic devices at high resolution. Typically, a soft elastomeric material (such as PDMS) is molded from a patterned mold fabricated using photolithography(53). These resulting micro-structures accurately mimic micro-scale architectures suitable for fluid handling and cell cultures(54). Benefits of this technique are its low production cost, optical transparency, gas permeability, ease of prototyping and is highly suited to create biomimetic platforms for on-chip observation(55). Furthermore, through the use of multiple soft lithographic layers, it is possible to construct complex micro-fluidic networks and valves that enhance the usability of the system(56). Some potential drawbacks are: absorption of material by tissues, material deformation under pressure and scaling issues, though continued progress in mold fabrication, incorporation of novel hybrid materials and large-scale fabrication will be able to address these issues in the future(57,58).

#### X. 3D BIOPRINTING

3D bioprinting has rapidly become an important biofabrication tool for the creation of OOC systems due to its ability to precisely organize cells, extracellular matrix materials and biological molecules within tissue structures(59). This is an additive manufacturing process where inks are printed layer-by-layer from a starting material containing living cells and ECM components in order to simulate in vivo microenvironments. One significant benefit over conventional fabrication techniques is the ability to print out complex heterogenous structures and vascular networks(60). A number of different bioprinting methods, such as inkjet printing, extrusion-based printing, and laser-assisted bioprinting, have already been used in organ-on-chip systems, and selection will depend on the required printing resolution and material properties(61). Key limitations include optimization of bioinks,

limitations on printing resolution, cell viability and long-term tissue culture; future research efforts are focused on creating viable and highly functional organ-on-chip platforms that would also be individually applicable in the clinical setting(62).

#### XI. MICROFABRICATION METHODS

The creation of highly controllable and miniaturized OOC devices hinges on microfabrication techniques. Photolithography, etching, laser micromachining, hot embossing, injection molding and xurography are just some examples of the different approaches that can be adopted when creating devices (depending on intended application)(63). Photolithography can be used to create high resolution microchannel architectures, whereas techniques such as injection molding and hot embossing, for polymer-based systems, will increase throughput and reproducibility for scaled production(64,65). Integration with bio-sensing technologies can further enhance the performance of OOC devices(66), and continuous improvements in microfabrication technology will undoubtedly aid the further application of OOCs in various areas(67).

#### XII. TYPES OF ORGAN-ON-A-CHIP MODELS

**Lung-on-a-chip:** Replicates the alveolar-capillary interface, it can be used to model respiratory diseases and inflammations and assess the effects of pharmaceuticals on the lung (68).

**Liver-on-a-chip:** These chips accurately simulate both liver structure and function in order to test liver specific drug metabolism and the prediction of hepatotoxicity(69).

**Heart-on-a-chip:** Replicates both the structure and contractile mechanics of a beating cardiac tissue; allows researchers to study the underlying physiology, as well as assess cardiotoxicities of pharmaceuticals(70).

**Brain-on-a-chip:** These devices model the microenvironment of the human brain to

accurately recreate the function of neural networks and to assess pathologies of degenerative diseases(71).

**Kidney-on-a-chip:** These are designed to replicate the functions of the kidney; mimicking the renal tubules and filtration system allow researchers to assess the effects of novel drug compounds in relation to renal toxicity (72).

#### XIII.APPLICATIONS

**Drug discovery:** Can predict the response of drugs in the human system more accurately than cell cultures alone and therefore reduce the costly and time-consuming use of animal studies(73).

**Toxicity testing:** The human-relevant physiological environment means that toxins and drugs will be evaluated more accurately. They are therefore highly suited for evaluating the safety of chemicals and drugs(74).

**Disease modeling:** By mimicking the pathological microenvironment of diseases, these organ chips allow the mechanisms of diseases and potential treatment therapies to be modeled and researched(75).

**Personalized medicine:** If used in combination with a patient's own cells, then the drugs can be tailored to individuals and treatment strategies optimized to them(76).

#### XIV.RECENT ADVANCES ANDFUTURE PERSPECTIVES

**Multi-organ chips:** Integration of different organ chips into one fluidic platform to mimic interactions between organs and to evaluate systemically distributed drugs(77).

**AI integration:** Automation and improved accuracy and prediction power through the implementation of artificial intelligence systems within OOC devices (78).

## XV. FUTURE CLINICAL APPLICATIONS

Medical applications in personal medicine, regenerative medicine and potential substitution for some animal tests in the clinical setting(79).

## XVI. CONCLUSION

Summary and future scope: Organ-on-a-chip systems represent a groundbreaking advance in the field of biomedical engineering due to their unique ability to replicate physiological relevant models of the human body. The advancement in microfabrication technology, hybrid biomaterials and computational integration will continue to fuel the development of these devices for the clinic and industry(80).

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